

Southern Society for Clinical Investigation  
and Southern American Federation for  
Clinical Research

Plenary Session

SSCI Young Investigator Award Finalists

SSCI Poster Award Finalists

SAFMR/SSCI/ Student Research Award

8:00 AM

Friday, February 19, 2016

362 HIGH DIETARY SODIUM BLUNTS EFFECTS OF  
MINERALOCORTICOID RECEPTOR ANTAGONISM ON  
LEFT VENTRICULAR HYPERTROPHY IN RESISTANT  
HYPERTENSION PATIENTS

L Ghazi, K Gaddam, LJ Dell'Italia, SG Lloyd, C Lin, D Calhoun, S Oapril,  
T Dudenbostel. University of Alabama at Birmingham, Birmingham, AL

10.1136/jim-2015-000035.361

**Purpose of Study** Patients with resistant hypertension (RHTN) commonly have primary aldosteronism (PA), which is associated with left ventricular hypertrophy (LVH). Aldosterone activates mineralocorticoid receptors (MR) and induces hypertrophy. Experimental studies indicate a paradoxical activation of the MR in sodium-loaded rats despite adequate suppression of aldosterone. MR antagonists slow down cardiac hypertrophy. We hypothesized that the MR antagonist spironolactone (SPL) would cause greater LVH reduction in patients on high Na diet independent of aldosterone.

**Methods Used** Overall 34 patients with RHTN, defined as BP $\geq$ 140/90 mmHg despite  $\geq$ 3 different medications, including a diuretic, were treated with SPL. Cardiac magnetic resonance imaging and biochemical evaluation was performed at baseline, 3 and 6 months in patients with PA and non-PA. PA was defined as renin activity (PRA) $<$ 1 ng/ml/h and urinary aldosterone  $\geq$ 12 ug/24 h. We dichotomized patients according to UNa level (UNa  $\geq$ 200 mEq/24 h: high Na diet) and PA status. LVH reduction was indexed by left ventricular mass (LVM) and interventricular septum thickness (IVS) regression.

**Summary of Results** LVM and IVS regression after treatment with SPL at 3 and 6 months was greater in patients with PA on a normal sodium diet and less pronounced

in patients on a high sodium diet suggesting that Na blunts the effects of cardiac MR when treated with SPL. However, in patients with non-PA high Na intake did not blunt the effects of SPL.

**Conclusions** Contrary to our hypothesis, high dietary Na blunted LVH regression in patients with PA treated with SPL. Further studies are needed to elucidate mechanisms for sodium dependent MR activation in patients with PA and non-PA.

Effect of spironolactone treatment in patients on LVM and in patients with and without PA at baseline, 3 and 6 months

363 THE PREB CELL RECEPTOR CHECKPOINT SELECTS  
FOR SPECIFIC AMINO ACIDS IN CDR-H3

M Khass, T Blackburn, P Burrows, M Walter, H Schroeder. UAB, Birmingham, AL

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**Purpose of Study** Immunoglobulin CDR-H3 plays a major role in antibody epitope recognition and binding. CDR-H3 is the direct product of VDJ rearrangement and lies at the center of the antigen binding site. The prevalence of individual amino acids within CDR-H3 is distinctly non-random. Much of the bias in amino acid usage derives from natural selection of D<sub>H</sub> and J<sub>H</sub> sequence. However, non-templated N addition has the capability to introduce amino acids that are disfavored in the germline sequence. The first checkpoint in B cell development to test the amino acid sequence of the H chain requires binding of surrogate light chain (VpreB and  $\lambda$ 5) to the nascent H chain. Cells that form a functional preB cell receptor undergo several rounds of cell division and then rearrange light chain. Cells that fail to create a preBCR undergo apoptosis. To test whether successful formation of a preBCR was influenced by CDR-H3 sequence

**Methods Used** We examined *in-vivo* preBCR formation and preB cell apoptosis and cell cycling in B lineage cells from the bone marrow of mice with altered germline sequence. We performed *in silico* structural analysis of sequenced heavy chains from sorted live and apoptotic cells.

**Summary of Results** We observed increased failure to create a functional preBCR in B cells that used non-tyrosine enriched D<sub>H</sub> sequence. We then sequenced and compared

Abstract 362 Table 1

	Primary Aldosteronism				Non-Primary Aldosteronism			
	LVM (g/m <sup>2</sup> )		IVS (mm)		LVM (g/m <sup>2</sup> )		IVS (mm)	
	UNa<200 (n=13)	UNa $\geq$ 200 (n=7)	UNa<200 (n=13)	UNa $\geq$ 200 (n=7)	UNa<200 (n=5)	UNa $\geq$ 200 (n=9)	UNa<200 (n=5)	UNa $\geq$ 200 (n=9)
Baseline	170.2	175.8	12.4	11.0	158.3	205.1	11.6	13.4
Difference between baseline, 3, and 6 month visits after addition of spironolactone								
Baseline to 3 months	-34.8	-16.0*	-1.5	0.1	-7.0	-33.2*	-0.4	-0.7
Baseline to 6 months	-52.0	-25.0*	-1.4	0.5	-19.8	-40.5*	1.2	-1.4

\* denotes statistical significance p<0.05

wild type H chain transcripts from apoptotic and living preB cells. Among cells that had successfully traversed the preBCR checkpoint, enrichment for tyrosine at specific amino acid position within CDR-H3 were observed. *In silico* structural analysis revealed key amino acids within the VpreB CDR-H3 sensing site that appear to play a critical role in H chain CDR-H3 selection.

**Conclusions** We conclude that the preBCR checkpoint selects both for H chains that can bind to L chains and for favored amino acids at the center of the antigen binding site and thus influence epitope recognition.

**364** **ADVANCED GLYCATION END PRODUCTS STIMULATE ANGIOTENSINOGEN EXPRESSION IN RENAL PROXIMAL TUBULE CELLS**

JM Garagliano, A Derbenev, A Zsombok, G Navar, R Sato. *Tulane SOM, New Orleans, LA*

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**Purpose of Study** Elevated plasma and tissue concentrations of advanced glycation end products (AGEs) are seen in hyperglycemic individuals and are implicated in renal dysfunction in diabetes mellitus (DM). In addition, AGEs and their receptor are involved in paracrine activation of other pathophysiological systems. The intrarenal renin-angiotensin system, including proximal tubular angiotensinogen (AGT), is activated in DM contributing to the development of nephropathy. However, the effect of AGEs on AGT expression in proximal tubular cells (PTC) has not been determined.

**Methods Used** To establish augmentation of intrarenal AGT and AGE levels in DM, urinary AGT and AGE levels in streptozotocin (200 mg/kg)-induced DM mice were determined by ELISAs. The stimulating effect of AGEs on AGT expression was tested using cultured rat PTC treated with 0–200 µg/ml AGE-BSA for 24 hours. AGT mRNA, intracellular AGT protein, and secreted AGT levels were measured by real-time RT-PCR, western blot analysis, and ELISA, respectively.

**Summary of Results** Urinary AGT and AGE levels were concomitantly greater in DM mice compared to control mice (AGT: 21.6±5.5 ng/day vs. 190.1±57.8 ng/day, AGE: 139.1±21.6 ng/day vs. 332.8±102.7 ng/day). Direct treatment of PTC with AGE-BSA increased AGT mRNA (3.43±0.11-fold compared to control), intracellular AGT protein (3.60±0.38-fold), and secreted AGT levels (2.11±0.18-fold). Non-glycated BSA serving as a negative control did not alter AGT levels. Expression of AGE receptor in cultured PTC was demonstrated by western blot analysis and immunocytochemistry. Adding recombinant soluble AGE receptor, which competes with AGE receptor on plasma membrane, to culture medium attenuated the AGE-induced AGT augmentation, suggesting that AGE-BSA stimulates AGT expression via activation of AGE receptor. Enhanced phosphorylation of ERK1/2, but not p38 MAP kinase, was observed in AGE-BSA-treated PTC.

**Conclusions** The results indicate that both AGEs and uAGT are increased in DM mice and that AGEs directly

stimulate AGT expression in PTC. ERK1/2 may serve as a signal transducer in this axis. The findings suggest that elevated AGEs contribute to intrarenal AGT augmentation in DM and development of diabetic nephropathy. The findings provide a rationale for targeting AGE-AGT axis to treat or prevent diabetic nephropathy.

**364A** **OMALIZUMAB AS A TREATMENT FOR CHRONIC RHINOSINUSITIS WITH NASAL POLYPOSIS**

BA Brunet, G Marshall. *University of Mississippi Medical Center, Jackson, MS*

10.1136/jim-2015-000035.364

**Purpose of Study** Chronic rhinosinusitis with nasal polyposis (CRS-NP) can have a severe adverse impact on quality of life. In patients who have failed topical intranasal corticosteroid (ICS) treatment and are not surgical candidates for polypectomy, an alternative therapy is needed to spare the patient from side effects of chronic oral CS (OCS) use. CRS-NP and asthma share histopathologic features including a predominance of eosinophils recruited by Th2 cells, and elevated local IgE production. These parallels allow a rationale for potentially effective treatment of NP by a proven therapeutic intervention for asthma—the monoclonal anti-IgE antibody omalizumab (OMA).

**Methods** A 64 yo AA male presented with CRS-NP. He failed ICS treatment and was managed with chronic OCS as he was not a surgical candidate due to multiple comorbidities. He did not meet criteria for aspirin exacerbated respiratory disorder. Several attempts at weaning OCS failed, and OMA was initiated as an alternative therapy.

**Summary of Results** The patient's CRS-NP was managed with oral and ICS, antibiotics, and nasal flushes for 26 months. He required 8 high dose OCS bursts and was tapered to 10 mg daily between each, but was unable to wean completely. He had one treatment of kenalog infused nasopores, and 2 budesonide nasal irrigation treatments, all without effect. He was treated with prolonged antibiotics for sinusitis flares on 4 occasions. While on chronic OCS, he had daily shortness of breath and cough. His clinical picture was consistent with asthma-COPD overlap syndrome with significant bronchodilator reversibility, moderate obstruction, and moderate decrease in gas exchange. Total serum IgE was 142 IU/dL. He thus met criteria for OMA therapy for his lung disease and began 300 mg every 4 weeks to provide an alternative therapy to chronic OCS. He was weaned off prednisone, and by his second infusion reported marked decrease in his nasal and respiratory symptoms and significant reduction in medication usage. By month 3, physical exam revealed no nasal polyps or intranasal obstruction.

**Conclusions** OMA was effective in resolving NP in this patient. In OCS-dependent patients who are not surgical candidates, OMA may be an effective alternative with a more favorable side effect profile in the management of CRS-NP.

### 364B HIV-1 TRANSGENE EXPRESSION IMPAIRS THE RESPONSE OF ALVEOLAR MACROPHAGES TO EXOGENOUS OXIDATIVE STRESS

R Ramonell,<sup>1</sup> E Egea,<sup>1</sup> X Fan,<sup>1</sup> B Staitieh,<sup>1</sup> DM Guidot<sup>1,2</sup>. <sup>1</sup>Emory University, Atlanta, GA; <sup>2</sup>Atlanta VA, Decatur, GA

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**Purpose of Study** The transcription factor nuclear factor (erythroid-derived 2)-like 2 (Nrf2) is the key mediator of the cellular response to oxidative stress in alveolar macrophages through its binding to the anti-oxidant response element (ARE), which promotes the expression of antioxidant genes. Previously we determined that HIV-1 transgene expression impairs Nrf2-ARE signaling and causes severe oxidative stress within the alveolar space, but the functional effects of that impairment are unknown. We therefore sought to develop an assay to assess the response of alveolar macrophages to oxidative stress *ex vivo* and apply this to our studies of how HIV-1 transgene expression alters Nrf2-ARE signaling and anti-oxidant defenses.

**Methods Used** We first developed an assay in which macrophages are challenged with a graded amount of hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) generated by glucose oxidase (GOX) and determined that treating the rat macrophage cell line (NR8383 cells) with 5 mU of GOX activated Nrf2-ARE signaling within 4 hours as reflected by increased gene expression of the ARE-dependent genes for Glutamate-cysteine ligase catalytic subunit (GCLC) and NAD(P)H dehydrogenase [quinone] 1 (NQO1). We next assessed the ability of primary alveolar macrophages from HIV-1 transgenic rats and wild type littermates exposed to GOX under these same conditions to clear H<sub>2</sub>O<sub>2</sub> as assessed by the Amplex red assay.

**Summary of Results** Alveolar macrophages isolated from HIV-1 transgenic rats had a significant impairment in their ability to clear exogenous H<sub>2</sub>O<sub>2</sub> by ~18% compared to alveolar macrophages isolated from their wild type littermates.

**Conclusions** We can model the exogenous oxidative stress to which alveolar macrophages are exposed *in vivo* using a GOX system and determined that the ability of alveolar macrophages from HIV-1 transgenic rats to clear extracellular H<sub>2</sub>O<sub>2</sub> is impaired. Whether or not this reflects an inability of these cells to activate the Nrf2-ARE signaling pathway in response to H<sub>2</sub>O<sub>2</sub> is unknown and is under current investigation in our lab.

### 364C YOU GOTTA USE A TOOL

H Sbahi, T Black, CB Keller, JM Di Palma, JA DiPalma. University of South Alabama, Mobile, AL

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**Purpose of Study** We previously performed a survey of primary care providers and gastroenterologists that found that clinicians either made an exclusionary diagnosis or used clinical criteria like the ROME criteria for the diagnosis of irritable bowel syndrome (IBS). In order to utilize ROME II criteria at least 17 questions must be answered by the patient. This investigation was designed to examine how often ROME II questions were asked and recorded by

clinicians.

**Methods Used** Records were reviewed of 100 patients who were seen for a suspected diagnosis of IBS by gastroenterology fellows and faculty in an academically-oriented center with expertise in IBS. A formal tool, ibsjennifer (www.ibsjennifer.com) which lists the various ROME questions, was subsequently used to confirm or exclude the IBS diagnosis.

**Summary of Results** On average, only 29.4% (5/17) of the ibsjennifer questions were recorded by the clinician. The four most frequently recorded questions were: 1. "In the last 3 months, did you have continuous or recurring abdominal pain or discomfort?" (94%); 2. "What is your predominant symptom?" (90%); 3. "In the last 3 months, how often did you feel bloated or that the abdomen was distended?" (76%); and 4. "Does this discomfort or pain get better or stop after you have a bowel movement?" (66%).

**Conclusions** Most questions that comprise the ROME criteria were not asked or recorded during clinical encounters. Using a questionnaire tool that includes IBS clinical criteria prompts is advised if clinical criteria are utilized to make the diagnosis of IBS.

### 365 ATRIAL ARRHYTHMIAS CORRELATE WITH QTc INTERVAL PROLONGATION

DM Flatt, R Bomb, MR Heckle, P Valasareddy, E John, JM Cronin, JB Jasper, TE Kasprovicz, BZ Heard, KT Weber. University of Tennessee Health Science Center, Memphis, TN

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**Purpose of Study** The duration of ventricular myocyte repolarization is reflected by the QTc interval on the electrocardiogram. When repolarization is delayed, there is an increased risk of ventricular arrhythmias. Irrespective of causality, prolongation of the QTc interval raises the risk of ventricular arrhythmias. Like ventricular musculature, the atria also consist of cardiomyocytes that can contribute to QTc prolongation. Herein we *hypothesized* that patients with demonstrated atrial arrhythmias on standard ECG will have a QTc of prolonged duration when compared to the QTc interval of patients who are in sinus rhythm.

**Methods Used** A retrospective chart review of 3202 patients at an urban medical center from January 1, 2014 to June 30, 2015 was performed. From this sample 2783 patients (51.7 yrs; 54.2% male) had stable renal function and were not receiving medications which can prolong the QTc interval. The duration of QTc (msec) interval and the presence or absence of atrial arrhythmias were noted on their standard 12-lead ECG.

**Summary of Results** Patient with atrial arrhythmias, including atrial fibrillation, demonstrated a statistically significant increase ( $p < 0.0001$ ) in QTc duration ( $490 \pm 3$  msec) when compared to the QTc duration of those ( $465 \pm 1$  msec) in sinus rhythm on standard 12-lead electrocardiogram.

**Conclusions** Our findings indicate the patients with atrial arrhythmias have a QTc of greater duration when compared to patients in sinus rhythm. It is therefore suggested that correction of QTc prolongation is advisable to avoid atrial arrhythmias. This would include careful surveillance

and correction of hypokalemia and hypomagnesemia. Drugs that prolong QTc should also be recognized and considered as potentially contributory to increased risk of atrial and ventricular arrhythmias as well.

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**MICRORNA-21 AND PDCD4 MEDIATE ANTIPROLIFERATIVE EFFECTS OF PPAR $\gamma$  IN HYPOXIA-EXPOSED HUMAN PULMONARY ARTERY SMOOTH MUSCLE CELLS**

DE Green, TC Murphy, CM Hart. Emory University / Atlanta VA Medical Center, Decatur, GA

10.1136/jim-2015-000035.368

**Purpose of Study** Pulmonary hypertension (PH) is a complex disease whose pathogenesis involves enhanced smooth muscle cell (SMC) proliferation. Programmed cell death (PDCD) 4 stimulates apoptosis, and its depletion is associated with dysregulated cancer cell growth and metastasis. However, little is known about PDCD4 expression and regulation in pulmonary vascular SMC. We previously demonstrated that activation of peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) with its pharmacological ligand, rosiglitazone (RSG), attenuated hypoxia-induced HPASMC proliferation and hypoxic increases in microRNA (miR)-21. This study examines interactions between PPAR $\gamma$ , miR-21 and PDCD4 to further explore antiproliferative mechanisms of PPAR $\gamma$ . The goal of these studies is to define novel targets for therapeutic intervention in PH.

**Methods Used** HPASMC were transfected with siRNA to deplete PPAR $\gamma$  or PDCD4 and protein and mRNA levels were measured. Selected HPASMC were exposed to hypoxia (1% O $_2$ ) for 72 hours or transfected with an adenoviral PPAR $\gamma$ -expression plasmid (AdPPAR $\gamma$ ,10 MOI)  $\pm$  activation with 10 mM RSG. A peroxisome proliferator response element (PPRE) luciferase reporter assay was employed to detect PPAR $\gamma$  transcriptional activity. Proliferative responses of HPASMC to hypoxia, PPAR $\gamma$  overexpression or PDCD4 and PPAR $\gamma$  depletion were determined using cell counting.

**Summary of Results** Hypoxia increased HPASMC miR-21 expression, reduced PDCD4 protein and mRNA levels and blunted PPRE luciferase reporter activity. AdPPAR $\gamma$  attenuated hypoxia-induced: a) reductions in PPRE activity, b) increases in miR-21 levels, c) reductions in PDCD4, and d) HPASMC proliferation. SiRNA-mediated depletion of PPAR $\gamma$  or PDCD4 reduced PDCD4 protein levels and enhanced HPASMC proliferation.

**Conclusions** Loss of PDCD4 drives proliferation in hypoxia-exposed HPASMC, and PPAR $\gamma$  activation inhibits HPASMC proliferation in part by restoring PDCD4 levels. These findings suggest that PPAR $\gamma$  restores PDCD4 levels by inhibiting increases in miR-21 which negatively regulates PDCD4. These findings are consistent with previous reports that PPAR $\gamma$  activation favorably regulates a spectrum of proliferative signals in the pulmonary vascular wall thereby providing a novel potential therapeutic target in PH.

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**EARLY 'OMIC' BIOMARKERS PREDICT BRONCHOPULMONARY DYSPLASIA (BPD)**

C Lal, N Ambalavanan. University of Alabama at Birmingham, Birmingham, AL

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**Purpose of Study** BPD is a multifactorial disease for which specific systems biology (*omic*) based biomarkers are warranted. We hypothesized that the *microbiomics*, *metabolo-* *omics* and *transcriptomics*(*microRNAomics*) of preterm airways at birth predict BPD.

**Methods Used** A prospective cohort study was conducted to correlate early (day 1) airway microbiome, metabolome and transcriptome of extremely low birth weight (ELBW) infants with BPD development. We collected tracheal aspirates (TA) from a total of 150 ELBW infants (22–28 week gestation) at neonatal ICU's at Birmingham, AL (*discovery cohort*), and Philadelphia, PA (*validation cohort*). For *discovery* and *validation* we analyzed TAs collected right after birth (day 1) from 23 ELBW infants and 14 ELBW infants respectively. Patients were divided into 'BPD Resistant' versus 'BPD Predisposed' based on pulmonary outcomes. Following analysis conducted after processing: *Microbiome Analysis* - 16S sequencing followed by extensive bioinformatics. *Metabolome Analysis* - Mass spectroscopy performed for positive and negative ion peaks followed by detailed pathway analysis. *MicroRNA Analysis* - Exosomal RNA analyzed for ~800 microRNAs by Nanostring technology followed by detailed pathway analysis.

**Summary of Results** All results of *discovery cohort* were confirmed using the *validation cohort*. *Validated findings: Microbiome:* Consistent temporal dysbiotic changes (Increased *Proteobacteria* and decreased *Firmicutes*) were seen from birth to the development of BPD. Relative abundance of genus *Lactobacillus* was decreased at birth in infants with chorioamnionitis, and in infants who developed BPD. *Metabolome:* Multiple metabolites of the pathways associated with fatty acid oxidation, and estrogen and androgen biosynthesis/metabolism were distinctly altered at birth in ELBW infants who developed BPD. *MicroRNA:* Multiple microRNAs including hsa-miR-876-3p, hsa-miR-378b, hsa-miR-130a-3p, has-miR-1252-5p, hsa-miR-1254, hsa-miR-20a-5p+hsa-miR-20b-5p were significantly decreased at birth in ELBW infants who developed BPD.

**Conclusions** Airway '*omic*' signatures *at birth*, can predict the resilience against, or the risk of development of BPD. These novel findings using state of the art systems biology analysis provide a better insight to the pathogenesis of BPD, and could facilitate novel therapeutic development.

### 368 ROLE OF HIGH SENSITIVITY TROPONIN T IN A HEMODYNAMICALLY SIGNIFICANT PATENT DUCTUS ARTERIOSUS IN PRETERM INFANTS

P Asrani, AM Aly, AK Jiwani, SK Jain. *Department of Pediatrics, University of Texas Medical Branch, Galveston, TX*

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**Purpose of Study** Hemodynamically significant PDA (hsPDA) stretches the cardiac myocytes due to dilatation of left atrium, which may increase the oxygen (O<sub>2</sub>) demand of the myocytes. We aim to see if hsPDA increases highly sensitive troponin T (hsTnT) which is a surrogate of myocardial ischemia in adults.

**Methods Used** In this prospective study, after IRB approval & consent, infants born  $\leq 1500$  g and  $\leq 34$  weeks were included. Infants with known major congenital or chromosomal anomalies were excluded from the study. An echocardiogram was done  $\leq 5$  days of life and blood was collected for hsTnT, NTproBNP and troponin I. If baby was treated for PDA, a 2<sup>nd</sup> echocardiogram and blood was collected after completion of treatment. After centrifuging blood, serum was saved in 2 aliquots at  $-20^{\circ}\text{C}$ . A hsPDA was defined as a PDA diameter  $> 1.5$  mm with a left atrial to aortic root ratio (LA:Ao)  $> 1.2$ . Serum is saved to measure troponin I and NTproBNP in the near future. Clinical, demographic, echocardiographic & biomarker data was analyzed using unpaired t test, Pearson's correlation coefficient and multiple regression analysis.

**Summary of Results** 70 infants were recruited with mean gestational age  $27.9 \pm 0.5$  weeks and mean birth weight  $1014.3 \pm 61.2$  g. 17 (24%) babies had a hsPDA and the remaining babies acted as controls without a hsPDA. The results are tabulated below.

**Conclusions** This is the first study that measures the hsTnT levels in premature infants. Our study shows that

hsPDA transiently increases the O<sub>2</sub> demand of myocytes measured by increased levels of hsTnT and after treating the hsPDA, O<sub>2</sub> demand comes back to normal. We speculate PDA causes stretching of myocytes, which increases O<sub>2</sub> demand of myocytes.

### 369 NONLINEAR RELATIONSHIP BETWEEN BIRTHWEIGHT AND VISCERAL FAT IN ADOLESCENTS

B Stansfield, J Bhatia, NK Pollock. *Georgia Regents University, Augusta, GA*

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**Purpose of Study** To determine the association of birthweight with markers of cardiometabolic disease in adolescents.

**Methods Used** In a cross-sectional study of 575 adolescents aged 14 to 18 years, birthweight was obtained by parental recall. Fasting blood samples were measured for glucose, insulin, lipids, adiponectin, leptin, and C-reactive protein. Subcutaneous abdominal adipose tissue (SAAT) and visceral adipose tissue (VAT) were assessed by magnetic resonance imaging.

**Summary of Results** When markers of cardiometabolic risk were compared across tertiles of birthweight adjusting for age, sex, race, Tanner stage, physical activity, socioeconomic status and body mass index, there were significant U-shaped trends for homeostasis model assessment of insulin resistance, leptin, and VAT (all  $P_{quadratic} < 0.05$ ). A significant linear downward trend across tertiles of birthweight was observed for triglycerides ( $P_{linear} = 0.03$ ). There were no differences in fasting glucose, blood pressure, total cholesterol, LDL cholesterol, HDL cholesterol, adiponectin, C-reactive protein, or SAAT across birthweight tertiles.

**Conclusions** In adolescents, both low and high birthweight tertiles are associated with insulin resistance and visceral adiposity.

**Abstract 368 Table 1** Mean hsTnT levels and echo data in infants with or without hsPDA

Study Population	Mean hsTnT levels (pg/ml)	PDA diameter (mm)	LA:Ao ratio
Group A (n=17) hsPDA	251.4 +/- 65.6	2.1 +/- 0.2	1.45 +/- 0.16
Group B (n=53) Without hsPDA (No PDA/insignificant PDA)	161.6 +/- 22.5	0.2 +/- 0.1	1.20 +/- 0.06
Group C (n=11) Post-treatment	203.8 +/- 96.5	0.8 +/- 0.6	1.26 +/- 0.17

**Abstract 368 Table 2** Statistical significance (p values)

	Group A v/s Group B	Group B v/s Group C
hsTnT	0.01	0.36
PDA diameter	<0.001	0.02
LA:Ao ratio	0.006	0.5

**Abstract 369 Table 1** Patient characteristics by birthweight tertiles<sup>1,2</sup>

	Tertile 1 2900g (<3100g)	Tertile 2 3400g (3100-3600g)	Tertile 3 3900g (>3600g)	P-value
n	189	199	187	
Age (y)	16.1±1.1	15.9±1.2	16.0±1.2	0.21
Females (%)	60.8	52.3	41.7	<0.01
Blacks (%)	59.3	44.2	33.2	<0.01
Tanner stage (1-5)	4.5±0.7	4.6±0.6	4.6±0.6	0.5
BMI percentile	62.0±27.5	58.7±28.8	66.9±0.02	0.02
Waist circumference (cm)	73.7±10.9	73.5±10.8	77.4±12.4	0.01
Moderate/vigorous PA (min/d)	41±30	45±27	46±30	0.25
Socioeconomic status	34±9	34±9	36±8	0.11

<sup>1</sup>Values are median (range) of birthweight in each tertile.

<sup>2</sup>Values are means±SD.

Abstract 369 Table 2

n	Tertile 1	Tertile 2	Tertile 3	<i>P</i> <sub>linear</sub>	<i>P</i> <sub>quadratic</sub>
	2900g (<3100g)	3400g (3100-3600g)	3900g (>3600g)		
	189	199	187		
SAAT (cm <sup>3</sup> )	931±58	855±54	940±56	0.917	0.238
VAT (cm <sup>3</sup> )	105±5.3	93±4.8	107±5.0	0.790	0.028
HOMA-IR	3.73±0.13	3.27±0.13	3.58±0.13	0.403	0.014
Plasma triglycerides (mg/dL)	72.8±3.1	67.2±2.8	63.3±3.0	0.026	0.798
Serum leptin (µg/L)	12.7±0.7	11.1±0.7	13.0±0.7	0.880	0.040

<sup>1</sup>Values are means±SEM.

### 370 NOVEL MARKERS OF HEPATIC INJURY CORRELATE WITH HISTOLOGICAL CHANGES OF NEONATAL PARENTERAL NUTRITION ASSOCIATED LIVER DISEASE

LM Keller,<sup>1</sup> J Kerecman,<sup>4</sup> Z Goodman,<sup>3</sup> N Mittal,<sup>2</sup> C Blanco<sup>2</sup>. <sup>1</sup>SAMMC, San Antonio, TX; <sup>2</sup>UTHSCSA, San Antonio, TX; <sup>3</sup>Center for Liver Disease, Fairfax, VA; <sup>4</sup>Eastern Maine Health System, Bangor, ME

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**Purpose of Study** Parenteral Nutrition (PN) Associated Liver Disease (PNALD) affects up to 60% of neonates on PN. Current serum markers lack accuracy to predict liver fibrosis or need for transplant. Liver biopsy may not represent overall disease. Our aim is to investigate if Hyaluronic Acid (HA), Tissue Inhibitor of Metalloproteinase-1 (TIMP-1) and Amino-terminal Propeptide of Type III Collagen (P3NP) alone or as an Enhanced Liver Fibrosis (ELF) score correlate with liver disease in neonatal baboons exposed to PN.

**Methods Used** Preterm baboons were delivered via C-section at 67% gestation (GA). They received PN for 14 days and either: Intralipid (IL) solution (PRT+IL) or no IL (PRT-IL) and chronic ventilation. Control preterm baboons delivered at 67% GA or at term were necropsied shortly after birth. Term animals delivered vaginally and enterally fed were also compared. Serum was collected prior to euthanasia and stored at -80 C. HA, TIMP-1 and P3NP concentrations were measured by ELISA. At necropsy, liver tissue was snap frozen. Histological scores were assigned by a blinded liver pathologist.

**Summary of Results** Birth weights were similar between like gestations. Extramedullary hematopoiesis (EMH) was increased in premature animals and decreased as GA advanced. Hepatocyte iron storage, portal tract development, kupffer cell hypertrophy and hemosiderosis were higher in the preterm groups when compared to controls ( $p<0.05$ ). There was tendency to more advanced liver fibrosis in the PRT-IL group ( $p=0.057$ ). HA, TIMP-1 and the ELF score were 10.8 fold, 2 fold and 1.5 fold higher in the PRT-IL group vs. controls respectively and higher than all other groups ( $p<0.05$ ). P3NP did not vary significantly across groups.

**Conclusions** Premature non-human primates develop liver disease after exposure to 14 days of PN and are a highly translational model for PNALD. Preterm baboons exposed to PN without IL exposure for 14 days tended to have more liver fibrosis. HA, TIMP-1 and ELF scores were

consistently higher when histological liver fibrosis is found. HA, TIMP-1 and the ELF score could potentially be utilized for monitoring of early hepatic injury due to PNALD in neonates. Further studies are warranted.

### 371 GLUCOCORTICOIDS ALTER BETA CELL VOLUME AND EARLY MARKERS OF BABOON PANCREATIC DEVELOPMENT

JL Palarczyk,<sup>1</sup> C Blanco,<sup>1</sup> A Quinn,<sup>1</sup> J Li,<sup>2</sup> C Li<sup>2</sup>. <sup>1</sup>UTHSCSA, San Antonio, TX; <sup>2</sup>University of Wyoming, Laramie, WY

10.1136/jim-2015-000035.373

**Purpose of Study** The fetal pancreas shows developmental plasticity to its metabolic environment. Prenatal glucocorticoid administration is the standard of care for pregnant women who are at risk of premature delivery. The study aim is to examine histological changes in the endocrine pancreas after fetal exposure to antenatal corticosteroids (ANS) both at preterm and term gestation and correlate to pancreatic markers for differentiation, function, and proliferation in non-human primates

**Methods Used** Twenty nine fetal baboons were delivered via Caesarean section: 125 dGA Control (CTR), 125 dGA +ANS, 175 dGA CTR, and 175 dGA +ANS (term=185 d). Betamethasone was given to female pregnant baboons at each gestation in either six or two doses at 170 µg.kg<sup>-1</sup>. Animals were euthanized after delivery. Pancreatic tissue was then obtained and immunohistochemistry (IHC) performed for insulin, glucagon, and somatostatin. Morphometric analysis was performed using the Computer Assisted Stereology Toolbox 2.0 system. In addition, IHC was done for IGF1, Ki67, PDX1 and HNF4α protein expression. NIH ImageJ software for fraction (area immunostained/area of the field x 100%) and density (arbitrary units) was used for analysis. Statistics were performed using SPSS, version 22.

**Summary of Results** Pancreatic beta cell percent area decreased by 56% after antenatal corticosteroid exposure when compared to control fetal baboons at 175 dGA ( $p=0.001$ ). Consistently, there was a tendency for beta cell percent area to decrease in 125 dGA exposed to ANS. When comparing dose effect to ANS, 175 dGA fetal baboons were significantly decreased by 38%, 73%, 62% in beta, alpha, and delta cell percent areas, respectively ( $p<0.005$  for all). Ki67 expression decreased by 42% in ANS 175 dGA animals when compared to their

counterparts ( $p=0.081$ ). No differences were found in IGF1, PDX1, or HNF4 $\alpha$  in term animals after ANS exposure

**Conclusions** The endocrine pancreas, in particular beta cells, are specifically altered by fetal glucocorticoid exposure depending on the stage of development. The decrease in beta cells is likely due to a decrease in proliferation during fetal organogenesis. Disruption of pancreatic development at these critical periods may have long lasting consequences.

### 372 MECHANISMS FOR ABNORMAL GLUCOSE HOMEOSTASIS IN PREMATURETY

L McGill-Vargas,<sup>1</sup> L Hanyu,<sup>2</sup> D Anzueto,<sup>1</sup> J Jordan,<sup>1</sup> N Musi,<sup>2</sup> C Blanco<sup>1</sup>. <sup>1</sup>University of Texas Health Science Center San Antonio, San Antonio, TX; <sup>2</sup>Medicine, University of Texas Health Science Center San Antonio, San Antonio, TX

10.1136/jim-2015-000035.374

**Purpose of Study** Both hyperglycemia and hypoglycemia are common in premature infants and increase the risk of morbidity and death. Furthermore, premature infants have significant long-term morbidities, including type 2 diabetes, essential hypertension and coronary artery disease. However, the adaptive changes necessary for normal hepatic glucose production in preterm infants remain unknown. The purpose of this study was to examine developmental differences in key hepatic gluconeogenic and insulin-signaling molecules in neonatal baboons.

**Methods Used** Twelve baboons were delivered prematurely (67% gestation) at borderline viability and mechanically ventilated for 2 weeks, and compared to similar postnatal term animals. Liver tissues were snap frozen and protein content and gene expression of key gluconeogenic/insulin signaling molecules were measured.

**Summary of Results** Changes in gluconeogenic enzymes were most apparent in PEPCK-C where mRNA expression in preterm baboons was decreased to 9% of term counterparts ( $p<0.001$ ), and protein content followed this same trend. In comparison, FBPase protein content and gene expression only trended lower in preterm animals (63% and 45% of term respectively,  $p=0.1$ ) and there were no differences in gene expression or protein content of the gluconeogenic enzymes G6Pase and PEPCK-M, or transcription factor FOXO1. In addition, hepatic insulin signaling also appeared to be impaired since insulin receptor gene expression and protein content were lower in preterm compared to term baboons (45% and 28% of terms respectively,  $p<0.05$ ), which may have contributed to decreased Akt mRNA expression in preterm animals (57% of term,  $p<0.01$ ).

**Conclusions** Decreased hepatic PEPCK-C and FBPase may delay gluconeogenesis leading to hypoglycemia of prematurity. Impaired hepatic insulin signaling (decreased IR and Akt) may contribute to the hepatic insulin resistance seen in prematurity. Whether abnormalities in insulin signaling and gluconeogenesis contribute to the metabolic syndrome seen in preterm infants as they mature to adults remains to be determined.

### 373 THERAPEUTIC REPLACEMENT OF AMINE PLACENTAL ENZYME INCREASES SURVIVAL, DECREASES SEVERITY OF NECROTIZING ENTEROCOLITIS IN MURINE MODEL

A Hanna, J Eckert, M Deel, H Chaaban. University of Oklahoma Health Sciences Center, Oklahoma City, OK

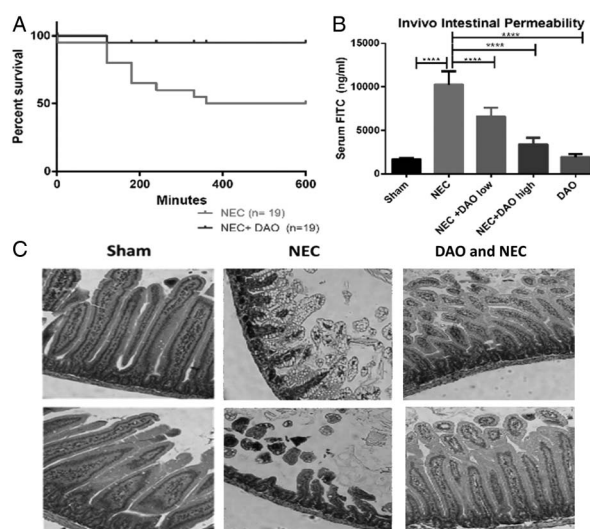
10.1136/jim-2015-000035.375

**Purpose of Study BACKGROUND:** Necrotizing enterocolitis (NEC) remains the most devastating emergency in low birth weight infants. Therapy remains supportive, as no targeted medications exist. Diamine oxidase (DAO) is an amine placental enzyme that is transferred in high concentrations through fetal circulation. Evidence shows that infants are born with significantly-elevated DAO levels that decrease to adult baseline levels at ~2 weeks-directly correlating with the peak onset of NEC. Interestingly, impaired DAO levels are associated with decreased intestinal integrity in adults. **OBJECTIVE:** We hypothesized that DAO attenuates the development of NEC by maintaining intestinal integrity. Our objective was to determine if administration of DAO in a murine NEC model reduces incidence of NEC and improves survival.

**Methods Used** We used the murine NEC model established by Zhang et al. DAO was administered IP (500 u/kg) 48 hrs, 24 hrs, and 1 hr prior to bacterial gavage. In-vivo intestinal permeability was determined by measuring serum FITC-dextran. Histological grading by H&E stain. Serum and tissue cytokine expression were measured by a ProcartaPlex immunoassay.

**Summary of Results** As seen in the graphic below, administration of DAO significantly improves survival, reduces intestinal permeability, and decreases intestinal injury.

**Conclusions** DAO maintains intestinal integrity and improves survival in a murine NEC model. Future investigation into the protective mechanism of DAO and its potential role in attenuating NEC in humans is needed.



Abstract 373 Figure 1

## Allergy, Immunology, and Rheumatology I

### Concurrent Session

2:00 PM  
Friday, February 19, 2016

#### 374 KILLER CELL IMMUNOGLOBULIN-LIKE RECEPTORS ARE ASSOCIATED WITH COMMON VARIABLE IMMUNE DEFICIENCY PATHOGENESIS

Y Wang, H Schroeder. *University of Alabama at Birmingham, Birmingham, AL*

10.1136/jim-2015-000035.376

**Purpose of Study** Common Variable Immune Deficiency (CVID) is the most common primary immunodeficiency seen by clinical immunologists in the United States, causing a considerable medical burden due to replacement gammaglobulin therapy. Killer cell immunoglobulin-like receptors (KIR) are expressed on natural killer (NK) cells, which are central to the anti-viral/anti-tumor innate immune response, as well as subsets of T cells. This study is to explore the possibility that *KIR/HLA* genotypes influence the risk of CVID pathogenesis.

**Methods Used** We genotyped 444 study subjects for *KIR* and *HLA*. In addition, we added previously identified study subjects to this pool and in total performed an ImmunoChip Assay on 489 unique genomic DNA samples. The grouped CVID/ICR/hypogammaglobulinemia (CHI) study subjects were compared with pooled control. SAS 9.1 was used for data statistical analyses. PROC FREQ was used to compute frequencies on individual variables. PROC LOGISTIC was used for categorical analyses to obtain odds ratios and 95% confidence intervals.

**Summary of Results** Analysis of the HLA data at the 2-digit level revealed a significant association between HLA-B\*08 and increased risk of disease. Several KIR genes were associated with disease risk, including the activating 2DS1 (OR=1.45; P=0.03) and 3DS1 (OR=1.54; P=0.01) as well as the inhibitory 2DL5 (OR=1.43; P=0.04). Four KIR/HLA show significant different frequency between CHI and CVID are 3DS1+Bw4, 3DS1+Bw480T, 2DL1+C2, 2DL3/2DL3+C1C2. While other KIR or KIR/HLA compound were risky genes for CVID pathogenesis, the strongly inhibitory *KIR2DL1+C group 2* was protective.

**Conclusions** This study is the first to demonstrate an association between *KIR* and CVID, which provides a potential immunogenetic pathogenesis mechanism for this primary immunodeficiency. Our findings indicate that *KIR* may have a discordant role as either protective or exacerbating factors in CVID. These findings warrant functional studies in order to define the role of NK cells (and/or T cells) in the pathogenesis of CVID. Finally, our results also raise the possibility of applying *KIR* and *HLA* ligand genotyping as a tool for predicting risk for CVID.

#### 375 IDENTICAL TWINS DISCORDANT FOR CVID EXPRESS UNIQUE ANTIBODY REPERTOIRE AND DIFFERENCES IN B CELL SUBSET

T Hwangpo,<sup>1</sup> ES Mroczek,<sup>2</sup> J Osborne,<sup>3</sup> Y Wang,<sup>3</sup> G Ippolito,<sup>4</sup> M Brand,<sup>1</sup> E Brown,<sup>3</sup> G Georgiou,<sup>5</sup> H Schroeder<sup>1,3</sup>. <sup>1</sup>University of Alabama at Birmingham, Hoover, AL; <sup>2</sup>Utica College, Utica, AL; <sup>3</sup>University of Alabama at Birmingham, Birmingham, AL; <sup>4</sup>The University of Texas at Austin Molecular Biosciences, College of Natural Sciences, Austin, TX; <sup>5</sup>The University of Texas, Austin, TX

10.1136/jim-2015-000035.377

**Purpose of Study** In this report, we detail two female twins discordant for CVID and RESPI and examine their clinical presentation, B cell subsets, antibody repertoire, and whole genome sequencing in order to explain the differences in their phenotype.

**Methods Used** Six B cell subsets were isolated via flow cytometry. RNA was then isolated from each subset and cDNA IgH libraries were constructed and high-throughput sequencing were done. Genomic DNA was also extracted and amplified using PCR to construct a genomic library suitable for 100bp Illumina paired end sequencing on the HiSeq2000 at the Heflin Center at UAB.

**Summary of Results** The CVID twin presented to PID clinic at age 56 as a referral for bronchiectasis, poor lung function, and notable decreases in IgG and IgM. The RESPI twin presented to the clinic a year later and she was noted to have normal immunoglobulins at presentation. Mature, memory Ig<sup>+</sup>, memory IgD<sup>-</sup>, and plasmacytes B cells were lower in total numbers in the CVID twin compared to the RESPI twin. Repertoire analysis showed the CVID twin to have a decrease in tyrosine usages in the memory IgG and all three plasmacyte B cell populations. Lastly, whole genome sequencing analysis showed 4 genes that are identical in both the RESPI and CVID twin but have potentially harmful SNPs in CD19, CD21, ICOSLG, and PLCG2.

**Conclusions** The CVID twin although sharing similar genetics to the RESPI twin exhibit distinctive quantitative B cell subsets and a unique B cell repertoire. The decrease in memory and plasmacyte B cells suggest a block in B cell development and maturation. An Ig repertoire that is markedly depleted of tyrosine may explain why the function of the Ig repertoire in CVID is more impaired than what might be expected by serum immunoglobulin levels alone.

#### 376 COMMON VARIABLE IMMUNODEFICIENCY: A QUESTION OF PRIMARY IMMUNODEFICIENCY VERSUS SECONDARY BELIMUMAB-INDUCED IMMUNODEFICIENCY

AB Schiffman, L Wild. *Tulane University, New Orleans, LA*

10.1136/jim-2015-000035.378

**Purpose of Study** Common Variable Immunodeficiency (CVID) is the most common symptomatic primary



immunodeficiency, with perhaps 5% presenting with inflammatory or autoimmune disease without recurrent infection. We present a case of CVID diagnosed subsequent to limited treatment of systemic lupus erythematosus (SLE) and suggest that belimumab, a monoclonal antibody that binds to B-cell activating factor (BLyS), inhibiting B-cell stimulation, accelerated the presentation of immunodeficiency in this patient.

**Methods Used** A retrospective chart review was performed of a patient who received 2 doses of belimumab, for SLE poorly responsive to anti-malarial and corticosteroid treatment, which was discontinued due to development of acute pancreatitis. An immune evaluation 2 years after receiving the BLyS-specific inhibitor, fulfilled diagnostic criteria for CVID and immunoglobulin replacement was initiated.

**Summary of Results** Two years after limited treatment with a humoral immunomodulator, an evaluation due to continued severe symptoms, without reported recurrent infections, revealed hypogammaglobulinemia, and sub-protective levels of pneumococcal and tetanus antibodies. Immune evaluation prior to therapy was not conducted, complicating the diagnosis of CVID as delayed diagnosis versus a secondary immunodeficiency.

**Conclusions** Although a small extension of a phase II study of belimumab demonstrated modest decrease in memory B cells and plasma cells, the possibility of provoked B-cell dysfunction exists. A case series identifying 11 patients with secondary rituximab-induced immunodeficiency, long after discontinuation of the anti-CD20 antibody, supports this supposition. As the utilization of immunomodulatory therapy increases, it will be important to perform baseline serum immunoglobulin levels and B cell population analysis prior to starting B-cell specific biologic therapies.

### 377 THE PREB CELL RECEPTOR CHECKPOINT SELECTS FOR SPECIFIC AMINO ACIDS IN CDR-H3

M Khass, T Blackburn, P Burrows, M Walter, H Schroeder. *UAB, Birmingham, AL*

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**Purpose of Study** Immunoglobulin CDR-H3 plays a major role in antibody epitope recognition and binding. CDR-H3 is the direct product of VDJ rearrangement and lies at the center of the antigen binding site. The prevalence of individual amino acids within CDR-H3 is distinctly non-random. Much of the bias in amino acid usage derives from natural selection of D<sub>H</sub> and J<sub>H</sub> sequence. However, non-templated N addition has the capability to introduce amino acids that are disfavored in the germline sequence. The first checkpoint in B cell development to test the amino acid sequence of the H chain requires binding of surrogate light chain (VpreB and  $\lambda_5$ ) to the nascent H chain. Cells that form a functional preB cell receptor undergo several rounds of cell division and then rearrange light chain. Cells that fail to create a preBCR undergo apoptosis. To test whether successful formation of a preBCR was influenced by CDR-H3 sequence

**Methods Used** we examined *in-vivo* preBCR formation and preB cell apoptosis and cell cycling in B lineage cells from the bone marrow of mice with altered germline sequence. We performed *in silico* structural analysis of sequenced heavy chains from sorted live and apoptotic cells.

**Summary of Results** We observed increased failure to create a functional preBCR in B cells that used non-tyrosine enriched D<sub>H</sub> sequence. We then sequenced and compared wild type H chain transcripts from apoptotic and living preB cells. Among cells that had successfully traversed the preBCR checkpoint, enrichment for tyrosine at specific amino acid position within CDR-H3 were observed. *In silico* structural analysis revealed key amino acids within the VpreB CDR-H3 sensing site that appear to play a critical role in H chain CDR-H3 selection.

**Conclusions** We conclude that the preBCR checkpoint selects both for H chains that can bind to L chains and for favored amino acids at the center of the antigen binding site and thus influence epitope recognition.

### 378 IDIOPATHIC CD4+ AND CD8+ LYMPHOPENIA IN A PEDIATRIC PATIENT WITH A MISTAKEN CASE OF PSORIASIS

L Moore, R Rodriguez. *UMMC, Jackson, MS*

10.1136/jim-2015-000035.380

**Case Report** Idiopathic lymphocytopenia (ICL) is a rare, heterogenous syndrome characterized by persistent CD4+ lymphocytopenia without an underlying immunodeficiency syndrome. ICL has been linked to autoimmune diseases and opportunistic infections; however, ICL linked to dysregulatory immune conditions such as psoriasis have only been briefly described in adult case reports. This case illustrates a pediatric patient presenting with both CD4+ and CD8+ lymphopenia in the setting of newly diagnosed psoriasis.

**Methods** A 6 y/o African American female, without a history of recurrent infections, presented for an immune evaluation secondary to presumed verruca vulgaris unresponsive to therapies. Immune evaluation revealed CD4+ and CD8+ lymphopenia. Negative HPV typing and repeat skin biopsy revealed psoriasis.

**Results** At 4 y/o this patient developed persisting skin lesions, identified as verrucous hyperplasia on biopsy. The patient failed multiple therapies and lesions worsened over time. At 6 y/o she was referred for an immune evaluation, revealing CD4+ and CD8+ lymphopenia. Initial ALC was 1105 with an absolute CD4+ and CD8+ count of 358 and 300 cells/ $\mu$ L respectively. Peripheral lymphocyte proliferative assays showed an absent response to tetanus toxin and candida antigens. Lymphocyte proliferation to mitogens showed low-normal responses to both PHA and Con A, and a normal response to pokeweed. Patient had normal absolute CD19+ and NK cell populations. Specific titers to *H.flu* and *tetanus* were normal, and response rate to Pneumovax-23 was mildly decreased. HIV-1/2 and HTLV-1 antibodies were negative. Genomic sequencing for the CXCR4 gene was negative. A repeat skin biopsy showed psoriasiform dermatitis and HPV typing was negative,

further supporting the diagnosis of psoriasis. The patient began topical steroids with resolution of plaques after 3 months. Approximately 4 months after plaque resolution, repeat testing showed improved but persisting CD4+ and CD8+ lymphopenia.

**Conclusions** In the absence of recurrent infections, patients with psoriasis do not routinely undergo immune evaluations past basic laboratory studies. While this patient doesn't meet criteria for ICL, the presence of lymphocytopenia in the setting of severe psoriasis raises the question of whether T cell dysregulation should be evaluated in these patients.

### 379 T-CELL CYTOKINE SUPPRESSION INDUCED BY STIMULATION OF LEUKOCYTE ASSOCIATED IMMUNOGLOBULIN-LIKE RECEPTOR-1 (LAIR-1)

SL Smith,<sup>1</sup> C Shaner,<sup>1</sup> JE Coligan,<sup>2</sup> S Kim,<sup>1</sup> D Brand,<sup>1</sup> E Rosloniec,<sup>1</sup> J Stuart,<sup>1</sup> A Kang,<sup>1</sup> L Myers<sup>1</sup>. <sup>1</sup>University of Tennessee Health Science Center, Memphis, TN; <sup>2</sup>NIAID, Rockville, MD

10.1136/jim-2015-000035.381

**Purpose of Study** Rheumatoid arthritis (RA) is an inflammatory disorder of unknown etiology but characterized by autoimmunity. Activating natural inhibitory receptors may be a novel method for suppressing autoimmune arthritis. One of these is Leukocyte Associated Immunoglobulin-Like Receptor-1 (LAIR-1, CD305). The ligand for LAIR-1 is collagen, and our preliminary data reveal a correlation between activation of LAIR-1 and suppression of inflammatory cytokines.

**Methods Used** T cells, both LAIR-1 +/+ and -/-, were isolated from mice and stimulated with CD3/CD28 in the presence or absence of a LAIR-1 ligand  $\alpha 1$ (II). The cells were surface stained for CD4 and an intracellular stain was used to detect T cell cytokines. Flow cytometry and FlowJo software determined the % cells positive for the intracellular cytokines.

**Summary of Results** When T cells were stimulated with CD3/CD28, both LAIR-1 +/+ and LAIR-1 -/- T cells showed significant increases in the production of T cell cytokines. There were  $0.057 \pm 0.008$  % WT CD4+ T cells positive for IFN- $\gamma$  when unstimulated compared to  $0.215 \pm 0.018$  when stimulated with CD3/C28 ( $p=0.009$ ). Similarly LAIR-1 -/- T cells stimulated with CD3/CD28 were  $0.473 \pm 0.263$  % positive for IFN- $\gamma$  compared to  $0.112 \pm 0.075$  without stimulation ( $p=0.009$ ). On the other hand, the addition of the LAIR-1 ligand  $\alpha 1$ (II) to the cultures resulted in significant differences in cytokine production. The stimulation of LAIR-1 +/+ T cells and LAIR-1 -/- T cells with CD3/CD28 led to  $0.586 \pm 0.2$  and  $0.605 \pm 0.38$  % positive CD4+ T cells for IL-2 respectively. The addition of a LAIR-1 ligand  $\alpha 1$ (II) decreased the numbers of IL-2+ CD4+ T cells, while LAIR-1 -/- T cells showed no change ( $0.338 \pm 0.19$  compared to  $0.0597 \pm 0.01$ ,  $p=0.009$ ).

**Conclusions** We have used flow cytometry to demonstrate that CD3/CD28 stimulation of T cells increases IFN- $\gamma$  production in both LAIR +/+ and LAIR -/- T cells. When a LAIR-1 ligand is added to T cells stimulated with CD3/CD28, there is a significant suppression of IL-2 production, while the collagen is unable to suppress IL-2 production in LAIR -/- T cells. These data suggest that suppression of T cell

cytokine production through LAIR-1 may provide a new approach to treating RA.

### 380 RHEUMATOID NEUTROPHILIC DERMATOSIS: AN UNUSUAL PRESENTATION IN A PATIENT WITHOUT JOINT INVOLVEMENT OF RHEUMATOID ARTHRITIS

S Gonnalagadda, J Wyatt, V Majithia. University of Mississippi Medical Center, Jackson, MS.

10.1136/jim-2015-000035.382

**Introduction** Rheumatoid Arthritis (RA) is a chronic systemic autoimmune inflammatory condition typically affecting the synovial joints. Rheumatoid nodules are the common cutaneous manifestation. Other cutaneous manifestations include Rheumatoid Neutrophilic Dermatitis (RND) which usually presents with active articular disease. We hereby describe a patient with neutrophilic dermatosis without any articular disease.

**Case description;** This is a 23 year old African American female who initially presented with a rash on her elbows and hands with significant swelling of her hands. The rash started as tender, raised lesions which progressively increased in size. On examination, she was noted to have tender, erythematous papules and plaques on her elbows and dorsal surface of both the hands. In addition she also had multiple small point hemorrhages around the proximal nail folds on several nails. Work up revealed elevated Rheumatoid factor and strong positive CCP, normal Erythrocyte sedimentation rate and C-reactive protein. Our initial differential included bywater lesions, RND, vasculitis/vasculopathy, thromboembolic process and infection. The patient had a skin biopsy and was started on hydroxychloroquine. Histology revealed heavy neutrophilic infiltration of dermis without any evidence of leucocytoclastic vasculitis which proved to be neutrophilic dermatosis. She was diagnosed as Rheumatoid Neutrophilic Dermatitis and was started on topical and oral corticosteroids and eventually on dapsone which improved her rash significantly.

**Discussion** Rheumatoid Neutrophilic Dermatitis was initially reported in 1978 and is very rare. RND typically presents as symmetric erythematous papules, plaques or nodules over extensor surfaces of joints. Treatment consists of topical and oral glucocorticoids, antimalarials like hydroxychloroquine, dapsone, colchicine, cyclophosphamide and etrenitate. A good history and physical examination by a vigilant dermatologist and appropriate work up helped diagnose this patient early and appropriate treatment.

**Conclusion** Rare cutaneous involvement of RA includes RND and should be considered in differential diagnosis even in absence of articular disease.

### 381 JOINT DEFORMITIES: A CLUE TO PERSISTENT HYPERCALCEMIA IN AN ELDERLY DEBILITATED PATIENT

D Ragesh Panikkath, T Denega, AG Adiga, K Nugent. TTUHSC, Lubbock, TX

10.1136/jim-2015-000035.383

**Case Report** Hypercalcemia is commonly caused by malignancy and primary hyperparathyroidism. In the elderly, etiology of hypercalcemia can sometimes be obscure as they often present with vague non-specific symptoms. We present a case of a 70-year-old man with newly diagnosed inflammatory joint disease causing severe hypercalcemia.

**Case report** A 70-year-old man was admitted with progressive weakness and fatigue of 1 year duration. His past history included neurogenic bladder, benign prostatic hyperplasia, and chronic kidney disease. He was malnourished on exam and had severe bilateral ulnar deviation, joint tenderness, boutonniere and swan neck deformities. Lab tests showed elevated calcium level of 15.2 mg/dL, high ionized calcium of 7.7 mg/dL, high phosphorus level of 5.7 mg/dL, creatinine of 3.8 mg/dL and eGFR of 19.30. He was given intravenous fluids, furosemide and one dose of pamidronic acid. He underwent work-up to rule out malignancy and primary hyperparathyroidism. He had low PTH at 9 pg/mL and low 25-OH-vit D at 13 ng/mL. PTH-related peptide was mildly elevated at 30 pg/mL. TSH level, serum and urine protein electrophoresis were normal. CT chest and abdomen were normal. Bone scan showed degenerative changes. His high calcium levels persisted even with the addition of calcitonin. Rheumatoid arthritis (RA) was then suspected in him. Rheumatoid factor was found significantly elevated at 154 IU/mL with high ESR at 52 mm/h. X-Rays of the hands showed metacarpal bone erosions, subluxation and osteopenia. Based on 2010 ACR criteria, he was diagnosed with RA (total score of 7). Prednisone was added to his treatment and this resulted in rapid normalization of his calcium level. He was discharged on tapering doses of steroids with good improvement in his symptoms.

**Discussion** There is direct correlation between disease activity in Rheumatoid arthritis and hypercalcemia. Increased cytokines like TNF alpha, IL-1, IL-6 and RANK-L in the joint synovial fluid and serum stimulates osteoclasts, promoting bone resorption and hypercalcemia. In our patient, active disease and immobilization which also leads to osteoclast stimulation contributed to hypercalcemia. Inflammatory disease like Rheumatoid arthritis should be considered in patients with joint disease and treatment resistant hypercalcemia.

### 382 IMPACT OF DIET DIFFERENCES ON SYSTEMIC SCLEROSIS

K Jensen,<sup>2</sup> R Adell,<sup>3</sup> J Young,<sup>3</sup> M Mansuy,<sup>1</sup> T Black,<sup>2</sup> M Kowalczyk,<sup>2</sup> T Frech,<sup>1</sup> V Steen,<sup>1</sup> L Saketkoo<sup>2,1</sup>. <sup>1</sup>Scleroderma Clinical Trials Consortium, New Orleans, LA; <sup>2</sup>Tulane University School of Medicine, New Orleans, LA; <sup>3</sup>LSU HSC, New Orleans, LA

10.1136/jim-2015-000035.384

**Purpose of Study** Systemic sclerosis (SSc) is a life-threatening autoimmune disease with a range of manifestations impacting lungs, heart, gastrointestinal (GI) tract, joints, kidneys, muscle and skin. The pathogenesis of SSc is not well understood, but believed to be inflammatory. Immune events lead to fibrosis of internal organs and integument. GI involvement is common with potential involvement between mouth and anus; causing pain,

bloating, nausea, diarrhea, bacterial overgrowth, malnutrition, obstruction and food intolerance as a result of GI dysmotility leading to potentially severe complications. Qualitative data (Saketkoo, yet unpublished) from SSc patients shows improvement in symptoms and quality of life (QoL) with a gluten-free diet; and expressed as patient research priority. No study to date has looked at the effects of diet on SSc GI symptoms. It is hypothesized the patient experience may be impacted by low FODMAP in those without celiac overlap.

**Methods Used** Combined literature review with panel of SSc GI expertise to: develop a randomized controlled trial (RCT) to quantify effects of a gluten-free vs. low FODMAP vs. sham diet with validated SSc instruments for treatment response. Use available data to develop a high yield recruitment study for 100 patients, stratify severity, and control for adherence while ensuring patient appropriateness and safety.

**Summary of Results** The following results were supported by literature and agreed upon by the panel as feasible, validated and safe: A RCT blinded to patients only comparing the effects of a 4 week gluten-free vs. sham diet vs. a low food-map diet. Patients will be recruited nationally through the Scleroderma Foundation. Co- endpoints include Scleroderma Health Assessment Questionnaire (SHAQ), the Geissen SSc GI Questionnaire, the SSc GIT, the SF-36, Cochin Hand Questionnaire and Fatigue Severity Scale. The Illness Behaviour Questionnaire and the MOS Adherence Scale control for behavior effects.

**Conclusions** Patients voiced in qualitative studies that diet impacts several SSc symptoms including GI, pain and fatigue. Larger scale RCT data collection is currently underway to support patient concerns and provide quantitative results of diet on SSc symptoms and QoL.

### 383 EFFECT OF TOBACCO SMOKE EXPOSURE ON CUTANEOUS MANIFESTATIONS OF SYSTEMIC LUPUS ERYTHEMATOSUS

M Li, D Kamen. *Medical University of South Carolina, Charleston, SC*

10.1136/jim-2015-000035.385

**Purpose of Study** The pathogenesis of systemic lupus erythematosus (SLE) is associated with various environmental factors in genetically susceptible individuals. Tobacco smoke is often implicated as a potential environmental factor- possibly due to smoking induced DNA damage that results in the formation of DNA adducts and ds-DNA antibodies. Our objective was to better understand the relationship between smoke exposure and cutaneous manifestations of SLE in a large registry of well-characterized patients.

**Methods Used** A longitudinal observational cohort design was used to examine exposure to tobacco smoke and cutaneous outcomes among patients with SLE. All patients met American College of Rheumatology classification criteria for SLE. Subjects completed questionnaires to assess for smoking history and were examined for manifestations of SLE. Cutaneous manifestations included discoid rash, malar rash, photosensitivity, and mucosal ulcers. The prevalence of manifestations was compared using appropriate statistical methods between smokers (both current and former

**Abstract 383 Table 1**

	All Lupus Patients N=520	Current Smokers N=61	Never Smokers N=392
Discoid Rash	25.0%	48.3%* p= 0.01	21.3%* p< 0.01
Malar Rash	49.2%	54.1%	48.7%
Photosensitivity	49.2%	69.6%	46.5%* p= 0.04
Oral Nasal Ulcers	38.0%	45.6%	38.3%

smokers) and non-smokers.

**Summary of Results** The study population included 520 participants, of which 128 were smokers and 392 were non-smokers. Patients were 90% female, 76% African American, and the average age of diagnosis was 30.6 years. Both African Americans and females were significantly less likely to smoke ( $p < 0.01$ ). Discoid rash and photosensitivity were significantly more common in smokers than non-smokers (Table 1). No significant differences were seen in malar rash and mucosal ulcers. Among the smokers, current smokers had higher rates of cutaneous manifestations overall compared to former smokers.

**Conclusions** Smoking was associated with several cutaneous manifestations of SLE. The incidence of discoid rash and photosensitivity was higher in smokers vs. non-smokers. However, smoking was not associated with the incidence of malar rash or mucosal ulcers. Smoking appears to be an environmental risk factor associated with the cutaneous manifestations of SLE, and this should be taken into account when counseling patients with this disease.

**384** **ROLE OF ANTIPHOSPHOLIPID ANTIBODIES IN VALVULAR HEART DISEASE AMONG PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS**

D Ruiz, M Taylor, D Kamen. *Medical University of South Carolina, Charleston, SC*

10.1136/jim-2015-000035.386

**Purpose of Study** Our aims were to evaluate whether antiphospholipid antibody (aPA) levels correlate with heart valve abnormalities and to determine the type & prevalence of hemodynamic dysfunction among patients with SLE.

**Methods Used** Patients with SLE were selected using a nested case-control design from a longitudinal database based on having either elevated or normal aPA titers, specifically anticardiolipin and anti- $\beta$ 2-glycoprotein IgM/IgG. High & low titer groups were matched for age, gender, SLE diagnosis age & duration. Echocardiograms were assessed for cardiac valve abnormalities and hemodynamic dysfunction. T-tests, Chi-squared, and regression analyses were performed as appropriate.

**Summary of Results** No differences were found in the aortic ( $p=0.933$ ), pulmonic ( $p=0.214$ ), or mitral ( $p=0.309$ ) valves based on aPA titer, but the high titer patients were more likely to have tricuspid valve disease

**Abstract 384 Table 1** Single Variable Regression: Tricuspid Valve

	Odds-Ratio	CI 95%	P-Value
aPA titer $\geq 20$	4.3	1.3–14.4	0.020
aPA titer $\geq 40$	3.2	0.1–9.1	0.033
African American	0.9	0.3–2.6	0.782
Female Gender	1.7	0.2–16.6	0.630
Childhood-Onset SLE (age<18 years)	0.5	0.2–1.5	0.229
Visit Age $\geq 40$ years	1.8	0.6–5.0	0.283
Disease Duration $\geq 10$ years	1.8	0.6–5.0	0.283
Thrombocytopenia	1.0	1.0–1.0	0.892

( $p = 0.015$ ). Most common abnormality was regurgitation (28 cases), stenosis (4 cases), an artificial valve (2 cases), or other (5 cases). No valve thickening or vegetations were noted. Multivariate logistic regression, adjusted for disease duration and age, showed a significant difference between the two groups for all four valves (OR=3.05, CI 95% 1.1–8.4,  $p=0.03$ ) and tricuspid valve (OR=4.4, CI 95% 1.2–16.0,  $p=0.03$ ). Table 1 shows single variable regression results for tricuspid valve associations.

**Conclusions** Elevated levels of anti-phospholipid antibodies correlate with the presence of valvular abnormalities among patients with SLE, most commonly tricuspid regurgitation. No difference was found between groups regarding African American ethnicity, gender, childhood-onset lupus, visit age, or disease duration. Future directions include a prospective study to examine the effect of lowering aPAs on the risk of future valvular disease.

**Cardiovascular I**  
**Concurrent Session**  
**2:00 PM**  
**Friday, February 19, 2016**

**385** **RELATIONSHIP BETWEEN THE ECG PATTERN OF LEFT VENTRICULAR HYPERTROPHY AND PROLONGED QT INTERVAL OF THE ECG**

MR Heckle, R Bomb, DM Flatt, BZ Heard, E John, TE Kasprovicz, JM Cronin, JB Jasper, P Valasareddy, KT Weber. *University of Tennessee Health Science Center, Memphis, TN*

10.1136/jim-2015-000035.387

**Purpose of Study** Many patients with electrocardiographic evidence of left ventricular hypertrophy (LVH) will have concurrent prolongation of corrected QT interval (QTc) of the ECG. Myocardial hypertrophy may lead to electrical remodeling and delayed repolarization with prolonged QTc interval. The objective of this study was to determine whether one ECG pattern of LVH is more susceptible than another to QTc prolongation and hence would have an increased propensity for arrhythmogenicity.

**Methods Used** A retrospective analysis of 3202 patients who presented to Regional One Medical Center, Memphis between January 1, 2014 and June 30, 2015 was

performed. ECG pattern of LVH was recognized as concentric, eccentric or combined. ECG-concentric LVH pattern was defined as limb lead (RI+SIII>25 mm and RaVL>13 mm) or chest lead eccentric LVH (SVI+RV5>35 mm). Patients taking QT prolonging medications were excluded. An independent sample *t*-test was performed to compare the average length of QTc with each pattern. Statistical analysis was performed using IBM SPSS v22.0.

**Summary of Results** Of the 1522 patients with ECG evidence of LVH, the QTc was  $460 \pm 0.84$  msec; 682 (45%) had concentric LVH with QTc of  $457 \pm 1.08$  msec; 692 (45%) patients had eccentric LVH with QTc of  $465 \pm 1.42$  msec; and 148 (9.7%) patients met both criteria with a mean QTc of  $455 \pm 2.54$  msec. A *t*-test showed that the difference in QTc interval between the two patterns of LVH was statistically significant ( $p < 0.05$ ). The length of the QTc interval was statistically different in favor of eccentric LVH being more prolonged.

**Conclusions** Thus, we conclude that there is an association between ECG-LVH pattern and length of the QTc interval favoring eccentric LVH. Further studies will be needed to address and correlate ECG and echocardiographic patterns of LVH, their relation to QTc interval and arrhythmogenicity.

### 386 CONTINUED IMPACT OF HURRICANE KATRINA ON INCIDENCE OF ACUTE MYOCARDIAL INFARCTION: NINE YEARS AFTER THE STORM

H Gonzales, D Albashaireh, M Raja, J Lawrence, C Westley, H Baydoun, K Yadav, S Srivastav, A Irimpen. *Tulane University Medical Center, New Orleans, LA*

10.1136/jim-2015-000035.388

**Purpose of Study** To analyze the chronic effects of a major natural disaster on the incidence of acute myocardial infarction (AMI) and risk factors for the development of coronary artery disease (CAD).

**Methods Used** Single-center, retrospective, observational cohort analysis conducted at Tulane University Health Sciences Center (TUHSC) including patients admitted for AMI two years prior to Hurricane Katrina and nine years after the reopening of TUHSC in February of 2006. We assessed the incidence of AMI admissions and patient demographic, psychosocial, and clinical CAD risk factors. Results were validated with chi-square analysis of cohort subgroups and unpaired student *t*-tests for mean analysis.

**Summary of Results** In the nine year combined post-Katrina cohort, there were 1,982 admissions for AMI out of a census of 75,720 admissions (2.5%), compared to the pre-Katrina cohort with 150 AMI admissions out of a census of 21,079 (0.7%,  $p < 0.0001$ ). In 2014, the AMI incidence at TUHSC was 2.9%, which is over three times the pre-Katrina incidence of 0.7% ( $p < 0.0001$ ). Post-Katrina patients were more likely to have a diagnosis of CAD (47.6% vs. 30.7%,  $p < 0.0001$ ), coronary artery bypass grafts (15% vs. 9.3%,  $p = 0.049$ ), diabetes (39.7% vs. 28.7%,  $p = 0.007$ ), hypertension (79.6% vs. 74%,  $p = 0.036$ ) and hyperlipidemia (58.8% vs. 45%,  $p < 0.0001$ ). They also had increased rates of smoking

(53.2% vs. 39.3%,  $p = 0.0007$ ), substance abuse (15.8% vs. 6.7%,  $p = 0.001$ ) and psychiatric comorbidities (14.9% vs. 6.7%,  $p = 0.0003$ ). They were more likely to be prescribed aspirin (50.1% vs. 31.3%,  $p < 0.0001$ ), beta-blockers (48% vs. 34%,  $p = 0.002$ ), ace-inhibitors or angiotensin-receptor blockers (52.3% vs. 36%,  $p = 0.0003$ ) and statins (51.8% vs. 28%,  $p < 0.0001$ ). The post-Katrina cohort had less employed (25% vs. 31%), less retired (37% vs. 46%) and more unemployed and disabled (39% vs. 23%) patients ( $p = 0.0005$ ). Post-Katrina patients also had a decrease in insurance coverage (88% vs. 94%,  $p < 0.02$ ).

**Conclusions** The continued increase of AMI incidence and CAD risk factors after Hurricane Katrina suggests that there is a prolonged effect of devastating natural disasters on cardiovascular health.

### 387 INFLAMMATION IN OBESITY AS A CAUSE OF OBSTRUCTIVE CORONARY ARTERY DISEASE IN YOUNG HISPANIC PATIENTS

JM Marcial, PI Altieri, HL Banchs. *University of Puerto Rico Medical Sciences Campus, San Juan, PR*

10.1136/jim-2015-000035.389

**Purpose of Study** A cross-sectional study examined adults aged 21 to 35 years who underwent left cardiac catheterization at the Cardiovascular Center of Puerto Rico and the Caribbean during 2008–2012 due to myocardial infarction. We intended to study the characteristic of the group in a society of 30% lower coronary artery disease than the U.S. A.

**Methods Used** Demographic characteristics, clinical risk factors, and the extent of CAD were documented. Chi-square statistic or Fisher's exact test was used to compare the distribution of demographic, clinical, and lifestyle characteristics across CAD extent. Polytomous logistic regression models were fitted to estimate the prevalence odds ratios (POR) with 95% confidence intervals (CI) for non-obstructive and obstructive coronary disease (OCD) compared with normal coronaries. Statistical analyses were performed using Stata 11.0.

**Summary of Results** Sixty-three ( $n = 63$ ) adults were evaluated (81% were men). The mean age was  $31 \pm 4$  years. The most frequent clinical risk factors were history of tobacco use, hyper tension, and dyslipidemia. Obesity was present in 45.9% of subjects and OCD was present in 52.38% of subjects. Obesity and family history of CAD were significantly associated with OCD when adjusted by age. Obese patients had 5.94 times the possibility of having OCD than normal weight patients. Obesity was the most important treatable predictor of premature obstructive CAD in our young adult population. 20% showed positive C-reactive protein, indicative of inflammation.

**Conclusions** This data shows the important role of inflammation inducing accelerated atherosclerosis in a society (Hispanic) with a lower coronary artery disease (30%) incidence compared with the U.S.A. Control of obesity in our society to reduce the incidence of (OCD) in the young population is mandatory.

### 388 STRESS REACTIVITY AND CARDIOVASCULAR COMPLICATIONS OF PREGNANCY

A Haugh, E Harville, K Kargbo-Reffell. *Tulane University School of Medicine, New Orleans, LA*

10.1136/jim-2015-000035.390

**Purpose of Study** Pre-eclampsia and gestational hypertension affect 5–8 % of all pregnancies yet the pathophysiology that drives these disorders is poorly understood. Women who are African American, having their first child, having a child with a new partner, or who are older or overweight are at increased risk for developing pre-eclampsia. It has been postulated that chronic stress and subsequent autonomic nervous system dysfunction could play a role in the aberrant development of maternal-fetal circulation that occurs in the disorder. This study examines maternal cardiovascular responses to certain stress factors in order to evaluate how stress might impact pre-eclampsia and gestational hypertension.

**Methods Used** We plan to recruit a total of at least 50 women who are between three months and two years post-partum for our preliminary study. 25 of the women will have had a history of either gestational hypertension or pre-eclampsia with the other 25 serving as controls. Exclusion criteria for both groups includes women who have chronic hypertension, have a heart condition or heart disease, or have a diagnosed anxiety disorder. After a short interview, participants will be hooked up to equipment that measures heart period variability and respiratory sinus arrhythmia. After a baseline heart rate and heart variability is established, participants will be asked to watch two short video clips and then to prepare and deliver a five minute speech detailing why they feel that they are a good mother to their child. The purpose of the speech is to determine how the variability of the heart rate changes when placed in a situation that most people would consider stressful. A greater heart change in heart rate during stress is indicative of normal autonomic nervous system function. Lower variability is a marker of chronic sympathetic activation. We hope to compare women with a history of pre-eclampsia or gestational hypertension to women with no history of these conditions to determine if heart period variability, which we consider a marker of chronic stress and nervous system dysfunction, differs between the two groups.

**Summary of Results** To date, 24 women have been recruited for the study. We are still actively recruiting participants.

**Conclusions** Study is ongoing to date.

### 389 RELATIONSHIP BETWEEN QTc INTERVAL DURATION AND LEFT ATRIAL ENLARGEMENT ON STANDARD ECG

E John, R Bomb, DM Flatt, P Valasareddy, MR Heckle, JB Jasper, TE Kasprovicz, BZ Heard, KT Weber. *University of Tennessee Health Science Center, Memphis, TN*

10.1136/jim-2015-000035.391

**Purpose of Study** We determined a relationship between QTc duration and left atrial enlargement as seen on the

standard 12-lead ECG. We also addressed the incidence of atrial arrhythmias in patients with left atrial enlargement and QTc prolongation.

**Methods Used** Standard 12-lead electrocardiograms of 2382 consecutive patients who presented to the Regional One Health in Memphis, Tennessee between July, 2013 and July, 2015 were retrospectively reviewed for left atrial enlargement, QTc interval duration and presence of atrial arrhythmias. Patients on medications that prolonged QTc were excluded. Left atrial enlargement was defined in lead II as bifid P wave with >40 msec between two peaks or total P wave duration >110 msec or in V1 as biphasic P wave with terminal negative portion >40 msec or >1 mm deep. Statistical analysis was conducted using IBM SPSS V20.0. Paired Student *t* tests were performed. Pearson chi square test was used to compare proportions.

**Summary of Results** Left atrial enlargement was present in 525 patients. Average QTc duration in patients with left atrial enlargement was  $468.2 \pm 1.27$  msec, which was longer ( $p < 0.001$ ) than the average QTc in patients with no left atrial enlargement ( $462.2 \pm 0.94$  msec). Incidence of arrhythmias in patients with QTc >450 msec and left atrial enlargement was 5/390 (1.3%) compared with 1/135 (0.7%) in patients with QTc <450 msec and left atrial enlargement ( $p < 0.06$ ).

**Conclusions** A statistically significant association was found between ECG evidence of QTc interval duration and left atrial enlargement. In patients with left atrial enlargement and prolonged QTc there was a tendency towards increased incidence of arrhythmias. It is therefore prudent to monitor QTc interval and correct any reversible factors that can contribute to its prolongation and increased propensity for atrial arrhythmias.

### 390 CARDIOVASCULAR RISK FACTOR TRAJECTORIES FROM CHILDHOOD TO ADULTHOOD AND DEPRESSION IN MIDDLE AGE

P Stuchlik,<sup>1</sup> N Allen,<sup>2</sup> E Harville,<sup>1</sup> W Chen,<sup>1</sup> L Bazzano<sup>1</sup>. <sup>1</sup>Tulane University, New Orleans, LA; <sup>2</sup>Northwestern University, Chicago, IL

10.1136/jim-2015-000035.392

**Purpose of Study** It is well known that depression and heart disease are closely linked. However, it remains unclear whether changes in cardiovascular (CV) risk factors over time may be related to depression. Few studies have examined the long term patterns of CV risk factors in relation to depression in middle age. We hypothesize that the trajectories of cardiovascular risk factors are associated with depression and depressive symptoms.

**Methods Used** We examined data from the Bogalusa Heart Study, a long-term community-based observational study of a biracial cohort, with first measurements in childhood in 1976. Adults who completed the CES-D in 2010 with at least two childhood and two adult CV measurements ( $n=913$ ) were included. Age, systolic blood pressure, antihypertensive treatment status, smoking status, total and HDL cholesterol, were used to calculate standardized 10-year Framingham CV risk scores at each follow-up. CES-D scores were categorized using established cut points (<8, 8–15, >15). Discrete mixture modeling was employed to identify

trajectory groupings of CV risk. The association between CV risk score trajectory and CES-D were determined using multivariable logistic regression adjusted for smoking, education, physical activity, and BMI in 2010.

**Summary of Results** Mean ( $\pm$ SD) age was  $43.06 \pm 4.48$  years, 57.9% were female, and 31.7% were black race. 27.7% of participants were current smokers in 2010. Mean ( $\pm$ SD) BMI was  $30.97 \pm 7.73$ . We identified three CV risk patterns: stable (63.8%), slightly elevated (28.8%), and increasingly elevated (7.5%). Relative to stable CV risk, the multivariable adjusted odds ratio of higher CES-D categorization, i.e. more depressed, for slightly elevated was 1.49 (95% CI, 1.08–2.06), and for increasingly elevated, 1.53 (95% CI, 0.90–2.59). Smokers had increased odds of higher CES-D categorization over nonsmokers (OR=2.16, 95% CI 1.58–2.95). One-unit increases of BMI were associated with 1.02 times greater odds of higher CES-D categorization (95% CI, 1.01–1.04).

**Conclusions** Trajectories of cardiovascular risk from childhood through adulthood are associated with depression in middle age. Individuals with elevated or increasing cardiovascular risk profiles may benefit from depression screening in early middle age.

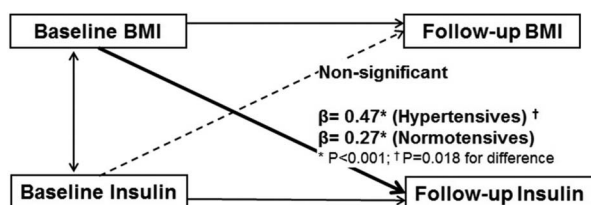
### 391 TEMPORAL RELATIONSHIP BETWEEN CHILDHOOD OBESITY AND HYPERINSULINEMIA AND ITS IMPACT ON ADULT HYPERTENSION: THE BOGALUSA HEART STUDY

T Zhang, H Zhang, S Li, Y Li, C Fernandez, E Harville, L Bazzano, J He, S Srinivasan, GS Berenson, W Chen. *Tulane University, New Orleans, LA*

10.1136/jim-2015-000035.393

**Purpose of Study** This study aims to delineate the temporal sequence between obesity and hyperinsulinemia in childhood and their impact on adult hypertension in a longitudinal cohort.

**Methods Used** The study cohort consisted of 990 adults (630 whites and 360 blacks) enrolled in the Bogalusa Heart Study. These subjects had BMI and fasting insulin measured twice 5.4 years apart in childhood (mean age=10.5 years at baseline and 15.9 years at follow-up) and blood pressure (BP) once 14.7 years later in adulthood (mean age=30.5 years). Cross-lagged panel analysis was used to examine the temporal relationship between childhood BMI and insulin. The path coefficients were compared between normotensive and hypertensive groups. Mediation effect of childhood insulin on BP was assessed in mediation analysis models.



**Abstract 391 Figure 1** Covariate-adjusted path coefficients from BMI to insulin during childhood in adult hypertensive and normotensive groups

**Summary of Results** After adjusting for age, race, gender, and follow-up years, the cross-lagged path coefficient ( $\beta=0.331$ ,  $p<0.001$ ) from baseline BMI to follow-up insulin was significantly greater than the path coefficient ( $\beta=0.002$ ,  $p>0.05$ ) from baseline insulin to follow-up BMI in childhood with  $p<0.001$  for the difference in  $\beta$ s. Blacks and whites showed similar patterns of the temporal relationship between childhood BMI and insulin. The path coefficient from BMI to insulin in the hypertensive group was significantly greater than that in normotensive group as shown in the figure below. The mediation effect of childhood insulin on the childhood BMI-adult BP association was estimated at 21.5% ( $p<0.001$ ) for systolic BP and 24.8% ( $p<0.001$ ) for diastolic BP.

**Conclusions** These findings provide strong evidence that higher BMI levels precede hyperinsulinemia during childhood, and this one-directional temporal relation plays a crucial role in the development of hypertension.

### 392 THE SPECTRUM OF COCAINE INDUCED ACUTE MYOCARDIAL INFARCTION IN A COMMUNITY HOSPITAL SUGGESTED MANAGEMENT

I Valle,<sup>2</sup> PI Altieri,<sup>1</sup> H Banchs<sup>1</sup>. <sup>1</sup>University of Puerto Rico, School of Medicine, San Juan, PR; <sup>2</sup>Municipal Hospital of San Juan, San Juan, PR

10.1136/jim-2015-000035.394

**Purpose of Study** Study the clinical characteristics of cocaine induced myocardial infarction (M.I.) and the management in a community hospital.

**Methods Used** A retrospective analysis of 21 patients (P) with cocaine induced M.I.

**Summary of Results** Twenty-one P were analyzed. Seventeen were males and 4 females. Six had stemi M.I. and 15 non-stemi. The stemi P came in congestive heart failure (C.H.F.) with an E.F. of 36%. The non-stemi was  $>55\%$ . All the P were catheterized after discharge, while One stemi P required angioplasty.

**Conclusions** This brings the conclusion that P who comes to the emergency room with cocaine related stemi MI should be catheterized immediately. Probably the EKG changes seen in the stemi group is due to coronary artery spasm with possible coronary lesions. They should be treated aggressively with intracoronary dilators to avoid severe myocardial damage, producing a reduced E.F. and the consequences of C.H.F. and its complications. The non-stemi P can be catheterized after discharge.

### 393 EARLY PHYSICIAN FOLLOW-UP AND HEART FAILURE READMISSIONS

AB Shah, ED Levine, GJ Stoffels, N Coplan. *Lenox Hill Hospital, New York, NY*

10.1136/jim-2015-000035.395

**Purpose of Study** Heart failure is the primary diagnosis in over 1 million hospital admissions annually and approximately 25% of these patients are readmitted within 30 days. Early post-discharge physician follow-up has been shown to lower 30-day readmission rates. We aimed to identify factors that influence early post-discharge physician visits.

**Methods Used** 132 consecutive patients discharged with a primary diagnosis of heart failure were included. Each patient was contacted twice. At 10 days, patients were asked if they were told to see a physician within 10 days of discharge and if they saw a physician since discharge. At 30 days, patients were asked if they had been readmitted. A chart review was performed for demographic data, ejection fraction, and to see if a post-discharge appointment was made. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

**Summary of Results** 27% (n=36) of patients were readmitted within 30 days. Patients who saw a physician within 10 days of discharge (n=78) were significantly less likely to be readmitted than those who did not (n=54), 17% vs. 43%, p=0.001. Patients who reported being told to see a physician within 10 days of discharge (n=112) were more likely to see a physician than patients who were not told (n=20), 70% vs. 0%, P<0.0001. Patients provided with an outpatient appointment (n=68) were more likely to see a physician than those who were not given an appointment (n=64), 72% vs. 45%, p<0.01. Patients who saw a physician within 10 days of discharge were more likely to be older (mean age 72.3 vs. 65, p<0.01) and caucasian (vs. black and hispanics, 75% vs 42% and 40%, respectively, p<0.001) than those who did not see a physician. Ejection fraction, gender, primary language, insurance, or the presence of a family member at home did not influence the likelihood of seeing a physician early post-discharge.

**Conclusions** Our findings support existing literature that early post-discharge follow-up decreases 30-day readmissions. Patients were significantly more likely to see a physician early post-discharge if they were given an appointment or were told to see their physician early after discharge. To increase the number of patients seeing a physician early post-discharge we suggest that patients should be provided with a follow-up appointment as part of discharge planning.

**394 ELEVATED PLASMA B-TYPE NATRIURETIC PEPTIDE IS ASSOCIATED WITH QTc INTERVAL PROLONGATION**

JB Jasper, MR Heckle, DM Flatt, R Bomb, JM Cronin, BZ Heard, E John, P Valasareddy, TE Kasprovicz, KT Weber. *University of Tennessee Health Science Center, Memphis, TN*

10.1136/jim-2015-000035.396

**Purpose of Study** Brain natriuretic peptide (BNP) is released from the heart in response to cardiac chamber distention with increased filling pressure. QTc prolongation involves delayed repolarization of cardiac myocytes and is a risk factor for supra- and ventricular arrhythmias. In this study we hypothesized elevated plasma BNP values would be associated with QTc prolongation.

**Methods Used** A retrospective chart review of 3202 patients at an urban medical center from January 1, 2014 to June 30, 2015 of QTc interval on standard 12-lead ECG was performed. 2811 patients (51.7±0.244 yrs; 52% male) were not receiving medications, which could prolong QTc. Of these patients, 785 had plasma BNP determined on admission and at the time of their ECG. The duration of QTc interval (msec) and BNP (pg/mL) were compared with QTc interval greater than 450 msec considered as

prolonged while BNP greater than 100 pg/mL was abnormally elevated.

**Summary of Results** 421 patients of the 785 (53.6 %) having diverse cardiopulmonary disorders had elevated BNP (1090.5±60.9 pg/mL). A statically significant difference (p<0.01) was found in patients with BNP greater than 100 (483±1.6 msec) vs. those with normal BNP values (454±2.0 msec). Additionally there was a statistically significant difference (p <0.0001) in BNP values in patients with QTc intervals greater than 450 msec (791.6 ±50.1 pg/mL) vs. those with QTc intervals less than 450 msec (161.3±33.6 pg/mL).

**Conclusions** Our findings indicate that elevation of plasma BNP is associated with QTc prolongation. At this time the underlying pathophysiology of this relationship is not fully understood. Nevertheless, it is advisable to be diligent in monitoring the QTc interval in patients with a diagnosis of heart failure, where BNP levels are elevated and there is an increased risk for atrial and ventricular arrhythmias.

**395 EMERGENT, OFF-HOUR TRANSTHORACIC ECHOCARDIOGRAMS INFREQUENTLY CHANGE CLINICAL MANAGEMENT**

A Kushal, D Tang, A Selby, N Coplan, G Perk. *Lenox Hill Hospital, New York, NY*

10.1136/jim-2015-000035.397

**Purpose of Study** The American Society of Echocardiography has established appropriate use criteria for transthoracic echocardiography (TTE), but there are no defined indications for emergent echocardiograms. Transthoracic echocardiograms require a highly-trained physician or sonographer, specialized equipment, and significant time to complete. Appropriate use criteria for its off-hour use would be helpful. This study evaluates the clinical utility of TTE in an emergent, off-hour setting.

**Methods Used** A single center, retrospective chart review was performed on all hospitalized patients who had a TTE performed outside normal business hours by the on-call cardiology fellow during a three month period (n=111). Change in management was defined as medication

**Abstract 395 Table 1**

Clinical Indication	Number of cases	Number of Cases Resulting in Change in Management (Percent with Standard Error)
Pericardial Effusion	22	8 (36%±10%)
CHF/Shock/Cardiac Arrest	22	4 (18%±8%)
UA/NSTEMI/STEMI	30	3 (10%±5%)
Other (Including Syncope, Arrhythmia, Valvular Disease, Endocarditis, Pulmonary Embolism, Preoperative Evaluation)	37	3 (8%±4%)
All Indications	111	18 (16%±3%)



adjustment or consideration of a procedure as a consequence of the echocardiographic findings.

**Summary of Results** Table 1 shows the clinical indications for the TTE and the number of studies that resulted in a change in management. Notably, only 18 out of 111 studies (16%) resulted in a management change. Emergent TTE was most likely to change management when used to evaluate suspected pericardial effusion.

**Conclusions** The results show that off-hour TTE often does not result in a change in management. Studies appear to be most useful in the evaluation of suspected pericardial effusion, but in many other cases (e.g. in ACS, syncope, arrhythmias, and suspected endocarditis) may be appropriately deferred until normal business hours. TTE should be used at the discretion of the provider, especially in unstable patients, but the current study may help guide the development of appropriate use criteria for emergent, off-hour transthoracic echocardiograms.

### 396 QTc PROLONGATION AND SERUM CALCIUM CONCENTRATION

TE Kasprovicz, R Bomb, DM Flatt, MR Heckle, P Valasareddy, AD Can, BZ Heard, JB Jasper, E John, KT Weber. *University of Tennessee Health Science Center, Memphis, TN*

10.1136/jim-2015-000035.398

**Purpose of Study** Prolonged QTc interval, caused by delayed myocardial repolarization, is a well-known risk factor for cardiac arrhythmias. Many causative factors have been identified in prolonging the QTc interval, including disturbances in serum cation concentrations (e.g., K<sup>+</sup> and Mg<sup>2+</sup>). The purpose of this study was to consider whether a relationship exists between the QTc interval found on the standard 12-lead ECG and serum calcium concentration.

**Methods Used** A retrospective study was undertaken which included 3202 patients (average age 51.7, 54.2% male). Data was collected between Jan. 1, 2014 to June 30, 2015. 388 patients were excluded for receiving medications known to prolong the QTc interval and three patients were excluded for insufficient data. The QTc interval (msec) was measured for each patient. Serum calcium levels were measured at the time of admission with ECG recording.

**Summary of Results** Average serum calcium was 8.50 ± 0.03. A statistically significant difference in QTc interval and serum calcium concentrations was found: average serum Ca<sup>2+</sup> in patients with QTc >450 msec was 8.1 ± 0.04, and average serum Ca<sup>2+</sup> in patients with QTc ≤450 msec was 9.1 ± 0.03, with a *t*-test *p* value of <0.001. An inverse relationship between QTc and Ca<sup>2+</sup> is suggested. Average QTc interval in patients with serum calcium >8.5 was 463.5 ± 0.9 msec, and average QTc interval in patients with serum Ca<sup>2+</sup> <8.5 was 478.9 ± 1.2 msec, with a *t*-test *p* value of <0.001.

**Conclusions** Our data suggests a statistically significant negative relationship exists between QTc prolongation and serum calcium concentration, as an independent inverse variable. Reductions in serum Ca<sup>2+</sup> concentration may prolong the QT interval and where hypocalcemia may increase the propensity for supra- and ventricular arrhythmias.

## Clinical Epidemiology and Preventive Medicine Concurrent Session 2:00 PM Friday, February 19, 2016

### 397 THE USE OF PEDIATRICIAN INTERVENTIONS TO INCREASE SCREENING, COUNSELING AND REFERRAL RATES AMONG SMOKING CAREGIVERS – A SYSTEMATIC REVIEW

KE Hall,<sup>3</sup> S Kisely,<sup>2</sup> F Urrego<sup>1</sup>. <sup>1</sup>Ochsner Health System, New Orleans, LA; <sup>2</sup>University of Queensland, Brisbane, QLD, Australia; <sup>3</sup>University of Queensland Ochsner Clinical School, New Orleans, LA

10.1136/jim-2015-000035.399

**Purpose of Study** Reducing second hand smoke (SHS) exposure among children is essential to decrease morbidity and mortality. Pediatricians play a vital role in SHS exposure, as caregivers visit their child's physician more frequently than their own. We undertook a systematic review on the effectiveness of various interventions to increase screening for SHS exposure, providing smoking cessation counseling and referring caregivers to smoking cessation programs.

**Methods Used** We performed a systematic literature search for interventions aimed at pediatricians using PubMed/Medline, Embase and PsychInfo through June 2015. Each eligible study was reviewed using the following parameters: study design, purpose of study, intervention method used, methods of measuring intervention success, follow up time period, outcomes, and conclusions.

**Summary of Results** Of 478 studies, 11 met inclusion criteria. Six used NCI's 5A's protocol, while 2 used the CEASE method. The remaining 3 used EMR prompts, motivational interviewing or behavioral feedback sessions. Smoking cessation materials were provided for pediatricians to distribute to caregivers in 6 studies. The success of the intervention was assessed using chart reviews, caregiver exit interviews or physicians' self-assessment.

**Conclusions** This literature review demonstrates that a short intervention using the NCI's 5A's protocol, in conjunction with distributable materials, may lead to an increase screening and referring rates among physicians. The CEASE method demonstrated a significant increase in providing smoking caregivers with cessation counseling. Other interventions demonstrated significant changes in some areas but not across all parameters. Future research is needed to determine the best material to distribute to caregivers during consultation to elicit optimal recollection of smoking cessation advice.

### 398 DIFFERENCES IN DETERMINANTS OF SELF-REPORTED MEDICATION ADHERENCE AMONG GENDER-RACE SUBGROUPS OF OLDER INSURED ADULTS WITH HYPERTENSION

L Williams,<sup>2,1</sup> C Joyce,<sup>1</sup> D Sarpong,<sup>2</sup> L Bazzano,<sup>1</sup> D Morisky,<sup>3</sup> E Peacock,<sup>1</sup> P Muntner,<sup>4</sup> M Krousel-Wood<sup>1,5</sup>. <sup>1</sup>Tulane University, New Orleans, LA; <sup>2</sup>Xavier University, New Orleans, LA; <sup>3</sup>UCLA School of Public Health, Los Angeles, CA; <sup>4</sup>University of Alabama at Birmingham, Birmingham, AL; <sup>5</sup>Ochsner Health System, New Orleans, LA

10.1136/jim-2015-000035.400

**Abstract 398 Table 1** Determinants of Low MMAS-8 in Gender-Race Subgroups

Participant Characteristics	Odds Ratio (95% Confidence Interval)			
	Women		Men	
	White (n =792)	Black (n=464)	White (n=678)	Black (n=188)
Age ≥75 years	0.60 (0.37, 0.95)	1.03 (0.62, 1.73)	0.58 (0.34, 0.98)	0.50 (0.17, 1.47)
Married	1.07 (0.67, 1.69)	1.22 (0.72, 2.05)	0.78 (0.42, 1.47)	3.03 (0.85, 10.76)
High school education or greater	0.89 (0.48, 1.66)	1.41 (0.82, 2.43)	1.06 (0.46, 2.44)	1.04 (0.37, 2.91)
Body mass index ≥25 kg/m <sup>2</sup>	1.27 (0.76, 2.11)	1.39 (0.65, 2.98)	<b>3.55 (1.54, 8.22)†</b>	3.05 (0.55, 16.90)
Not satisfied with overall healthcare	1.92 (0.72, 5.10)	1.30 (0.53, 3.18)	0.73 (0.20, 2.73)	2.71 (0.51, 14.42)
Reduced antihypertensive medications due to cost	<b>5.37 (1.80, 15.97)†</b>	<b>2.48 (1.10, 5.58)†</b>	<b>8.63 (3.10, 24.00)†</b>	2.22 (0.42, 11.73)
≥ 2 alcoholic beverages/week	<b>2.13 (1.26, 3.60)†</b>	1.16 (0.43, 3.11)	1.19 (0.71, 1.98)	0.51 (0.15, 1.70)
Reduced sexual functioning	1.26 (0.78, 2.04)	1.33 (0.77, 2.31)	<b>1.94 (1.14, 3.31)†</b>	<b>3.16 (1.19, 8.40)†</b>
Depressive symptoms	<b>1.96 (1.11, 3.46)†</b>	<b>2.89 (1.58, 5.29)†</b>	0.61 (0.24, 1.58)	1.84 (0.55, 6.09)
Low social support	0.89 (0.55, 1.44)	1.22 (0.74, 2.02)	1.14 (0.66, 1.98)	2.68 (0.98, 7.35)
Complementary and alternative medicine use	1.16 (0.70, 1.92)	1.62 (0.96, 2.72)	0.88 (0.48, 1.61)	<b>6.16 (2.18, 17.38)†</b>
≥ 2 Lifestyle Modifications	<b>0.54 (0.32, 0.91)†</b>	0.52 (0.25, 1.10)	<b>0.45 (0.26, 0.80)†</b>	0.72 (0.16, 3.27)

†p&lt;0.05 ‡p&lt;0.01

**Purpose of Study** Gender and racial differences in adherence to antihypertensive medications have been reported; less is known about differences in determinants of low adherence among elderly gender-race subgroups. To address this gap, we examined differences in factors associated with low antihypertensive medication adherence among gender-race subgroups of elderly adults.

**Methods Used** Cross-sectional analysis data from the Cohort Study of Medication Adherence in Older Adults (CoSMO, n= 2,122). Antihypertensive medication adherence was measured using the 8-item Morisky Medication Adherence Scale (MMAS-8); low adherence was defined as a MMAS score <6. Separate multivariate logistic regression models examined factors associated with low adherence in white men, black men, white women and black women.

**Summary of Results** Low adherence was identified in 11.8% white men, 15.4% black men, 12.4% white women, and 19.4% black women, p-value <0.001. Determinants of low adherence for each subgroup are included in the table below.

**Conclusions** Differences in factors associated with low adherence to antihypertensive medications were identified in gender-race subgroups of older insured adults.

### 399 URBAN PENALTY IN IMMUNIZATION RATES IN LIMA, PERU

MT Cooper,<sup>1</sup> DM Thompson,<sup>2</sup> PM Darden<sup>1</sup>. <sup>1,2</sup>University of Oklahoma, Oklahoma City, OK

10.1136/jim-2015-000035.401

**Purpose of Study** To search for evidence of urban penalty in immunization uptake in Lima, Peru. Urban penalty is the concept that some health indicators of urban poor populations are worse than those of their wealth-matched counterparts living in rural areas.

**Methods Used** The study examines the disaggregated data of the Perú Encuesta Demográfica y Salud Familiar (ENDES) 2012. The ENDES employs complex survey design to appropriately reflect health indicators in the Peruvian population. Outcomes were the rates of children age 18–29 months who

received all required vaccines as defined by the Peruvian government (hence referred to as “fully vaccinated”) and rates of those who received newly introduced pneumococcal and rotavirus vaccines. Participants were subdivided by geographic region (Lima metropolitan area, urban non-Lima, and rural), and ranked according to a pre-defined wealth measure. Immunization rates of the lowest quintile of Lima residents (Lima poor - reference population) were compared with rates of their wealth-matched counterparts in the other two geographic regions for an immunization rate comparison by absolute wealth. Additionally, immunization rates of the lowest quintile in Lima were compared to rates of those in the lowest quintiles of the other two geographic regions for an immunization rate comparison by relative wealth. Both measures were needed to construct a complete picture due to the large wealth disparity between the three regions defined above.

**Summary of Results** Rates for the lowest wealth quintile of Lima children (18–29 months of age) were “fully vaccinated” – 62.7%, pneumococcal – 38.1%, rotavirus – 51%. Rates for absolute wealth-matched children in the rural areas were: “fully vaccinated” – 73.8% (p=0.2029), pneumococcal – 69.6% (p=0.0006), rotavirus – 71% (p=0.0278). Rates for children in the lowest quintile (relative wealth) of the rural area were: “fully vaccinated” – 58.7% (0.6864), pneumococcal – 57.8% (p=0.0481), rotavirus 60.3% (p=0.3196).

**Conclusions** Evidence for urban penalty exists in immunization uptake in Lima regardless of the measure of wealth used for the comparison. These findings emphasize the need to improve vaccine delivery to poor children in Lima.

### 400 THE USE OF ELECTRONIC CIGARETTES AS CESSATION AIDS AND IN CONJUNCTION WITH CONVENTIONAL CIGARETTES IN ADULTS: A REVIEW OF THE SURVEY EVIDENCE

JD Pane,<sup>1</sup> JS Murray,<sup>1</sup> R Nugent,<sup>1</sup> M Orellana-Barrios,<sup>2</sup> J Payne,<sup>2</sup> RM Medrano-Juarez,<sup>2</sup> K Nugent<sup>2</sup>. <sup>1</sup>Carnegie Mellon University, Pittsburgh, PA; <sup>2</sup>Texas Tech University, Lubbock, TX

10.1136/jim-2015-000035.402

**Purpose of Study** To review the existing literature on 1) the concurrent use of e-cigarettes and conventional cigarettes ("dual use") in adults and 2) the use of e-cigarettes for smoking cessation. We focus on population-level estimates of these behaviors based on surveys.

**Methods Used** A PubMed search on articles from 1/1/07 to 1/31/15 using relevant search terms involving e-cigarettes was performed; 721 articles were found. We identified 101 articles based on surveys via their titles. Of these we identified 14 articles dealing with dual use and 21 studying smoking cessation. Five of these were based on the National Adult Tobacco Survey (NATS), a nationally representative telephone survey of U.S. adults conducted by the CDC. Others used a range of data collection mechanisms, from web-based surveys using commercial panels like Knowledge Networks (which relies on probability sampling) to collecting convenience samples via social networks.

**Summary of Results** The most recent NATS data (2013) estimates that 1.9% (95% CI: 1.3%, 2.6%) of U.S. adults are current dual users. Estimates from other data sources ranged from 1.29% to 7.01%. Overall, the evidence is weak or inconclusive for differential dual use among subgroups, except in younger cohorts: One study found that 18–24 year olds are nearly 4 times as likely to be dual users compared to adults over 40 (OR: 3.7, 95% CI: 1.2, 11.1). The NATS does not ask about use in support of cessation directly. Of the articles reporting use of e-cigarettes in support of cessation the estimates are highly variable, ranging from 27% to 59%. There is no evidence in the existing literature that the use of e-cigarettes as cessation aids varies across subgroups.

**Conclusions** Significant fractions of adults report using dual use and the use of e-cigarettes as part of cessation efforts. Several factors hamper the comparison of results across studies. Many used inconsistent definitions of key variables like "dual use". The reference population varies across surveys, as does the survey methodology. These directly impact the quality and comparability of the results. We discuss a range of strategies for new studies to improve the evidence base.

401 **EPIDEMIOLOGY OF GUNSHOT WOUNDS AT CHILDREN'S OF ALABAMA AND THE UNIVERSITY OF ALABAMA EMERGENCY DEPARTMENTS OVER 6 YEARS**

L Marzullo, A Haas. *University of Alabama at Birmingham, Birmingham, AL*

10.1136/jim-2015-000035.403

**Purpose of Study** Gunshot wounds remain the second leading cause of death for American youth, second only to MVA's. With a coordinated public health response, childhood firearm injuries and deaths could decrease dramatically, as occurred with childhood cigarette smoking. Public health professionals hoping to design such an intervention have a paucity of data, and thus are ill equipped to build their programs. The current study is a retrospective review of 6 years of firearm injuries in patients 0 - 18 presenting to the two urban emergency departments associated with the University of Alabama at Birmingham: Children's of Alabama (COA) and the adjacent UAB ED. The purpose is

to characterize all gunshot wounds treated in these Emergency Departments irrespective of disposition.

**Methods Used** The study analyzes information related to: patient demographics, type of gun used, location of the incident, whether or not the shooting was violent, the type of physical injury incurred, the length of hospital stay and the medical outcome.

**Summary of Results** As of the writing of this abstract n=244 and represents only Children's of Alabama patients. Upon preliminary analysis, certain trends are evident: The residences of our patients were clustered in discrete zip codes, predominately contiguous low socioeconomic neighborhoods. Injuries were predominately (53%) acquired in the patient's home. 77% of victims were male. The best represented age groups were teenagers (43%) and school-age children (age 6–12, 39%). Nonviolent injuries, defined as accidental discharge or play associated, accounted for 75% of all gunshot wounds. BB or pellet guns were involved in 52% of all incidents, with a marked covariance with non-violent injury. The data collection from UAB is not complete, and will reflect the wounds incurred in the 16–18 age group. These data may well demonstrate a different trend in terms of intent and extent of injury.

**Conclusions** Our data suggests most pediatric firearm injuries at COA are incurred by schoolage and young teen boys in certain low socioeconomic neighborhoods at home with non-violent intentions. Results support interventions for specific communities, potentially middle schools, that address gun safety, and mitigate the attraction to gun play before these children graduate to intentional firearm use.

**Gastroenterology  
Concurrent Session  
2:00 PM  
Friday, February 19, 2016**

402 **PNEUMATIC DILATION CAN NOW BE SUCCESSFULLY PERFORMED WITH NO PERFORATION RATE: A SINGLE CENTER EXPERIENCE.**

Y Jia, M Bustamante, S Moraveji, R McCallum. *Texas Tech University Health Sciences Center, Paul L. Foster School of Medicine, El Paso, TX*

10.1136/jim-2015-000035.404

**Purpose of Study** Patients with dysphagia and impaired lower esophageal sphincter (LES) relaxation defined as an elevated integrated relaxation pressure (IRP) may undergo pneumatic dilation (PD) to stretch and tear LES muscle fibers in a controlled manner. Although PD is clinically effective, esophageal perforation rates are reported as high as 10%. We conducted a retrospective study at a University Motility Center to access the current perforation rate of PD when used to treat dysphagia attributed to abnormal IRP.

**Methods Used** A chart review was conducted to identify patients referred for high resolution esophageal manometry and who received PD from January 2010 to Sept 2015. Their demographic and clinical data, treatment and complications were analyzed. PD was performed by 1 physician (RMC) under general anesthesia utilizing a Rigiflex system

with a guidewire and fluoroscopic monitoring after endoscopy (EGD) had identified LES location and debrided the esophagus. The balloon was slowly inflated while documenting position and disappearance of a “waist” to a maximum diameter (10–15 PSI) and then sustained for 60 second for 2 or 3 sessions, based on satisfactory positioning. EGD was repeated immediately after PD and a gastrografin swallow was obtained to detect perforations and patients clinically monitored.

**Summary of Results** 153 patients were referred for esophageal manometry during this time frame. 53 (29 F/24 M), mean age 52 y/o (Range 22–83), underwent PD: 40 patients had achalasia (10 type I, 26 type II, 4 type III; IRP 16.8–48.6 mmHg), 8 had GE junction outlet obstruction (IRP 18.3–28.1 mmHg), and 5 hypertensive LES (2 Jackhammer and 3 Nutcracker, IRP 36.2–45.7 mmHg). 53 patients underwent an initial PD utilizing the 30 mm diameter Rigiflex balloon; 18 subsequently a 35 mm size, and 8 went on to 40 mm balloon. Therefore, a total of 79 PDs were performed and no perforations were documented by EGD, gastrografin swallow or by clinical course.

**Conclusions** PD of the LES by an experienced gastroenterologist, utilizing a specific, consistent technique can be successfully performed without perforation. Hence, the already known therapeutic efficacy of PD can now be combined with the knowledge that there is essentially no accompanying perforation rate.

**403 CORRELATION OF GASTROESOPHAGEAL REFLUX DISEASE ASSESSMENT SYMPTOM QUESTIONNAIRE SCORE TO ESOPHAGEAL MULTICHANNEL INTRALUMINAL IMPEDANCE-PH MEASUREMENTS IN CHILDREN**

S Prachuapthunyachart, D Gremse. *University of South Alabama, Mobile, AL*

10.1136/jim-2015-000035.405

**Purpose of Study** Esophageal Multichannel Intraluminal Impedance-pH (MII-pH) monitoring has become one of the preferred tests to correlate observed reflux-like behaviors with esophageal reflux events. The Gastroesophageal reflux disease Assessment Symptom Questionnaire (GASQ) is a validated tool used to distinguish infants with gastroesophageal reflux disease (GERD) from healthy children [Deal et al. *JPGN* 2005;41:178–185]. The aim of this study was to determine whether the GASQ Composite Symptom Scores (CSS) and Individual Symptom Scores (ISS) correlate with outcomes in esophageal MII-pH monitoring.

**Methods Used** Twenty-six patients with GERD associated symptoms, aged 0–2 years, who completed both esophageal MII-pH monitoring and GASQ survey were included in the study. GASQ score data was collected by asking parents about frequency from 7-day recall and severity using Likert scale, which contributed to each ISS. CSS is the sum of all ISS. Results from MII-pH study were then compared to GASQ data by using Pearson correlation.

**Summary of Results** Among 26 patients, a total number of 2817 (1700 acid and 1117 non acid) reflux episodes and 845 clinical reflux behaviors were recorded. There were significant correlations between reflux index and ISS for

choking ( $r^2=0.2842$ ,  $p=0.005$ ), impedance score (IS) and CSS ( $r^2=0.2916$ ,  $p=0.004$ ), IS and ISS for choking ( $r^2=0.2482$ ,  $p=0.009$ ), IS and ISS for vomiting ( $r^2=0.1569$ ,  $p=0.045$ ), and reflux symptom index of acid-related choking and ISS for choking ( $r^2=0.1900$ ,  $p=0.026$ ). However, there were no significant correlations between abdominal pain-related MII-pH results and ISS for abdominal pain.

**Conclusions** The impedance scores from MII-pH studies correlate with ISS for choking and vomiting in infants with GERD. There are no significant correlations among reflux index and impedance score versus GASQ scores for abdominal pain. We conclude that MII-pH studies are more useful in evaluating whether GERD is related to symptoms of coughing, choking, or gagging compared to evaluating the association between GERD and pain in infants.

**404 DIETARY FATTY ACID UTILIZES THE CAVEOLIN-1 CONTAINING ENDOCYTIC VESICLES (CEV) AS A VEHICLE FOR TRANSPORT INTO THE INTESTINAL ENDOPLASMIC RETICULUM (ER)**

L Morris,<sup>1</sup> T Siddiqi,<sup>1</sup> CM Mansbach,<sup>1,2</sup> S Siddiqi<sup>1,2</sup>. <sup>1</sup>University of Tennessee Health Science Center, Memphis, TN; <sup>2</sup>Veterans Administration Medical Center, Memphis, TN

10.1136/jim-2015-000035.406

**Purpose of Study** How dietary fatty acids (FA) are transported to the ER is not well established. Here we tested the hypothesis that the caveolin-1 containing endocytic vesicle (CEV) that we proposed as the major mechanism for dietary fatty acid absorption (BBA 183; 1311, 2013) also transports fatty acids into the intestinal endoplasmic reticulum (ER).

**Methods Used** Native ER and <sup>3</sup>H-cytosol were obtained from the enterocytes of wild type (WT) and caveolin-1 (Cav-1) knockout mice. CEV were isolated from 1% Triton X-100 treated cytosol using an OptiPrep gradient, known to be able to separate detergent resistant membranes (DRM) from detergent soluble membranes (DSM). An *in vitro* binding assay was performed using these fractions with native ER, and then re-isolated ER was analyzed for lipid and protein content.

**Summary of Results** In WT cytosol, 60% of <sup>3</sup>H oleate appeared in the CEV, while 20% was associated with DSM. In Cav-1 KO cytosol, no <sup>3</sup>H oleate was found in DRM, whereas 54% of <sup>3</sup>H oleate was associated with DSM. When WT ER was incubated with CEV, 68% of the <sup>3</sup>H oleate was transported to the ER; greater than the ER incubated with whole cytosol (36%) and DSM (17%). In the Cav-1 KO mice, 21% of <sup>3</sup>H oleate was transferred to the ER when incubated with whole cytosol or DSM. Dietary lipid analysis of the re-isolated ER with both genotypes showed that 89% of the FA had been metabolized into triacyl glycerol (TAG) and diacyl glycerol (DAG) by the end of the 15 min incubations. The amount of Caveolin-1 (Cav-1) and (fatty acid translocase) CD36 showed incremental increases in the ER after binding with CEV; while liver fatty acid binding protein (FABP1) was not increased.

**Conclusions** The most dietary oleate is absorbed by associating with caveolae in apical BB. The caveolae are

endocytosed and appear in cytosol as CEV (BBA 183; 1311, 2013). We conclude that CEVs deliver the dietary FA to the intestinal ER for esterification to TAG, independent of FABB.

**405 SAFE AND EFFECTIVE USE OF FISH OIL-BASED LIPID EMULSION IN THE TREATMENT OF PARENTERAL NUTRITION ASSOCIATED CHOLESTASIS: 8 YEAR EXPERIENCE IN A TERTIARY NEONATAL INTENSIVE CARE UNIT**

MH Premkumar. *Baylor College of Medicine, Bellaire, TX*

10.1136/jim-2015-000035.407

**Purpose of Study** With increasing survival of extremely premature infants and infants with congenital gastrointestinal surgical conditions, Parenteral Nutrition Associated Cholestasis (PNAC) is becoming exceedingly common. The use of Fish Oil- based Lipid Emulsions (FOLE) has been shown to reverse PNAC. The purpose of this study was to describe the outcomes in infants receiving FOLE for treatment of PNAC over a period of 8 years in a single tertiary neonatal intensive care unit.

**Methods Used** Infants enrolled in the compassionate use protocol to receive FOLE (IV Omegaven) at 1 g/Kg/d in the treatment of PNAC at Texas Children's Hospital, Houston Texas during the period July 2007 to September 2015 were prospectively included in this study. Infants were eligible if they were more than 14 days and less than 6 years old, had conjugated bilirubin (CB) of  $\geq 2$  mg/dL, and were expected to receive PN for at least 28 days.

**Summary of Results** 182 infants received FOLE (IV Omegaven), with M:F ratio of 2:1. The mean gestational age (GA) at birth was  $29.6 \pm 5$  weeks. The mean post menstrual age at the start of FOLE therapy was  $39.2 \pm 11$  weeks. The mean CB level at start of FOLE was  $5.8 \text{ mg} \pm 4.3 \text{ mg/dL}$  (Range 2 - 26 mg/dL). Resolution of cholestasis was noted in 149/182 (81%) infants within a mean duration of  $45 \pm 29$  days. Of these 149 infants, 136 achieved full enteral feeds. 13 infants achieved partial enteral feeds and continue to require PN and IV Omegaven. 23 (12.6%) infants died secondary to either: multi-organ failure, complications of prematurity or sepsis. 3 infants required orthotopic liver transplants. In 4 infants IV Omegaven was discontinued following the diagnosis of biliary atresia (2 infants), PFIC and IPEX disease (one infant each). There were no associated complications attributed to the use of FOLE. The ALT, AST and GGT levels improved but did not normalize completely.

**Conclusions** Compassionate use therapy with FOLE improved survival and facilitated resolution of cholestasis in majority of infants with PNAC. This improvement in survival and decreased morbidity was not associated with any complications following FOLE therapy. Studies to explore the efficacy of optimum FOLE therapy in prevention of PNAC in this high risk group of infants is highly required.

**406 PULMONARY NODULES IN PATIENTS WITH HEPATOCELLULAR CARCINOMA: A SERIES OF EIGHT PATIENTS**

F Kamal,<sup>1</sup> C Tombazzi,<sup>1,2</sup> A Weir,<sup>1,2</sup> AH Appelbaum,<sup>2</sup> GE Jones,<sup>2,1</sup> SR Vera,<sup>2,1</sup> A Mathew,<sup>2,1</sup> B Waters<sup>1,2</sup>. <sup>1</sup>University of Tennessee Health Science Center, Memphis, TN; <sup>2</sup>VA Medical Center, Memphis, TN

10.1136/jim-2015-000035.408

**Purpose of Study** Pulmonary nodules are frequent in patients with Hepatocellular Carcinoma (HCC). In a recent study of patients with Hepatocellular Carcinoma, 76.2% had pulmonary nodules. Most lung lesions were stable and only 16 patients required tissue diagnosis. Only 3 patients had metastatic HCC (Lee C, Liver Transplantation, 2015). This study is an additional review of patients with lung nodules and HCC.

**Methods Used** Retrospective chart review of VA Liver Tumor Board patients from 2013–2015. Diagnosis of HCC was by biopsy or radiographic criteria. Tissue diagnosis of the lung nodules was performed by bronchoscopy or resection.

**Summary of Results** 8 male, 0 female; 5 Caucasian, 3 African American; Etiology of Cirrhosis: 6 Hepatitis C, 2 Non-Alcoholic Steatohepatitis. 8 Smokers, 0 Non-smoker: 6 Pre-Liver Transplantation, 2 Post Liver Transplantation. Diagnosis of HCC by 6 tissue diagnosis; 2 by Radiographic criteria. The 8 patients had a tissue diagnosis of 10 pulmonary nodules. 2 patients had Histoplasmosis. 2 patients had metastatic HCC. 4 patients had primary lung adenocarcinoma. One patient with primary lung adenocarcinoma additionally had 2 carcinoid tumors. The nodules which were biopsied included: the nodules which grew larger on serial CT scans and nodules with suspicious appearance (spiculated, non-calcified, irregular, presence of desmoplastic reaction, presence of mediastinal or carinal lymphadenopathy). 3 of the 4 patients with primary lung adenocarcinoma had Hepatitis C associated HCC.

**Conclusions** Although the lungs are most frequent site of metastatic HCC only 2 of 8 patients requiring lung biopsy had HCC. The pulmonary evaluation delayed ablative therapy and transplantation. In the pre-transplantation patients with lung nodules, 4 had primary lung adenocarcinoma and 2 had Histoplasmosis. Metastatic HCC was seen only in the two post-liver transplantation patients. Lung lesions in patients with Hepatocellular Carcinoma should not be assumed to be pulmonary metastasis.

**407 ACCURACY OF ENDOSCOPIC ULTRASOUND IN EARLY RECTAL CANCER STAGING**

CR Tombazzi,<sup>2,1</sup> P Loy,<sup>1,2</sup> JI Ruiz,<sup>1</sup> R Interiano,<sup>1</sup> B Waters,<sup>1,2</sup> V Bondar,<sup>1</sup> C Tombazzi<sup>1,2</sup>. <sup>1</sup>VAMC Memphis, Germantown, TN; <sup>2</sup>University of Tennessee, Memphis, TN

10.1136/jim-2015-000035.409

**Purpose of Study** Appropriate treatment of rectal cancer requires adequate staging. Endoscopic ultrasound (EUS) has been a recognized as one of the tools for rectal cancer

staging. The objective of this study was to show the accuracy of endoscopic ultrasound in early rectal cancer staging. **Methods Used** We performed a retrospective chart review of all patients who underwent endoscopic ultrasound from 01–2011 to 08–2015. Patients with stage I (T1–2 N0 M0) by surgery or EUS were included. As a gold standard we used either surgery and/or clinical and imaging follow-up. **Summary of Results** Seventy two patients with rectal cancer were identified during this time period. Fifty eight of these patients had early rectal malignancy defined as T1 or T2 NO MO. 30/58 had adenocarcinoma and 28/58 had carcinoid tumor. All patients underwent either surgery or endoscopic resection. Those with endoscopic resection had follow-up endoscopic ultrasound every 3–6 months. Endoscopic ultrasound established the appropriate staging in 54 of the 58 patients (93%). Sensitivity: 95 % (CI: 83.2–98%); Specificity: 100 % (CI: 81.4–100%). All four patients with divergent staging were over-staged by EUS. No patients were under-staged by EUS. **Conclusions** In this series, endoscopic ultrasound is highly accurate in early rectal cancer staging. Over-staging is more likely than under-staging.

#### 408 ANTIPROTEINASE 3 (PR-3) POSITIVITY CAN BE USED TO PREDICT A MORE SEVERE COURSE OF ULCERATIVE COLITIS

BW Acker, JA DiPalma. *University of South Alabama, Mobile, AL*

10.1136/jim-2015-000035.410

**Purpose of Study** Antiproteinase 3 (PR-3) is an ANCA subset whose epitope is expressed on neutrophils and monocytes. In small vessel vasculitides, PR-3 positivity predicts increased risk of relapse as well as lower survival rates. Since ulcerative colitis and small vessel vasculitides are marked by autoimmune hyperactivity, they may also share predictors for durability of remission and illness severity. This analysis examined if PR-3 positivity was associated with more severe ulcerative colitis.

**Methods Used** This was a retrospective cohort study that included review of 20 randomly selected charts of ulcerative colitis patients seen in an academic gastrointestinal specialty center. The cohort was divided into 2 groups representing those with and those without PR-3 positivity. Each group was comprised of 10 patients. Disease severity was measured according to the endoscopic Mayo Score (0–3). A positive PR-3 was defined as >3.5 U/ml.

**Summary of Results** In the PR-3 positive group the mean Mayo Score was 1.9. The mean PR-3 value in this group was 9.51 U/ml (3.9–30.6). Patients in this group required dose escalation in 70% (7/10) of cases. The mean Mayo Score in the PR-3 negative group was 0.9 and dose escalation was seen in only 20% (2/10) of cases. P values in regards to Mayo Scores and dose escalation in each group were 0.0072 and 0.0268 respectively.

**Conclusions** In a retrospective cohort study we showed that patients with ulcerative colitis who had a positive PR-3 level had more severe luminal disease than those with negative PR-3 level, as evidenced by higher mean Mayo Scores. Patients with a positive PR-3 were also more likely to require escalation of therapy to biologic and/or

immunosuppressive agents. These observations, while they suggest that serum PR-3 may be a useful marker to predict ulcerative colitis severity and disease course, will need confirmation in larger, prospective studies.

#### 409 SIGNIFICANCE OF GLUCOSE LEVELS IN INTERPRETING GASTRIC EMPTYING RESULTS IN DIABETIC PATIENTS

A Havey, A Dwivedi, I Sarosiek, J Diaz, R McCallum. *Texas Tech University Health Sciences Center, El Paso, TX*

10.1136/jim-2015-000035.411

**Purpose of Study** Studies in normal subjects have shown that glucose values >160 mg/dL induced nausea and vomiting with irregular electrical recordings, suggesting impairment of gastric emptying (GE) (Hasler et al-*Gastroenterology* 1995). In Nuclear Medicine Departments, where diabetics are undergoing GE studies, there is debate as to whether elevated baseline glucose levels could contribute to the findings of delayed GE. Our goal was to reassess the relationship between fasting glucose levels in diabetics and their GE results.

**Methods Used** We retrospectively reviewed GE reports from 2009 to 2012 for 218 diabetics presenting with upper GI motility symptoms. All patients had baseline glucose levels determined prior to ingesting a radionuclide-labeled standardized egg meal. Delayed GE (DGE) was defined as >10% retention at 4 hours. Rapid GE (RGE) was defined as <70% retention at 30 minutes or <35% at 1 hour. Glucose levels for DGE (n=69), RGE (n=72), and normal GE (NGE) (n=77) subgroups were compared, as well as any correlations between glucose levels and GE rates. Comparison of median gastric retention/hour was also performed for patients with defined glucose categories: <200 mg/dL (n=177); 200–250 mg/dL (n=30); >250 mg/dL (n=11).

**Summary of Results** Mean baseline glucose levels (mg/dL) among DGE (152.1), RGE (153) and NGE (159.3) subgroups were not statistically significant (p=0.669). In the RGE subgroup there was a significant negative correlation between 30 min GE and glucose levels (p=0.038), as well as a weak negative correlation for GE at 1, 2, 3, and 4 hours. Otherwise, there were no significant correlations with glucose in the DGE and NGE subgroups. Finally, there was no statistically significant difference in median retentions for each GE time period for patients in defined glucose categories.

**Conclusions** 1) Glucose levels in diabetics do not predict the outcome of gastric emptying scintigraphic studies. 2) With the exception of hyperglycemic ketoacidosis states, fasting glucose levels do not have an inhibitory effect on gastric emptying results.

#### 410 CYCLIC VOMITING SYNDROME IN ADULTS IS TREATABLE AND CURABLE

M Milad, B Alvarado, R McCallum. *Texas Tech University Health Sciences Center, El Paso, TX*

10.1136/jim-2015-000035.412

**Purpose of Study** Cyclic vomiting Syndrome (CVS) in adults is underdiagnosed because it is not well recognized by physicians and accounts for up to 20% of vomiting referred to GI practice. The dramatic attacks of nausea, vomiting and abdominal pain are interspersed with periods of remission with essentially minimal symptoms. Goals of therapy are to induce remission with Tricyclies while addressing the known predisposing factors such as stress, migraine, diabetes, marijuana use and post traumatic stress syndrome (PTSD). Our goal was to review our experience with CVS management at a major Referral Center for GI Motility Disorders.

**Methods Used** Our database for patients with CVS from 2011–2015 was reviewed and patients able to be personally contacted to assess current status were interviewed and their experience reviewed.

**Summary of Results** 25 patients were able to be personally contacted and interviewed. 1) 5 patients had been able to stop or taper Amitriptyline dosing to 10–20 mg/day and experienced no breakthrough cycles within 3 years of diagnosis; 2) 15 patients were stable on Anitriptyline doses of 50–150 mg/day with a reduction in mean annual CVS attacks leading to loss of work, requiring ER visits, or hospitalizations; 3) 5 patients had a mean of 4 relapses per year, requiring ER visits and reported variable abdominal pain between attacks. The profile of those patients involved: psychiatric disorders, continued marijuana use, poorly controlled migraine as well as ongoing narcotic use.

**Conclusions** 1. 20% of adult CVS patients can be essentially cured and are asymptomatic on no medication after inducing remission of symptoms with Amitriptyline and addressing the triggering factors; 2. 60% of patients are fully controllable and functioning with ongoing Tricyclic therapy; and 3. 20% of CVS patients have ongoing breakthroughs due to unresolved predisposing trigger factors.

#### 411 NOVEL USE OF PHYSICIAN SOCIAL NETWORK AND FELLOWSHIP DATA TO MAP THE GEOGRAPHICAL DISTRIBUTION OF GASTROENTEROLOGY WORKFORCE IN THE UNITED STATES

H Arshad, A Krikorian. *University of Illinois/Advocate Christ Medical Center, Oak Lawn, IL*

10.1136/jim-2015-000035.413

**Purpose of Study** Prevalence and Mortality Maps published by the National Cancer Institute indicate discrepantly higher colon cancer mortality rates in the Midwest and Southern United States, raising, among others, the question of access to the appropriate number of gastroenterologists in these areas. Little work has been done in past 20 years to map the gastroenterology workforce in the USA, with the last attempt made by Meyer et al. in 1996. We propose to use social network and online fellowships data to assist in such interventions.

**Methods Used** De-identified data about the number of board-certified gastroenterologists by US zip code was obtained from the Dximity physician database. This database is refreshed monthly and contains upto-date data from a variety of sources. This data was mapped using Google Fusion Tables and the results were compared to the available National Cancer Institute maps for Colorectal Cancer prevalence and mortality. Gastroenterology Fellowships

data was also gathered using NRMP and AMA FREIDA for all the training programs in United States. Again, Google Fusion Table were used to map all fellowship programs in United States. These maps were compared with already made 'gastroenterologists map' and Colon Cancer maps.

**Summary of Results** A total of 12,994 gastroenterologists were identified in United States. Gastroenterologists tend to be more concentrated in the Northeast and Southwest continental US. When this 'heat map' was compared to Colon Cancer prevalence and mortality maps, significant discrepancies with physician availability were noted, especially with regards to Southern Midwest region which exhibits the highest mortality rates from Colon Cancer in United States. Data collected for gastroenterology fellowship spots throughout United States indicated a similar pattern.

**Conclusions** The discrepancy between the lack of gastroenterologists and the high mortality rates of Colon Cancer in certain geographic areas highlights the need for targeted interventions to balance the workforce. One approach could aim to increase fellowship spots in Midwest and Southern United States as previous studies have repeatedly shown physicians tend to practice in areas where they trained.

## Hematology and Oncology I Concurrent Session 2:00 PM Friday, February 19, 2016

### 412 EMERGING ROLES OF MICROVESICLES DELIVERED BY LYMPH NODE STROMAL CELLS IN THE PATHOGENESIS OF HUMAN COLORECTAL CANCER

R Sullivan,<sup>1</sup> X Zhang,<sup>2</sup> G Maresh,<sup>2</sup> P Miller,<sup>3</sup> L Hellmers,<sup>2</sup> Z Lin,<sup>2</sup> H Green,<sup>3</sup> E Flemington,<sup>4</sup> L Li,<sup>2</sup> D Margolin<sup>3</sup>. <sup>1</sup>Ochsner Clinical School, New Orleans, LA; <sup>2</sup>Ochsner Medical Center, New Orleans, LA; <sup>3</sup>Ochsner Medical Center, New Orleans, LA; <sup>4</sup>Tulane University Health Science Center, New Orleans, LA

10.1136/jim-2015-000035.414

**Purpose of Study** Colorectal cancer (CRC) is the second leading cause of cancer death in the US. The prognosis greatly depends on extra-nodal metastasis. Our previous data has shown that lymph node stromal cells (LNSCs) provide supportive roles for CRC growth *in vitro* and tumor progression and metastasis *in vivo*. Recently, microvesicles (MVs) have emerged as novel mediators for cell-cell communication and as a potential source of biomarkers for cancer. To understand the role of LNSCs in CRC, we isolated MVs from CRC patient derived LNSCs (Pt-LNSCs), analyzed their components, and investigated their pathological role in tumor progression.

**Methods Used** LNSCs were isolated from 40 CRC patients' mesentery LNs from the Department of Colon and Rectal Surgery. Time-lapse experiments were performed to visualize interactions between MVs from Pt-LNSCs or stromal cell line HK (tagged with MV-specific marker CD63-RFP) to the CRC cell line HT-29GFP (tagged with luciferase/GFP) with deconvolution microscopy. MVs from Pt-LNSCs and HK cells were isolated by ultra-centrifugation and utilized for tumor growth assays *in vivo* and *in vitro* using six CRC cell lines with a titration to effect. Comprehensive characterization of RNA gene

expression in MVs and their parent cells (Pt-LNSCs and HK) was conducted using high-throughput RNA sequencing (RNA-seq).

**Summary of Results** MVs are actively secreted from LNSCs cells, traffic to, and are taken up by HT-29 cells. MVs derived from LNSCs promote CRC cell growth in vitro and tumorigenesis in vivo. RNA-seq revealed that over 150 RNAs were selectively enriched in the MVs among the 53,723 genes identified from LNSCs and HK cells. Each gene was subsequently clustered for its reported function.

**Conclusions** MVs act as an active intercellular communication pathway between LNSCs and CRC cells. Analyzing the key components in MVs may identify effector RNAs involved in CRC development and metastasis.

#### 413 THE ROLE OF CANCER STEM CELLS IN COLORECTAL CANCER METASTASIS

MC Kemp,<sup>1,2,4</sup> J Pummer,<sup>1,3,2</sup> Y He,<sup>1,2,3</sup> J Hooper,<sup>3,2,1</sup> B Reuter,<sup>1,2,4</sup> T Borgovan,<sup>1,2,4</sup> X Zhang,<sup>1,2,4</sup> R Sullivan,<sup>1,2,4</sup> G Maresh,<sup>1,2,4</sup> H Green,<sup>1,4,2</sup> L Del Valle,<sup>1,4</sup> D Margolin,<sup>4,2,1</sup> L Li<sup>1,4,2</sup>. <sup>1</sup>Ochsner Health System, Kenner, LA; <sup>2</sup>University of Queensland, New Orleans, LA; <sup>3</sup>Mater Cancer Research, Brisbane, QLD, Australia; <sup>4</sup>Ochsner Clinic Foundation, New Orleans, LA

10.1136/jim-2015-000035.415

**Purpose of Study** Cancer stem cells (CSC) are believed to be pivotal in metastatic spread of colorectal cancer (CRC), causing death in 90% of patients. We previously showed that the number of CRC-CSC in primary tumors positively correlates to lymph node (LN) metastasis, which is mediated by interaction between CD133+CXCR4+ CSC and the LN stromal microenvironment. Our goal is to validate CD133 and CXCR4 as CSC biomarkers, further identify additional CSC biomarkers such as CD318, Ki67, LGR5, NGFR, and PD-L1.

**Methods Used** CSC markers (CD133, CXCR4, CD318, Ki67, LGR5, NGFR, and PD-L1) were detected by flow cytometry on CRC cell lines and patient CRC cells, and by immunohistochemistry (IHC) staining on paraffin embedded tissue microarrays (TMA) with primary (n=68) and metastatic (n=23) tumor lesions. Their expression levels were quantified by an established digital analysis method using deconvoluting microscopy and Image-Pro software. The CSC biomarker CD318 was targeted by shRNA technique in sphere formation assay *in vitro* and mouse xenograft model *in vivo*.

**Summary of Results** Flow cytometry showed that CD318 was over-expressed on CD133+CXCR4+ CSC in CRC cell lines and patient tumorspecimens. CD318-silenced CRC cells formed less spheres *in vitro* and smaller tumors in mouse xenograft model. Metastatic tumor lesions showed increased CD133, CXCR4, and Ki67 expression (p<0.05) than primary tumor lesions, but no difference in CD318 expression. TMA data confirmed CD133 and CXCR4 as well as Ki67 as a CSC biomarkers in CRC.

**Conclusions** CD318 is likely a candidate as another CSC marker, but less likely to be a significant contributor to CRC metastasis. It is likely that the combination of CD133, CXCR4, and Ki67 rather than individual biomarker expression is important for CSC function. Analysis of additional markers may further elucidate the characteristics of CSCs.

#### 414 COMPARING THE DESMOPRESSIN CHALLENGE TEST BIOLOGICAL RESPONSE TO DESMOPRESSIN CLINICAL RESPONSE IN PEDIATRIC PATIENTS WITH VON WILLEBRAND DISEASE: A SINGLE CENTER EXPERIENCE

M Al-Ghafry, D Nadella, H Imran, A Siddiqui. University of South Alabama, Mobile, AL

10.1136/jim-2015-000035.416

**Purpose of Study** Von Willebrand Disease (VWD) is characterized by both quantitative and qualitative defects of the von Willebrand Factor (VWF) and generally manifests as menorrhagia, epistaxis and easy bruising. Initial treatment involves the use of desmopressin (DDAVP) that induces the release of VWF from the endothelium. A challenge test with intravenous (IV) DDAVP determines a patient's biological response prior to its clinical use, and assesses the need for a plasma derived product (PDP). This study examines the clinical outcome of patients started on intranasal DDAVP after completing this costly and lengthy challenge test.

**Methods Used** A retrospective cohort study of patients 18 years or younger with VWD who underwent the DDAVP challenge test between 2005 and 2015 was conducted at the University of South Alabama. A complete response was defined as a 2-fold increase in VWF level 1-hour post-infusion. Patients' clinical records were reviewed for initial presentation and response to DDAVP. Demographic and laboratory data analysis was performed with frequencies and paired t-tests for comparison where appropriate.

**Summary of Results** Out of 84 patients with VWD, 74 pediatric patients were identified. Almost half had type 1 disease and 75% were females. Forty-six patients underwent the challenge tests. Eighty-three percent of the patients had biological response to DDAVP and were started on intranasal DDAVP spray. However, over a third of biological responders were switched to a PDP for lack of clinical response or side-effects. In our cohort, the positive predictive value of the DDAVP challenge test was 61% and negative predictive value was 80%.

**Conclusions** A high proportion of our patients with VWD responded to the DDAVP challenge test, but subsequently required therapy with a PDP. Therapeutic trial of intranasal DDAVP in all patients, except where contraindicated, may be a more practical approach in routine management. Patients being managed with IV DDAVP prior to surgery would still benefit from the DDAVP challenge test.

#### 415 REDUCED CYTOTOXIC T CELL MEDIATED LYSIS IN STRESS-INDUCED DRUG RESISTANT MELANOMA CELLS

H Keller,<sup>1,3</sup> X Zhang,<sup>1</sup> L Li,<sup>1</sup> H Schaidler,<sup>4</sup> J Wells<sup>2</sup>. <sup>1</sup>Ochsner Clinic Foundation, New Orleans, LA; <sup>2</sup>UQ Diamantina Institute, Woolloongabba, QLD, Australia; <sup>3</sup>UQ/Ochsner School of Medicine, New Orleans, LA; <sup>4</sup>School of Medicine, Faculty, Woolloongabba, QLD, Australia

10.1136/jim-2015-000035.417

**Purpose of Study** CD8+ T cells, or "cytotoxic" T lymphocytes (CTL) are critical for recognizing and directly



destroying virally infected and malignant cells. In melanoma, tumor cells can exhibit an early stress-induced drug tolerant state following short term drug exposure, hypoxia, or nutrient deprivation. This may enable them to evade CTL-mediated lysis through the upregulation of inhibitory molecules such as PD-L1 or CD271, or through downregulation of differentiation antigens like Melan-A and tyrosinase. However, it is currently unknown whether the loss of melanoma-associated target antigens during the stress response substantially prevents recognition and killing by melanoma-specific CTLs.

**Methods Used** In order to assess CTL killing in stress-induced melanoma cells, we began by confirming CD271 expression on melanoma cell lines stressed with chemotherapy for 12 days. We then induced drug tolerance in B16 mouse melanoma cells under hypoxic conditions or with chemotherapy for 7 days. Using a CTL assay analyzed by flow cytometry, mouse B16 melanoma cells were labeled with CFSE, incubated with tyrosinase-related protein 2 (TRP-2) transgenic mouse CTLs, then co-stained with 7-AAD to directly determine tumor lysis.

**Summary of Results** CD271 expression was upregulated on human melanoma cells following hypoxia or docetaxel induced stress in vitro. Furthermore, the lysis of murine B16 melanoma cells by TRP-2 transgenic CTLs was reduced from 71.4% lysis of unstressed control to 42.8% and 43.3% lysis under hypoxic conditions or following 5 nM of docetaxel treatment, respectively.

**Conclusions** Stressed melanoma cells in mice appear resistant to CTL killing, due to either a reduced surface expression of TRP-2, or to the upregulation of inhibitory molecules. To determine clinical relevance, we intend to assess whether drug resistant states in human melanoma also reduce the capacity of CTL to kill melanoma.

#### 416 BREATHTAKING CONCERNS FOR THE USE OF TNF-ALPHA ANTAGONISTS

M Oglesbee, R Paccione, LS Engel, R Tejedor. *LSU Health Sciences Center, New Orleans, LA*

10.1136/jim-2015-000035.418

**Introduction** There is a known association of Crohn's disease and intestinal carcinoid tumor. Previous reports have proposed that treatment with TNF-alpha antagonists may play a role in the increasing incidence of this combination Crohn's disease and carcinoid cancer.

**Case** A 43-year-old woman with a past medical history of mild intermittent asthma and Crohn's disease chronically treated with adalimumab presented with three days of shortness of breath, cough, productive sputum, and fevers greater than 103°F. Clinically, the patient was found to have decreased breath sounds and increased fremitus to bilateral lower lung fields. An x-ray showed obliteration of the right hemidiaphragm concerning for pleural fluid and pneumonia. The patient was treated with moxifloxacin for 3 days with minimal clinical improvement and continued fevers. A repeat chest x-ray revealed consolidation in the right lower and middle lobes with continued right hemidiaphragm opacification. Pleuracentesis demonstrated negative cytology and an exudative effusion. Chest CT without

contrast revealed a 1.6 cm right upper lobe endobronchial mass. The patient was diagnosed with post obstructive pneumonia. The endobronchial lesion was visualized via bronchoscopy and biopsy demonstrated non-atypical carcinoid tumor. The patient was stabilized and then underwent right lower and middle pulmonary lobectomy with a bronchoplasty closure of the bronchus and an intercostal pedicle muscle flap. Standard mediastinal lymph node dissection was performed which showed no metastatic disease.

**Discussion** This is the second known case presented in two years of a healthy young patient with no other risk factors, other than Crohn's disease, presenting with an endobronchial primary carcinoid tumor while taking adalimumab. This case not only showcases a rare and interesting finding of endobronchial primary carcinoid tumor of the lung in a patient with Crohn's disease, but also highlights the concern for increased cancer risk in patients taking TNF-alpha antagonists. The use of TNF-alpha antagonists has previously been shown to increase the risk of many cancers and the increasing incidence of case reports highlighting otherwise rare tumor instances is both concerning and worthwhile of further investigation.

#### 417 FIVE YEAR RELAPSE FREE SURVIVAL WITH MAINTENANCE LOW DOSE CYTARABINE IN ELDERLY ACUTE MYELOID LEUKEMIA

V Tabassum, ND Patel, D Jaishankar. *Quillen College Of Medicine, East Tennessee State University, Johnson City, TN*

10.1136/jim-2015-000035.419

**Case Report** Treatment of elderly patients with Acute Myeloid Leukemia (AML) remains a challenge. While patients aged over 60 years with AML have a poorer prognosis than those under 60, the outlook for the older adults (over 80 years of age) is bleak. Age and cytogenetics are the dominant prognostic determinants in AML with multivariate analysis revealing age over 60 as a statistically significant poor prognostic factor for complete remission (CR), overall survival (OS), remission duration, and relapse-free survival (RFS). Studies report 3 and 5-year survival rates of 10%, and less than 5% respectively, in patients over age 60, compared with 5-year survival rates near 50% for younger patients. Poor outcome has traditionally been considered to be the result of biologically poor risk disease and concurrent comorbidities leading to less intensive therapy in this population. A fit 84 year old lady presented with pancytopenia and work up revealed 90% cellularity with 80% myeloblasts on a bone marrow biopsy. A diagnosis of intermediate risk AML (M1) based on normal cytogenetics with negative NPM1 and FLT3 status was established. Given her advanced age, patient was not a candidate for standard induction therapy and started treatment with Low Dose Cytarabine (Ara-C: L-DAC) 20 mg twice daily for ten days, every 4 weeks as per the MRC-14 regimen. Complete remission (CR) was established after 2 cycles. Post remission therapy with LDAC was continued with dose modifications via home health assistance. Patient has tolerated therapy well with minimal toxicity. Low dose Cytarabine is an effective treatment

option for elderly patients with AML. The optimal induction and post remission regimen for older patients is yet to be determined. Once CR is achieved, post remission strategies are not well defined, especially in the older non transplant patient. The MRC-14 trial reported an average of 6 cycles and upto 14 cycles of LDAC, with 10% of patients alive at the 2 year mark and almost none at 3 years. Our patient has now received a total of 35 cycles of Low dose Ara-C and is alive, well, and relapse free at 56 months.

**418 A RARE CASE OF CONGENITAL PRO B CELL ACUTE LYMPHOBLASTIC LEUKEMIA – PRESENTATION AT 12 HRS OF LIFE, LEUKEMIA CUTIS IN THE SETTING OF A LYMPHOID NEOPLASM AND NEGATIVE FOR MIXED LINEAGE LEUKEMIA GENE**

H Menghani, M Velez. *Louisiana State University Health Sciences Center, New Orleans, LA*

10.1136/jim-2015-000035.420

**Case Report** Congenital acute leukemia is an extremely rare disease with an incidence of about 5–8/10<sup>6</sup> live births. In the neonatal age group acute myeloblastic leukemia (AML) is more common than acute lymphoblastic leukemia (ALL). Neonatal AML has much better survival rates than ALL, the latter associated with a far worse prognosis and a disease-free survival rate lower than 20%. ALL in infants is more often associated with a higher tumor load at diagnosis, a rearrangement in the mixed lineage leukemia (MLL) gene, and very immature B-cell phenotype (pro-B ALL). Leukemias with MLL gene rearrangement have a very poor prognosis and often become refractory to treatment. Approximately 25–30% of patients with congenital leukemia develop cutaneous infiltration by leukemic cells (leukemia cutis). This usually occurs in patients with myeloid leukemia. Here we present a rare case of a newborn with pro B cell lymphoblastic leukemia with a solitary scalp lesion, hyperleukocytosis and negative for MLL gene rearrangement. A 12 hour old male baby born full term with no complications. In the postnatal period was noted to have ecchymosis and bruising. Complete blood count (CBC) performed at this point revealed a white cell count of 260000/ $\mu$ l and platelet count of 17000/ $\mu$ l. On examination there was hepatosplenomegaly and generalised lymphadenopathy and a solitary 3–4 cm firm raised purple nodule on the right side of scalp. The initial CBC showed 98% abnormal cells which were identified to be blasts on morphology. Flow cytometry confirmed the diagnosis of pro b cell congenital lymphoid leukemia. MLL rearrangement was not detected. Fine needle aspiration of the scalp lesion was performed and confirmed the diagnosis of leukemia cutis. After complete evaluation patient was started on chemotherapy for infantile ALL. This case was unique in a lot of different ways. Most cases of congenital leukemia are myeloid in nature and our patient presented with lymphoid neoplasm. Leukemia cutis is rare in lymphoid neoplasm but was seen in our patient. Most of congenital leukemia patients have positive MLL gene rearrangement (60–70%), which was negative in our case.

**419 A VERY RARE OCCURENCE OF SEVERE APLASTIC ANEMIA WITH A PAROXYSMAL NOCTURNAL HEMOGLOBINURIA CLONE IN AN ADOLESCENT WITH SICKLE CELL DISEASE SUCCESSFULLY TREATED WITH STEM CELL TRANSPLANT**

H Menghani, R Gardner. *Louisiana State University Health Sciences Center, New Orleans, LA*

10.1136/jim-2015-000035.421

**Introduction** Sickle-cell disease (SCD) is one of the most common severe genetic disorders worldwide. In SCD, individuals demonstrate an increased adhesiveness of blood cells, including red blood cells, neutrophils, eosinophils and platelets; this plays a fundamental role in the vaso-occlusive process. Aplastic Anemia (AA) is characterized by peripheral blood pancytopenia and a hypocellular bone marrow. Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hemolytic disease associated with intravascular hemolysis and thrombosis. Here we would present a very rare occurrence of severe aplastic anemia (SAA) with a PNH clone in a teenager with SCD and the clinical challenges that this combination presents.

**Case Report** A 12-year-old African American female with SCD was following in our comprehensive care clinic. She was initially found to have isolated thrombocytopenia which later progressed to pancytopenia. Bone marrow done was consistent with the diagnosis of SAA. She was started on cyclosporine as Immune suppressive therapy (IST) and responded transiently but eventually became transfusion dependent. 12 months later her PNH clone was increased and she declared herself with PNH. At this point she underwent transplant with unrelated donor (7/8 DRB1 molecularly matched) without any complications. Currently she is 12 months post transplant with no evidence of PNH clone, stable counts and hemoglobin electrophoresis consistent with sickle cell trait.

**Discussion** AA is a rare, life-threatening disorder, which is thought to be due to immune-mediated destruction of hematopoietic cells in the bone marrow. IST and Bone marrow transplant are the first line treatment options. About 30 % of AA children will not respond to primary IST and will require second-line therapy, 15–30% of those who respond will relapse. Clonal evolution of hematopoiesis and PNH is thought to occur in about 10–15% of AA patients, with the clonal abnormality frequently detected at diagnosis. Clonal hematopoiesis and PNH may also develop years after IST treatment. These patients require a long-term follow up by a specialized care center knowledgeable in late manifestations of disease.

**420 PLATELETS PLUNGE: HEPARIN-INDUCED THROMBOCYTOPENIA (HIT) OR HEMODIALYSIS (HD)?**

S Ozair, P Rigby. *Louisiana State University Health Science Center, New Orleans, LA*

10.1136/jim-2015-000035.422

**Case Report** A 37 year old female with systemic lupus erythematosus, chronic kidney disease, and antiphospholipid

syndrome (APS) presented with nausea and paresthesia. On admission, with a blood urea nitrogen of 70 mg/dL and creatinine of 12 mg/dL, HD was initiated with heparin per standard protocol. After two HD sessions, the platelet count decreased from 173,000 to 31,000/UL over 4 days. The hemoglobin and white blood cell count remained at a baseline of 10 g/dL and 7,000/UL, respectively. A presumptive diagnosis of HIT was made. Her 4Ts score was 6 indicating a high probability. All heparin products were discontinued and a non-heparin anticoagulant, argatroban was started. Anti-Platelet Factor 4 (PF4) and Serotonin Release Assay (SRA) were sent for analysis. Anticoagulation was a challenge in a patient with APS, as she had a prolonged baseline activated prothrombin time (aPTT) of 70–90 seconds. Argatroban is titrated by the aPTT level, however in this case the argatroban was titrated to an INR of 2.0–3.0. Despite this, the patient continued to have low platelet counts. Correlation of platelet counts and HD sessions revealed a consistent decline in her platelets. Thus, it was suspected that the thrombocytopenia was HD induced. The dialyzer was switched from a F160 synthetic polymer membrane to a 15S Rexeed dialyzer that has a fiber inner gel layer minimizing platelet activation. After this change, the patient's platelet levels began to recover. The anti-PF4 was found to be minimally elevated and the SRA was negative, and argatroban therapy was discontinued. Thrombocytopenia is common in the inpatient setting and often multifactorial. Prompt diagnosis and management of the underlying etiology is important in order to prevent life threatening complications. Less than 5% of patients exposed to heparin develop HIT. Once there is a clinical diagnosis of HIT, all heparin products should be stopped, and anticoagulation to prevent thrombosis should be initiated. HD patients have an increased risk of forming antibodies to PF4 as they are frequently exposed to heparin. This case demonstrates why it is important to keep a broad differential. In our patient with APS, she was more susceptible to profound thrombocytopenia, and interestingly the chemistry of the membrane served as the ultimate trigger.

## Infectious Diseases I

### Concurrent Session

2:00 PM

Friday, February 19, 2016

#### 421 INFANT MUCOSAL RSV-SPECIFIC IGA RESPONSE DYNAMICS DURING AND AFTER INFECTION.

N Mulroy,<sup>1</sup> J DeVincenzo,<sup>1,3</sup> B Bagga,<sup>1</sup> E Meals,<sup>1</sup> L Harrison,<sup>1</sup> B Sealy,<sup>2</sup> J Hurwitz,<sup>2</sup> L Benhabiles,<sup>1,3</sup> S Cormier,<sup>1,3</sup> DR Hijano<sup>1,2</sup>. <sup>1</sup>University of Tennessee Health Science Center, Memphis, TN; <sup>2</sup>St. Jude Children's Hospital, Memphis, TN; <sup>3</sup>CFRI LeBonheur, Memphis, TN

10.1136/jim-2015-000035.423

**Purpose of Study** RSV is the leading cause of lower respiratory tract infection and the most common cause of hospitalization of US infants. Our previous studies in adults show that mucosal RSV-IgA provides functional resistance to infection. Mucosally-active RSV vaccines have potential to reduce population-based RSV disease burden through

herd immunity. We therefore studied the kinetics of RSV-specific mucosal IgA in infected children.

**Methods Used** Previously healthy, <2 yo RSV-infected Infants without immune deficiency, steroid use, prematurity, chronic lung or heart disease were enrolled on day 0. Aspirates were collected on study days 0–5, 7, 9, 11, 13, 15, ≈21 and ≈28. An indirect ELISA quantified RSV F-protein specific IgA in aspirates. Plates were coated with purified recombinant RSV-F protein. Assays were developed with mouse MAb  $\mu$ human IgA<sub>1</sub>/IgA<sub>2</sub>, and goat polyclonal  $\mu$ human IgG-HRP. Specimens were run in duplicate and each patient's samples were grouped on a single plate. Values (mcg/ml) were read from duplicate internal standard curves employing RSV-IgA of known concentration. Results were compared with previously generated RSV-IgA results in experimentally infected adults.

**Summary of Results** RSV-specific IgA was measured longitudinally in 43 patients N=189 samples. Compared to RSV infected adults who had a rapid >4-fold rise in RSV-IgA over 12 days, infants had poor responses. Mean infant RSV-IgA from symptom day 1–4 (N=39 samples) was 133 mcg/ml. Mean infant RSV-IgA from symptom day 25–33 (N=12 samples) was 183 mcg/ml, representing only a 1.37-fold antibody rise over ≈4 weeks. Dynamics of infant RSV-IgA responses showed mild increases during days 6–13 post symptom onset, with subsequent fall in RSV-IgA concentrations thereafter.

**Conclusions** Infants fail to produce significant mucosal immune responses to RSV infection. These poor mucosal responses likely contribute to a relative inability to control viral replication and to prevent future infections. They also produce herd-based conditions which drive annual RSV epidemics of children and adults. Boosting doses of mucosal vaccines will likely be required to overcome these mucosal deficiencies.

#### 422 NOROVIRUS AND ROTAVIRUS IN PEDIATRIC HOSPITAL-ACQUIRED DIARRHEA

J Yi,<sup>1</sup> BK Sederdahl,<sup>1</sup> K Wahl,<sup>2</sup> RR Jerris,<sup>3,4</sup> CS Kraft,<sup>4,4</sup> S Gillespie,<sup>1</sup> AE Kirby,<sup>2</sup> CL Moe,<sup>2</sup> A Shane,<sup>1,3,2</sup> EJ Anderson<sup>1,4</sup>. <sup>1</sup>Emory University School of Medicine, Decatur, GA; <sup>2</sup>Emory University, Atlanta, GA; <sup>3</sup>Children's Healthcare of Atlanta, Atlanta, GA; <sup>4</sup>Emory University School of Medicine, Atlanta, GA

10.1136/jim-2015-000035.424

**Purpose of Study** The epidemiology and clinical implications of norovirus (NoV) and rotavirus (RV) healthcare associated infections are largely unknown.

**Methods Used** Residual stool specimens from children ≤18 years of age with diarrhea and/or vomiting submitted for clinical testing from July 2012 to June 2013 were tested for NoV GI and GII (reverse transcriptase polymerase chain reaction) and RV (enzyme immunoassay, Rotaclone®). Hospital-acquired illness was defined as specimens obtained ≥48 hours after admission. Retrospective chart and state vaccine registry review were performed. Those who were born in 2006 and after and ≥8 mo of age were considered RV vaccine eligible.

**Summary of Results** Two hundred seven specimens were collected. All children had at least 1 medical condition, and

48% of specimens were from immunocompromised children including 60% (12/20) of those with RV and 57% (4/7) of those with NoV. RV and NoV were identified in 20 (10%) and 7 (3%) specimens ( $p=0.016$ ), respectively. Compared to RV, children with NoV tended to be younger, median age 27 months (mo) (IQR 18–45 mo) versus 56.5 mo (IQR 15–159.5 mo),  $p=0.11$ . NoV tended to occur earlier after admission [median 106 hours (hrs) (IQR 86–623 hrs) versus 401 hrs (IQR 209.5–1610.5 hrs),  $p=0.085$ ]. Clinicians only requested RV testing on 8 (40%) of RV positive specimens. Of children who were eligible for RV vaccine, 27% (3/11) RV positive and 57% (4/7) NoV positive were vaccinated for RV.

**Conclusions** Children with medical conditions and prolonged hospitalization are at risk for hospital-acquired diarrhea. RV was more commonly identified as a cause of hospital-acquired diarrhea than NoV. However, only 40% of RV positive specimens were submitted by the clinical for standard of care clinical testing. Children with RV tended to be older and hospitalized for a longer period. These findings stress the importance of infection control measures (e.g., hand hygiene and proper isolation) and testing (when possible) of children with diarrhea in preventing hospital-acquired diarrhea.

#### 423 SYPHILIS OSTEITIS IN AN IMMUNOCOMPROMISED HOST

R Ali, C Baldeo, J Perez, C Isache. *UF Jacksonville, Jacksonville, FL*

10.1136/jim-2015-000035.425

**Case Report** A 36 year old male presented with a disseminated rash, worsening over 6 weeks. He was diagnosed with HIV 10 years ago and had been off therapy for the past 8 years. The rash began as a blister on his lip, evolving to a crusted lesion which involved the face. Four weeks later a maculo-papular rash developed at the limbs, trunk and soles. He complained of pain and swelling at both wrists and ankles. Serology for RPR was positive with a 1:64 titer and a confirmatory VDRL. Skin biopsy demonstrated spirochetes. Xrays of the hands and feet showed polyostotic cortical irregularities consistent with syphilitic osteitis. Bone scintigraphy corroborated these findings, with the forearms, tibia and fibula also affected. CD4 count was 54 cells/uL and viral load was 365,000 copies/mL. Due to an unknown penicillin allergy and an unavailability of allergy skin testing, the patient was treated with Doxycycline 100 mg twice/day for 6 weeks. He was also started on antiretroviral therapy. The arthropathy and rash resolved upon completion of the antibiotics. Bone involvement is a rare complication of primary and secondary syphilis, with osteitis being suspected because of mucocutaneous findings or adenopathy. Radiographs show round osteolytic areas with demineralization or sclerosis, however bone scintigraphy is more sensitive for early detection. The secondary spirochetemia that results after primary infection can lead to involvement of the deeper vascular areas of the periosteum and extension into the Haversian canals, with resultant osteitis and osteomyelitis. The presence of organisms on biopsy is variable. Pathological examination can demonstrate perivascular infiltration of the bone. Conceivably, the

clinical presentation of syphilis may be more aggressive or atypical in patients with concurrent HIV infection. The usual treatment for secondary syphilis is benzathine penicillin G. Doxycycline and azithromycin are alternatives. Despite no specific recommendations, the tendency is toward a prolonged treatment with penicillin G intravenously for 4 to 6 weeks. Given our patient's unknown penicillin allergy, the inability to perform skin allergy testing and the reluctance for a trial on intravenous penicillin, we resorted to an extended course of doxycycline for 6 weeks, which yielded good results.

#### 424 THE DYNAMICS OF RESPIRATORY SYNCYTIAL VIRUS (RSV) REPLICATION REVEALS AN AGE-RELATED FUNCTIONAL MATURATION OF THE INFANT ANTIVIRAL IMMUNE RESPONSE

CR Miller,<sup>1</sup> A Shah,<sup>1</sup> L Harrison,<sup>1,2</sup> E Meals,<sup>1,2</sup> C Hyrne,<sup>1,2</sup> B Bagga,<sup>1,2</sup> Y Kim-Hoehamer,<sup>1,2</sup> L Benhabiles,<sup>2</sup> S Cormier,<sup>2,2</sup> J DeVincenzo<sup>1,2,2</sup>. <sup>1</sup>Miller and Shah Co-First Authors; CFRI at Le Bonheur Children's Hospital, Memphis, TN; <sup>2</sup>University of Tennessee Health Science Center, Memphis, TN

10.1136/jim-2015-000035.426

**Purpose of Study** RSV is the leading cause of lower respiratory tract infection of infants and young children. RSV is associated with prolonged symptoms and the long-term development of asthma. We have previously shown that true RSV replication is best measured by PCR. The full course of RSV replication has never been evaluated in infants.

**Methods Used** We therefore enrolled 60 infants hospitalized for RSV infection and serially quantitatively collected their nasal aspirates for up through one month; measuring 4 separate N-gene-based RSV quantitative PCR (qPCR) viral loads from each time point to improve precision.

**Summary of Results** RSV persisted at higher viral loads for far longer than previously considered, producing an RSV viral load area under the curve of  $>1,131 \log \text{PFUe} \times \text{hr/ml}$ , significantly higher than measured in adults ( $p<0.0001$ ), and with RSV still detectable in 62% of subjects at the last study-collected time point. Individuals cleared RSV erratically with 29% of longitudinally-evaluable subjects showing viral rebound ( $\geq 1 \log \text{PFUe/ml}$  at  $\geq 2$  consecutive time points after nadir), occurring after timing of initiation of cell mediated immune responses (8<sup>th</sup> day of symptoms). Young age predicted viral rebound ( $p<0.05$ ) with all but one subject who rebounded being less than 70 days old.

**Conclusions** RSV replicates much more extensively in children than previously recognized and often exhibits an age-dependent previously-undescribed viral rebound phenomenon during failed rapid clearance.

#### 425 VARICELLA ZOSTER VIRUS-INDUCED ACUTE RETINAL NECROSIS IN A NATALIZUMAB-TREATED PATIENT

CM Rolle, AK Mehta. *Emory University School of Medicine, Atlanta, GA*

10.1136/jim-2015-000035.427

**Case Report: Introduction** Natalizumab is an anti-integrin monoclonal antibody used for the treatment of Multiple Sclerosis (MS) and has been associated with Progressive Multifocal Leukoencephalopathy (PML) but not other severe opportunistic infections. Below, we describe a case of varicella-zoster virus (VZV)-induced acute retinal necrosis in a patient being treated with Natalizumab.

**Case Description** A 34 year old female with MS on Natalizumab presented with 1 week of worsening vision. She described blurred vision worse in the left eye, "floating shadows in her central vision" and bilateral scleral injection and pain. MRI of the brain 2 months previous was unremarkable. An exam demonstrated bilateral scleral injection and loss of central vision in the left eye. Neurological exam was normal except for an unsteady gait. Fundoscopic exam revealed severe vitritis, retinal vasculitis and patchy retinal necrosis consistent with Acute Retinal Necrosis (ARN). Aqueous chamber fluid PCR studies for Toxoplasma, HSV and CMV were negative, but positive for VZV. MRI/MRA of the brain did not reveal any acute abnormalities and HIV testing was negative. Natalizumab was discontinued and she was treated with IV Acyclovir and intravitreal Foscarnet and Ganciclovir. Two months later she developed elevated intraocular pressures and worsening retinal inflammation. She was placed on PO steroids but later developed retinal detachment and underwent vitrectomy with membrane peeling. She lost significant vision in her left eye and has not been re-started on MS therapy given risk of infection relapse.

**Discussion** Despite the association between Natalizumab and PML, there are few reports linking Natalizumab to other infections. Only two case reports in the literature describe VZV infections in patients treated with Natalizumab. The role of Natalizumab in the development of infections seems to be related to its mechanism of action as an antibody targeting the alpha-4 integrin adhesion molecules found on WBCs. These adhesion molecules are responsible for interacting with receptors on the surface of endothelial cells to mediate WBC extravasation from the circulation into inflamed tissues. In our patient Natalizumab likely inhibited the ability of cytotoxic T-lymphocytes to migrate into the eye to fight infection.

#### 426 GORDONIA SPUTI INFECTION IN A PEDIATRIC PATIENT

J Bentley, C Boston, A Vitter, MT Bolton. *Our Lady of the Lake, Baton Rouge, LA*

10.1136/jim-2015-000035.428

**Case Report** *Gordonia* species are gram-positive aerobic bacilli rarely known to cause of human disease, most notably catheter-related sepsis as well as skin and soft tissue infections. We describe the first reported pediatric case of invasive disease due to *Gordonia sputi*. A 9 year old female with synovial cell sarcoma who was undergoing chemotherapy developed fever at home and presented to our hospital for evaluation. Blood cultures were taken from her central line as well as peripheral venipuncture. During her admission, her fever persisted and despite broad-spectrum

antimicrobials. Her blood cultures revealed coryneform-like bacteria with eventual identification confirmed as *Gordonia sputi* from both central and peripheral cultures. Due to persistently positive cultures, her central line was removed. She was continued on intravenous (IV) vancomycin and had a new central line placed once her cultures were negative for 72 hours. She completed two weeks of IV vancomycin and had clinical recovery from her bacteremia. This is the first known reported case of invasive disease secondary to *G. sputi*. Prior case reports detail adult patients who similarly had immunocompromising conditions that likely lead to the development of such an infection. One prior case report suggests pulmonary involvement, and while our patient did have some lung opacities noted on chest imaging during her admission, these were felt to be more related to her oncologic disease based on serial scans revealing the same lesions well before and after this clinical illness. As *Gordonia* species can be incorrectly reported as *Corynebacterium* species, care must be taken to accurately identify this genus in immunocompromised individuals.

#### 427 RISK FACTORS FOR RECURRENT CLOSTRIDIUM DIFFICILE INFECTION IN DIALYSIS PATIENTS

SL Coffin,<sup>1</sup> J Waller,<sup>1</sup> MF Kheda,<sup>2</sup> S Baer,<sup>3,1</sup> R Colombo,<sup>1</sup> L Huber,<sup>1,3</sup> S Nahman<sup>1,3</sup>. <sup>1</sup>Medical College of Georgia, Augusta, GA; <sup>2</sup>Southwest Georgia Nephrology Clinic, Albany, GA; <sup>3</sup>Charlie Norwood VA Medical Center, Augusta, GA

10.1136/jim-2015-000035.429

**Purpose of Study** Clostridium difficile infection (CDI) is a serious nosocomial infection in dialysis (ESRD) patients. Previous research has shown that the greatest relative risk (RR) for initial CDI in ESRD patients was in those with HIV, age > 65 years, bacteremia, and diabetes, but did not investigate risk factors for recurrence. Here, we re-queried this cohort from the United States Renal Data System (USRDS) in order to define the risk for recurrent CDI (rCDI).

**Methods Used** Patients were queried for a diagnosis of CDI and associated comorbidities (ICD-9 codes). rCDI was defined as occurring > 14 days following the first CDI and within one year of the first CDI. Using bivariate and multivariable logistic regression models and backwards elimination of non-significant variables, a final model was obtained. The RR and corresponding 95% CI of rCDI were determined for each risk factor.

**Summary of Results** rCDI occurred in 4,215/ 17,840 (23.6%) patients after the initial CDI. The only risk factor of significance for rCDI was HIV (RR=1.05, 95%CI 1.02–1.08).

**Conclusions** The appearance of HIV as a risk factor reflects current understanding of the risk for rCDI among the immunocompromised population. Surprisingly, other factors reflecting identified risk factors for rCDI in the general population did not appear in our analysis. The reason for this observation is unclear, but we would speculate that it may be related to improved treatment adherence from closer monitoring in the outpatient dialysis setting.

#### 428 CARDIAC TAMPONADE DUE TO TUBERCULOUS PERICARDITIS

U Iguobadia, U Narsinghani, W Blackwood. *Medical Center Navicent Health, Macon, GA*

10.1136/jim-2015-000035.430

**Purpose of Study** Tuberculosis (TB) is a disease with varied presentations. TB pericarditis is an important but rare complication of Pericarditis in the United States. It occurs in 1–2% of patients with TB pneumonia. Diagnosis can be difficult and can lead to death.

**Methods Used** 16yo Senegalese female presented with 2 day history of left sided moderate chest pain associated with dry cough, generalized weakness and decreased appetite. She denied fever, dyspnea or weight loss. Physical Exam revealed a well nourished teenager with vital signs of heart rate 117, respiratory rate of 18, and blood pressure of 122/83 mm Hg and SpO<sub>2</sub> of 100%. She was found to have pulsus paradoxus, pericardial friction rub, cap refill <2 seconds, good peripheral pulses but cold extremities. She was admitted to the PICU and underwent diagnostic evaluation and management.

**Summary of Results** Chest radiograph showed cardiomegaly and left sided pleural effusion. Echocardiogram showed large pericardial effusion with otherwise normal structure and function. Patient underwent echo guided pericardiocentesis and 2 liters of serosanguinous fluid was removed that was consistent with exudates. PPD was negative. Fluid Gram stain and AFB stain were negative. CT scan of chest revealed mediastinal lymphadenopathy and necrotic lymph nodes. Lymph node biopsy showed the presence of Necrotizing Granulomas. Quanteferon Gold test was positive, AFB Culture of pericardial fluid, Pleural fluid, and Axillary lymph node were positive for Mycobacterium Tuberculosis. Patient was started on Rifampin, Isoniazide, Pyrazinamide, Ethambutol, Vitamin B6 and 6 weeks of Steroid therapy.

**Conclusions** The clinical manifestations of TB pericarditis can be nonspecific; fever, weight loss, and night sweats generally precede cardiopulmonary complaints. Symptoms may include cough, dyspnea, chest pain, night sweats and weight loss. Physical findings may include fever, tachycardia, increased jugular venous pressure. Initial evaluation consists of chest radiography, echocardiography and evaluation of sputum for acid-fast bacilli smear and culture. Pericardiocentesis is warranted for routine evaluation of suspected TB pericarditis, particularly if cardiac tamponade is present. Corticosteroids may play a role in preventing constrictive pericarditis especially in high risk patients that have large effusions or with early signs of constriction.

#### 429 A CASE OF ATYPICAL LEMIERRE SYNDROME

IM Remedios, A Gastanaduy, J Hescoek. *LSUHSC, New Orleans, LA*

10.1136/jim-2015-000035.431

**Purpose of Study** Discussion of an unusual presentation of Lemierre Syndrome.

**Summary of Results** A 3 year old girl was sent to the emergency room by her pediatrician with concern for

meningitis. She presented with 5 days of fever (T<sub>max</sub> of 40°C), irritability, and a stiff, painful neck. She had a suspected untreated otitis media 3 weeks prior to presentation. On physical exam, she was febrile (38° F), irritable but consolable. Her neck was rotated to the right, and she was unable to rotate it to the left. Spontaneous flexion-extension of the neck was noticed, but she resisted neck manipulation. The left tympanic membrane was red, dull and bulging, and she had minimal oropharyngeal erythema. Kernig and Brudzinkski signs, as well as other signs of meningitis were negative. The rest of the physical exam was normal. CBC showed a mild leukocytosis (WBC 13.86×10<sup>3</sup>). BMP was normal, and blood cultures were obtained. Computerized tomography (CT) of the head and neck showed a left otitis media and mastoiditis, and a focal non-occlusive thrombus in the left internal jugular vein (LIJV). The patient was admitted, and given her presentation with lack of oropharyngeal involvement, IV ceftriaxone and vancomycin were started. Fevers resolved, and neck pain and motility improved. Repeat CT was similar to the first one, plus a right upper lobe pulmonary nodule. Initial blood cultures grew *Fusobacterium necrophorum* sensitive to metronidazole. Treatment continued with IV ceftriaxone and metronidazole. She had a left mastoidectomy on hospital day 6 and was treated with IV antibiotics for 16 days. At discharge, the patient had significant clinical improvement, and imaging revealed a stable LIJV thrombus and decreased size of the pulmonary lesion. She was discharged to continue treatment with oral metronidazole.

**Conclusions** Septic thrombophlebitis can occur in any vein. In 1936, Lemierre described 20 cases of internal jugular vein (IJV) septic thrombophlebitis with a 90% mortality rate. Lemierre Syndrome classically affects previously healthy adolescents and young adults with preceding oropharyngeal infection, followed by thrombophlebitis and bacteremia caused by *F. necrophorum*, and septic emboli to the lungs, bones, liver, brain, etc. Therapy requires long-term antibiotics. Anticoagulation is controversial. This case is atypical because of the age of the patient and the initial focus of infection.

#### 430 DESCRIPTION OF PATIENTS WITH HIV/AIDS ATTENDING A SUPPLEMENTAL PALLIATIVE CARE CLINIC AND IMPACT ON VIRAL LOAD SUPPRESSION, HOSPITALIZATION, AND RETENTION IN CARE

E Gilliams, M Nguyen, R Friedman-Moraco, A Shahane, E Farber, VC Marconi. *Emory University School of Medicine, Atlanta, GA*

10.1136/jim-2015-000035.432

**Purpose of Study** Unaddressed physical, psychosocial, or spiritual needs may contribute to poor antiretroviral therapy adherence, decreased clinic attendance, and poor health outcomes in individuals living with HIV. Early palliative care services have been shown to improve quality of life, decrease hospitalizations and prolong survival, but this has not been well studied in patients with HIV. This study evaluated patients who were referred to a multidisciplinary palliative care team in an urban clinic treating patients with advanced HIV in Atlanta, GA. Patterns of health care use before and after palliative care intervention were assessed.

**Methods Used** A retrospective analysis of medical charts from patients who were referred to the palliative care clinic was performed. Descriptive statistics were used for baseline characteristics. T-test was used to compare admission rates.

**Summary of Results** 98 patients attended one or more palliative care clinic visits (average  $2.3 \pm 0.2$ ) between July 2011 and May 2015. The majority of patients were male (65%), average age 47.2, African American (78%), mean CD4 T lymphocyte count 277 ( $\pm 28$ ). Median observation prior to first palliative care visit was 457 days (IQR 181–824), and 298 days (IQR 67–857) in follow-up. Prior to first visit with palliative care, this group had a median percentage of 17% (IQR 0–100%) “not detectable” VL measurements, and an average rate of 1.9 ( $\pm 0.4$ ) hospital admissions per year. Following first palliative care visit, median percentage of “not detectable” VL measurements was 66% (IQR 0–100%), with an average of 1.2 ( $\pm 0.3$ ,  $p=0.14$ ) admissions per year.

**Conclusions** Most patients had limited involvement with the palliative care team, usually 1 or 2 visits. Many patients had suboptimal viral suppression, but trended toward improvement following the intervention. No difference was seen in rate of hospital admission. Early palliative care addresses varied concerns, and as such, this group may be heterogeneous with respect to severity of illness and use of healthcare. Further description of impact on patient quality of life is needed.

#### 431 HISTOPLASMA CAPSULATUM MENINGITIS IN A CHILD WITH HYPERIMMUNULOGLOBULIN E SYNDROME

EA Buescher, R Welliver. *OU Children's Hospital, Oklahoma City, OK*

10.1136/jim-2015-000035.433

**Purpose of Study** Autosomal Dominant Hyper IgE Syndrome is a multisystem disorder in which patients are functionally immunocompromised. Previously reported fungal infections seen in the setting of this syndrome are *Candida albicans*, *Cryptococcus neoformans*, and *Coccidioides immitis*. Immunocompromised patients exposed to *Histoplasma capsulatum* typically present with a non-specific febrile illness which can rapidly progress to disseminated disease and death. Histoplasmosis is a rare cause of opportunistic infection in the setting of hyperimmunoglobulin E syndrome (HIES). We present a case of histoplasma meningitis in a 7 year old boy with a history of autosomal dominant (AD) HIES.

**Methods Used** A 7 year old boy with a history of AD HIES and developmental delay presented to OU Children's Hospital with a one month history of decreased appetite, decreased activity, intermittent low grade fevers (max 38.7), and weight loss of 4 kg over 2 months. He denied recent travel, animal exposure, tuberculosis exposure, or visitors from outside Oklahoma City. On admission, WBC was 13 K/mm<sup>3</sup>. CMP showed no abnormalities, ESR was elevated at 28, and CRP was elevated at 16.4. His CSF showed WBC of 32, glucose of 38, and protein of 51 consistent with a fungal meningitis. The urine, stool, blood, and CSF cultures remained negative. His brain MRI showed foci of restricted diffusion in bilateral thalami and

peritrial white matter of right lateral ventricle concerning for cerebritis. He had daily fevers lasting 6 days, which resolved 2 days after the initiation of Amphotericin B. His activity and appetite improved and he was discharged with presumed fungal meningitis.

**Summary of Results** Urine histoplasmosis antigen was found to be positive, confirming histoplasmosis infection. He completed a one month course of IV Amphotericin B and Flucytosine. His appetite and activity continued to improve resulting in a 4 kg weight gain in 4 months. He will remain on a lifelong regimen of Itraconazole.

**Conclusions** We present this interesting case, to emphasize that histoplasma meningitis may occur in patients with HIES, even in a geographic location in which histoplasmosis is only mildly endemic. This case shows that with proper antifungal management histoplasmosis can be treated effectively, though timely diagnosis is essential.

## Neurology and Neurobiology

### Concurrent Session

2:00 PM

Friday, February 19, 2016

#### 432 ACTIGRAPH SLEEP-WAKE VARIABLES ASSOCIATED WITH CONFUSION STATUS IN INTENSIVE CARE UNIT PATIENTS

JE McGovern,<sup>1</sup> L Tynes,<sup>2</sup> G Jones<sup>2</sup>. <sup>1</sup>LSU, Baton Rouge, LA; <sup>2</sup>OLOL/LSU Psychiatry Residency Program, Baton Rouge, LA

10.1136/jim-2015-000035.434

**Purpose of Study** Delirium is associated with increased mortality, hospital length of stay, and health-care costs. Because the etiology of delirium remains poorly understood, preventing delirium can be a challenge. Studies suggest sleep-wake cycle disturbances may precede delirium. Additionally, confusion is present in approximately 76% of delirium cases and is more often assessed than delirium in ICU settings. Earlier detection of delirium risk may prevent its associated adverse effects. The present study employed actigraphy to explore which sleep-related variables associated with documented confusion in ICU patients. This is the first study known to these authors to look at confusion status in relation to actigraphy.

**Methods Used** This pilot study enrolled a convenience sample of adult ICU patients within 36 hours of hospital admit with no history of dementia or delirium who wore wrist actigraphs during their ICU stay. Patients were counted as "became confused" if their medical chart had subsequent documentation of confusion and/or disorientation in the routinely administered (about every 4 hours) mental status exam. Of N=21 patients who wore the actigraph for at least 24 hours, n=4 became confused (BC) and n=17 never became confused. Biserial correlations were used to explore which actigraph variables associated with confusion status.

**Summary of Results** BC patients trended toward having longer sleep latency ( $r_b=.564$ ,  $p=.075$ ), longer mean wake bouts ( $r_b=.601$ ,  $p=.057$ ), and more mobile minutes ( $r_b=.538$ ,  $p=.089$ ). One BC patient later developed delirium and another was suspected of having delirium.

**Conclusions** Even below the threshold of "delirium," at the level of "confusion," differences in sleep-wake patterns were detected. ICU patients with a 24-hour sample of actigraph data showed large correlations between confusion status and taking longer to fall asleep, having longer periods of wakefulness, and spending more minutes moving overall. That such large effects were only significant at trend levels suggests the present study was underpowered; thus, replication studies may require a larger samples. Actigraphy may be a useful in monitoring onset of sleep-wake disturbances in ICU patients.

433 **<sup>123</sup>I]-FP-CIT STRIATAL UPTAKE IN TREMOR VS. NON-TREMOR TYPE PARKINSONIAN SYNDROME**

S Goel, J Huang, S Hussain, V Vijayakumar, A Auchus. *University of Mississippi, Madison, MS*

10.1136/jim-2015-000035.435

**Purpose of Study** Presynaptic dopamine transporter imaging such as [<sup>123</sup>I]-FP-CIT single photon emission computed tomography (SPECT) has been widely used to differentiate essential tremor from tremor due to degenerative parkinsonian syndromes. However, the utility of [<sup>123</sup>I]-FP-CIT-SPECT in non-tremor type Parkinsonian Syndrome has not been well established. This study is to assess whether non-tremor dominant Parkinsonian syndrome (nT-PS) have a different pattern of [<sup>123</sup>I]-FP-CIT uptake than tremor dominant Parkinsonian syndrome (T-PS) by using DaTQUANT, an automated semi-quantitative software tool.

**Methods Used** A retrospective chart review was conducted for 50 consecutive patients with [<sup>123</sup>I]-FP-CIT-SPECT imaging performed at UMMC from 2012–2015. Those patients with abnormal [<sup>123</sup>I]-FP-CIT-SPECT were diagnosed as degenerative Parkinsonian syndrome and were further classified as tremor dominant (T-PS) or non-tremor dominant (nT-PS) based on clinical presentations. Measurements of striatal binding ratios (SBR) were performed using DaTQUANT. The following volume of interests (VOIs) were analyzed: total striatum, caudate, anterior putamen and posterior putamen. The SBRs were estimated by ratios of radioligand uptake intensity in the above VOIs to radioligand uptake intensity in background that normally does not contain dopamine transporters (DAT) (occipital cortex).

**Summary of Results** Seventeen of the 30 patients determined to have abnormal [<sup>123</sup>I]-FP-CIT-SPECT had source images available for DaTQUANT analysis and were included in this study. Of these 17, 11 (averaged age 67, M/F: 9/2, averaged disease duration 4.5 years) manifested T-PS and 6 (averaged age 72, M/F: 3/3, averaged disease duration 4.8 years) manifested nT-PS. Patients in the nT-PS group showed more reduction of [<sup>123</sup>I]-FP-CIT uptake as measured by SBRs in all analyzed striatum regions when compared to the T-PS group: total striatum (0.69 vs. 1.08), caudate (0.95 vs. 1.46), anterior putamen (0.62 vs. 0.91) and posterior putamen (0.34 vs. 0.50), all p values > 0.05.

**Conclusions** In preliminary analysis, we found that nT-PS patients tend to have lower striatum [<sup>123</sup>I]-FP-CIT uptakes compared to T-PS patients although the difference was not

statistically significant likely due to small sample sizes. Further prospective large sample studies are needed to validate our observation.

434 **COMPARATIVE VOLUMETRIC ASSESSMENT OF A MURINE XENOGRAFT MALIGNANT GLIOMA MODEL VIA GADOLINIUM ENHANCEMENT PATTERN AND EXTENT OF TISSUE FLUORESCENCE (FLUORESCIN SODIUM)**

JJ Audry, M Petersen, A Perez. *University of Mississippi School of Medicine, Jackson, MS*

10.1136/jim-2015-000035.436

**Purpose of Study Background** Intraoperative fluorescence guidance has become a valuable tool to maximize resection of high-grade gliomas. Currently there are two fluorophores (5-ALA and fluorescein sodium) in use for this purpose and several others being studied for potential clinical use. Gross total resection of malignant glioma is currently defined as resection of 98% or more of the enhancing tissue. While the correlation between fluorescence and neoplastic tissue has been studied, little is known about the correlation between gadolinium enhancement and fluorescence at the tumor margin.

**Methods Used Methods** Approximately fourteen Sprague-Dawley rats have undergone direct implantation of C6 glioma cells. They have subsequently been imaged with Gadolinium-enhanced MRI, administered the fluorescent compounds and sacrificed. Analysis includes volumetric data obtained by software algorithms from contrasted MRI and manually derived volumetric measurements of histological frozen sections. A qualitative component includes evaluation at the fluorescent tumor margin *versus* the histopathological margin.

**Summary of Results** We have obtained volumetric Gadolinium results and are anticipating comparison of this data with volumetric Fluorescein data. The data provides capacity for both quantitative volumetric comparison and qualitative comparison at the tumor margins tantamount to extent of tumor penetrance by Gadolinium or the fluorescent marker.

**Conclusions** The aim of this study is to elucidate any differential volumetric and marginal parameters between traditional methods of intracranial tumor demarcation and newer, fluorescence-based, techniques that also lend a dynamic, intraoperative, real-time component to resection. Continued validation of the latter will provide insight into its practical applicability and potential limitations in malignant glioma surgery.

435 **SUB-CLASSIFICATION AND MANAGEMENT OF THORACOLUMBAR SPINE INJURIES BY THORACOLUMBAR INJURY CLASSIFICATION AND SEVERITY SCORE ASSESSMENT**

JR Miller, J Wilson, E Fannin. *LSU SOM - New Orleans, New Orleans, LA*

10.1136/jim-2015-000035.437



**Purpose of Study** Thoracolumbar spine injuries constitute more than 50% of all spine traumas that involve acute spinal cord injury. The Thoracolumbar Injury Classification and Severity Score (TLICS) is a widely used system with high inter-observer reliability. Despite advancements in surgical management, limitations of TLICS exist when patients are scored 4 (scale of 0 - 10), and may be treated either non-operatively ( $\leq 3$ ) or operatively ( $\geq 5$ ). TLICS score is based on 3 components: injury morphology, integrity of posterior column, and neurologic status. This study aims to provide evidence-based insight when weighing the benefits and risks associated with surgical vs. non-surgical intervention of injuries with TLICS 4 scores.

**Methods Used** In this retrospective study, we reviewed medical records of patients with acute thoracolumbar injuries admitted to our Level I Trauma Center between January 2010 and December 2014. Patients without a 6-month follow-up were excluded. Pertinent data, such as GCS score, ASIA score, and imaging, was analyzed to determine the TLICS score. Follow-up status was determined by patient pain assessments and neurologic function tests. We evaluated 327 patient encounters, of which 37 were considered TLICS 4 scores. Of these 37 patient encounters, we excluded 10 for lack of follow-up appointments assessing their post-surgical function.

**Summary of Results** Our preliminary findings show that of the patients who were non-operative, 35% had a positive outcome, 40% had a neutral outcome, and 25% had a negative outcome. Compared to patients who underwent surgery, 14% had a positive outcome, 43% had a neutral outcome, and 43% had a negative outcome. Additionally, logistic regression and chi-squared statistical tests were performed using key variables (Age, Gender, Race, Length of Stay, GCS, Mechanism), but no significance was found relative to outcome or surgical decision.

**Conclusions** We believe that conservative, non-surgical medical management of TLICS 4 patients is supported by observational findings of fewer negative outcomes, and more positive outcomes, than surgical management, for similarly situated patients. We are working to further increase our sample size to add greater statistical power to our results.

#### 436 HASHIMOTO'S ENCEPHALITIS PRESENTING AS NON-CONVULSIVE STATUS EPILEPTICUS

SH Khan, S Mula. *Baylor Scott and White, Temple, TX*

10.1136/jim-2015-000035.438

**Case Report: Introduction** Hashimoto's Encephalitis remains a diagnosis of exclusion made all the more difficult to diagnose given its diversity in presentation. Neurologic patterns vary with non-specific features of encephalopathy, behavioral changes, and seizures. While 2/3 of patients present with seizures, it is unclear how many present with non-convulsive status epilepticus (NCSE).

**Case Report** We report a 56 year old woman with past medical history significant for hypothyroidism, anxiety, and hypertension who presented with a 10 month history of memory loss and gait disturbance. Her initial presentation warranted EEG monitoring at which time she was found to

be in NCSE. Significant findings on neurologic exam included an MMSE of 18/30, decreased sensation to pin-prick bilaterally in her lower extremities, and normal gait with decreased arm swing bilaterally. After successful resolution of her seizures with anti-epileptic therapy, the etiology of her symptoms was worked up extensively with serum electrolytes, CSF analysis, paraneoplastic panel, auto-immune studies, and MRI of the brain. Anti-microsomal (1:400) and anti-thyroglobulin (1:160) antibodies suggested Hashimoto's Encephalitis as the remainder of her labs and imaging were non-contributory. Our patient responded favorably to high-dose steroids for five days and would require long-term steroid therapy with intent to taper at follow up.

**Discussion** Our patient would meet criteria for Hashimoto's Encephalitis with encephalopathy on presentation, positive anti-thyroid antibodies, and favorable response to steroid therapy. Given the patient's description of her symptoms it is uncertain how long she had been having intermittent episodes of NCSE. Recurrent status epilepticus as the main feature of Hashimoto's Encephalopathy has been described in the literature before; however, the patient's non-convulsive variant may have contributed to a delay in seeking care. Our patient's hypothyroidism was appropriately addressed, though it has long been established that thyroid status does not contribute to the severity of Hashimoto's Encephalopathy. In a patient with NCSE in whom metabolic, CSF, and imaging studies are negative a diagnosis of Hashimoto's Encephalitis, though rare, should be considered.

#### 437 SERONEGATIVE NEUROMYELITIS OPTICA: TYPICAL DISEASE PRESENTATION WITH NEGATIVE SEROLOGY

BR Zambetti, F Kamal, MS Harrison, H Akbar, A Seth. *University of Tennessee Health Science Center, Memphis, TN*

10.1136/jim-2015-000035.439

**Case Report** Neuromyelitis optica (NMO) is a disorder of CNS caused by immune mediated demyelination of nerves. Common presentations include optic neuritis and other neurological symptoms including transverse myelitis. It most commonly occurs in age of 30s and 40s with a female predominance. The evaluation of a suspected case of NMO involves a complete history and Physical examination, Imaging including MRI, serologic tests including anti-aquaporin 4 antibodies (AQP4) assay and CSF analysis. AQP4 ab assay is an important diagnostic marker with a sensitivity ranging from 72–91% and a specificity from 91–100% and it is also involved in the pathogenesis of the disease. The diagnosis is typically made by clinical suspicion in combination with serology and neurologic imaging. We present a case of NMO with negative serology including AQP4 antibodies. This patient was a 27-year-old Caucasian male who presented with optic neuritis, numbness to the mid-chest, lower extremity weakness, urinary retention and MRI evidence of demyelination. A complete serologic panel, including anti-aquaporin 4, ANCA, RNP IgG, Smith, Phosphatidylinositol immunoglobulins, SS-A, SS-B, Rheumatoid Factor, were all negative. He was treated with prednisone and plasmapheresis per standard of care

treatment of NMO and had complete resolution of symptoms. This case of seronegative NMO shows the importance of clinical judgment and the limitations of serological assays in clinical medicine. Though some studies have questioned the incidence of seronegative NMO with the increasing sensitivity of modern assays, this patient had his CSF and serum analyzed at multiple institutions using the latest techniques, yet still based on symptomatology, radiology, and clinical course had NMO. This case represents the need for further investigation into the pathogenesis of NMO as well as the serology associated with it.

**438 METACHRONOUS SUPRATENTORIAL INTRACRANIAL MALIGNANT TUMORS IN TWO PEDIATRIC PATIENTS WITH INFRATENTORIAL MEDULLOBLASTOMA ON HORMONE THERAPY**

JJ Audry, M Petersen, A Perez. *University of Mississippi School of Medicine, Jackson, MS*

10.1136/jim-2015-000035.440

**Introduction** Medulloblastomas are classified by the WHO as embryonal tumors and comprise the most common of the malignant pediatric brain tumors while accounting for twenty percent of all pediatric brain tumors. The phenomenon of second malignancy is uncommonly seen in cases of uniform histology and are more rare when they are of a different histological type. The authors report two cases of infratentorial medulloblastomas that subsequently developed a grade IV glioma in one case, and a second medulloblastoma in the other.

**Presentation** An eleven year-old female had been experiencing vision difficulty with right eye deviation and emesis. MRI showed a partially-enhancing posterior fossa mass lesion. Four years later, she was discovered to have a right parietal ring-enhancing lesion on routine surveillance. A four year-old female presented to our institution with a one-month history of headaches and emesis and a posterior fossa mass lesion. Three and a half years later, subsequent routine surveillance revealed a new enhancing lesion of the left temporal region with a higher *Ki-67* labeling index.

**Treatment** Our first patient underwent sub-occipital craniotomy and gross-total resection for her medulloblastoma followed by chemoradiation under a COG protocol consisting of Vincristine, Cisplatin, and Cyclophosphamide and 23.4 Gy with a posterior fossa boost of 30.6 Gy. She underwent craniotomy for the GBM with GTR followed by maintenance chemotherapy. Our second patient underwent similar therapy with GTR for both lesions then was initiated after the second resection on a COG trial consisting of Bevacizumab, Temodar, and Irinotecan. Of note, both patients were on hormone therapy: GH and Lupron.

**Conclusions** We report two cases of infratentorial medulloblastoma with subsequent development of supratentorial lesions with discrepant histological profiles. A second malignancy of different cellular origin is rare, and molecular profiling of the two metachronous medulloblastomas will reveal whether they represent unique entities. Due to clinical and radiographic progression of their cerebral disease, the two patients are now deceased.

**439 PRIMITIVE NEUROECTODERMAL TUMOR PRESENTING WITH DIFFUSE LEPTOMENINGEAL ENHANCEMENT AND INCREASED INTRACRANIAL PRESSURE IN AN 18 YEAR OLD FEMALE**

S Chaudhry, O Moore, J Plante, S Silliman. *University of Florida - Jacksonville, Jacksonville, FL*

10.1136/jim-2015-000035.441

**Case Report** Primitive Neuroectodermal Tumors (PNETs) are a type of neuroepithelial tumor known as embryonal tumors, and account for less than 5% of all CNS embryonal tumors. PNETs usually present in the first one to two decades of life, with 80% usually presenting before the age of 10. They are categorized into supratentorial vs infratentorial. This case report describes an 18 year old female presenting with right eye visual impairment and signs of increased intracranial pressure, who on biopsy was found to have a primitive neuroectodermal tumor. The case is unique in two aspects. First, initial magnetic resonance imaging of the brain and spine revealed only leptomeningeal enhancement and dural thickening with no obvious intracranial, cervical, or thoracic masses. Second, on follow up imaging at 5 months, masses presented simultaneously both supratentorially and infratentorially. A literature review revealed a total of 5 adult and pediatric cases of PNETs presenting with only leptomeningeal enhancement without identifiable CNS masses. Most cases of PNETs are supratentorial, and are found to have CNS masses at the time of diagnosis. Our case demonstrates that leptomeningeal enhancement can be an early sign of PNET presentation.

**440 MYASTHENIC CRISIS PRECIPITATING TAKOTSUBO CARDIOMYOPATHY**

S Seago,<sup>1</sup> M Greene<sup>1,2</sup>. <sup>1</sup>Scott and White Memorial Hospital, Temple, TX; <sup>2</sup>Texas A&M College of Medicine, Temple, TX

10.1136/jim-2015-000035.442

**Introduction** Approximately ten to twenty percent of all patients with myasthenia gravis will experience at least one myasthenic crisis over the course of their disease. While mortality rates for myasthenic crisis have fallen dramatically in the past fifty years following the development of intravenous immunoglobulin and plasma exchange, myasthenic crisis is still associated with significant morbidity including prolonged mechanical ventilation, sepsis and even stress induced or takotsubo cardiomyopathy.

**Case Description** A seventy-two-year-old female with known myasthenia gravis presented with progressive shortness of breath after missing several doses of pyridostigmine due to a recent gastrointestinal illness. On admission, her negative inspiratory force was negative fifteen and she was emergently intubated for ventilatory support. Bloodwork illustrated an elevated troponin with ST segment elevation in the anterior leads on electrocardiogram. Emergent cardiac catheterization revealed no angiographic evidence of coronary artery disease; however, a left ventriculogram illustrated severe hypokinesis of the apical, inferior and inferior basal walls consistent with takotsubo cardiomyopathy. During her hospitalization, she was treated with

intravenous immunoglobulin for myasthenic crisis with rapid improvement in her respiratory status. Her takotsubo cardiomyopathy was managed conservatively with great improvement in her cardiac function on repeat imaging two months after discharge.

**Discussion** A careful literature review uncovered a handful of cases of takotsubo cardiomyopathy associated with myasthenic crisis. A common hypothesis for this correlation is that myasthenic crisis precipitates a catecholamine surge, resulting in takotsubo cardiomyopathy. Recent research highlights the association between catecholamine excess and takotsubo cardiomyopathy with measured serum catecholamine levels noted to be significantly higher in patients with takotsubo compared to myocardial infarction. Though unusual, this case highlights an increasingly recognized association between myasthenic crisis and takotsubo cardiomyopathy and encourages all physicians to maintain a broad differential diagnosis when presented with atypical clinical presentations.

#### 441 CHASING THE DRAGON: A CASE OF HEROIN INHALATION LEUKOENCEPHALOPATHY

LS Engel, R Darcey Weems, W Probasco, S Struthers. *LSU Health Sciences Center, New Orleans, LA*

10.1136/jim-2015-000035.443

**Introduction** "Chasing the Dragon" is a slang term which refers to the inhalation of the heated vapors of heroin. First described in 1982, heroin inhalation leukoencephalopathy (HIL) is a rare but serious complication of heroin use by inhalation.

**Case Description** A 35 year old incarcerated woman with a history of intravenous heroin use was brought in by the sheriff's office for three days of altered mental status. The jail physician noted "unsteady gait, weakness, delayed responses, and lethargy". She complained of headache and generalized weakness, which she attributed to "withdrawing." Her last heroin use was four days prior to presentation. On exam, she was noted to be apathetic with generalized psychomotor slowing. Her neurologic exam was significant for right lower extremity weakness and diminished sensation, brisk patellar reflexes, and bilateral ankle clonus. She was uncooperative with cerebellar testing and was unable to stand due to right extremity weakness. Initial labs revealed a slight leukocytosis (13.6) without left-shift, hypokalemia (2.9), transaminitis (AST 292 U/L, ALT 147 U/L) and elevated CK (1864). Urine drug screen was positive for opiates and benzodiazepines. Brain MRI demonstrated symmetric cortical/subcortical T2 hyperintensities in the watershed territories of the bilateral parietal and occipital lobes consistent with leukoencephalopathy. Spine MRI, EEG, CSF studies, rheumatologic panel, MS panel, and infectious work-up were unremarkable. On further questioning, she admitted to heroin use by inhalation which led us to the diagnosis of HIL. She was started on a trial of coenzyme Q and received intensive physical therapy resulting in improved mentation and physical function.

**Discussion** Symptoms of HIL include cerebellar dysfunction, psychomotor retardation, soft speech, and apathy. Symmetric T2 hyperintensities in the posterior cerebral hemispheres and cerebellum are seen on MRI. Heroin vapors may be directly toxic to mitochondria, and result in a vacuolar degeneration of myelin sheaths. Treatment includes supportive care; anti-oxidants such as coenzyme Q have been used anecdotally. HIL should be considered in patient's presenting with a history of heroin inhalation and new onset neurologic or behavioral changes.

#### 442 AMIODARONE USE WITH ALCOHOL INTAKE PRESENTING AS STROKE MIMIC

M de Lima. *UF Health, Jacksonville, FL*

10.1136/jim-2015-000035.444

**Introduction** Nearly 33 to 50% of cases that present to the emergency departments as suspected strokes turn out as stroke mimics. Proper evaluation of stroke relies on a complete physical exam, imaging and a thorough history. We report a case of alcohol use potentiating amiodarone neurotoxicity in a patient who presented as a stroke alert.

**Case** An 86 year old Caucasian man was airlifted to the hospital for stroke-like symptoms for two hours. His past medical history is significant for a left insular infarction 5 years ago and atrial fibrillation on novel oral anticoagulation. History was obtained from the wife who describes that the patient became acutely dysarthric and off balance after dinner. Symptoms worsened and the wife became concerned for a possible stroke. The patient had drunk two scotches and a glass of wine with dinner, his usual intake. She also noted that he was started on amiodarone 2 days before for arrhythmias found on ICD interrogation. Physical exam revealed severe dysarthria, ataxia and gait unsteadiness. CT/CTA studies had no evidence of an acute arterial occlusion. The patient's dysarthria and ataxia slowly improved over 18 hours with his daily dose of amiodarone being held.

**Discussion** Amiodarone is a class III antiarrhythmic drug that is prescribed for atrial fibrillation and ventricular arrhythmias. While most practitioners are familiar with the more prominent adverse effects, many are unaware of the neurotoxic effects associated with amiodarone therapy. Estimates of amiodarone-associated neurotoxicity range from 3% to 74% with symptoms presenting on a continuum including peripheral neuropathy, insomnia, impaired memory, ataxia or tremor. The majority of studies on neurotoxic effects with amiodarone use found in the literature were associated with duration of use. Those with neurotoxic effects took amiodarone for significantly longer (mean, 31.6 months). Our patient was on day 2 of amiodarone before exhibiting neurologic effects with the addition of alcohol intake. Our case is also the first to report dysarthria as a possible effect of amiodarone use. Clinicians who deal with acute stroke should be aware that a new start of amiodarone in a patient that uses alcohol could possibly potentiate toxicity and induce a stroke mimic.

## Nutrition

## Concurrent Session

2:00 PM

Friday, February 19, 2016

443 **EXTREMELY PREMATURE INFANTS REQUIRE PREMATURE TRANSITIONAL FORMULAS POST-DISCHARGE FOR CATCH-UP GROWTH**

A Fernandes,<sup>1</sup> A Hair<sup>2,3</sup>. <sup>1</sup>St. Agnes Academy, Houston, TX; <sup>2</sup>Baylor College of Medicine, Houston, TX; <sup>3</sup>Texas Childrens Hospital, Houston, TX

10.1136/jim-2015-000035.445

**Purpose of Study** Premature infants are at risk for post-natal growth failure, especially if their post-discharge diet is not closely monitored. The use of premature transitional formulas may positively impact the growth of preterm infants, but the ideal duration to continue these formulas is unclear. Our aim was to evaluate the effects of post-discharge nutrition on the growth of extremely premature infants fed an exclusive human milk (HM)-based diet in the neonatal intensive care unit (NICU).

**Methods Used** A retrospective chart review was conducted and infants' diets and anthropometric measurements were obtained at 12–15 months corrected gestational age. The duration of time the infants received premature transitional formula after discharge was also collected.

**Summary of Results** We studied 51 infants (52.6% male, gestational age of 27.8±2.6 weeks (Mean±SD)). 86% of infants received premature transitional formula (22, 24, 27 kcal/oz) for 8.9±4.9 months post-discharge. The weight increase of these infants ranged from 11.7±3.3 to 16.2±1.2 (g/day), which exceeds WHO normal growth standards of 5–9 g/day (12–16 months). Total time on premature transitional formula in months did not significantly impact growth (weight, length or head circumference; p=0.51). Growth of infants consuming HM in addition to formula was no different than those consuming formula only (15.4±3.2 vs. 14.5±3.4 (g/day) respectively, p=0.36). Further, a longer duration of HM consumption did not impact weight gain within the group of infants receiving HM in addition to formula (p=0.09).

**Conclusions** The majority of extremely premature infants require premature transitional formula for catch-up growth post-discharge during the first year of life. Infants who received HM in addition to formula displayed similar growth compared to infants receiving only formula.

444 **FEEDING REGIMEN IS SIGNIFICANTLY ASSOCIATED WITH NECROTIZING ENTEROCOLITIS IN INFANTS WITH COMPLEX CONGENITAL HEART DISEASE.**

A Cognata,<sup>1</sup> P Griffiths,<sup>2</sup> S Maskatia,<sup>1</sup> D Rios,<sup>1</sup> A O'Donnell,<sup>1</sup> A Mehollin-Ray,<sup>1</sup> J Hagan,<sup>1</sup> J Placencia,<sup>1</sup> A Hair<sup>1</sup>. <sup>1</sup>Baylor College of Medicine, Houston, TX; <sup>2</sup>Phoenix Children's Hospital, Phoenix, AZ

10.1136/jim-2015-000035.446

**Purpose of Study** Infants with complex congenital heart disease (CHD) have an increased risk of necrotizing enterocolitis (NEC). Among infants with CHD, multiple studies have shown that a PDA, or other abnormal connection that

results in diastolic steal, increases the risk for developing NEC. Evidence-based practices for feeding neonates with CHD are not well characterized. This is a retrospective cohort study designed to evaluate feeding risk factors associated with NEC during the pre-operative period (POP) in infants with complex CHD.

**Methods Used** This study included all infants with an isolated high-risk cardiac lesion admitted to Texas Children's Hospital within the first 72 hours of life between Jan 1, 2010- Jan 1, 2015. NEC was defined based on modified Bell's Criteria. Information on feeding regimen along with possible confounders were collected on all patients. Bivariate associations with NEC were examined by fitting a logistic regression model separately for each hypothesized risk factor. Risk factors exhibiting statistical significance were included in a multivariate logistic regression model.

**Summary of Results** Approximately 30% of NEC cases developed in the POP. Infants receiving fortified feeds (OR=4.2, p<0.05) or feeds >100 ml/kg/day (OR=3.6, p<0.05) were significantly more likely to develop NEC during the POP. Infants who received exclusively human milk diets (mother's own milk or donor milk) were significantly less likely to develop NEC in the POP (OR=0.2, p<0.05). Starting feeds while a UAC was in place and receiving feeds via a nasogastric tube were not significantly associated with developing NEC in the POP. Feeding volume, fortification, and an exclusive breastmilk diet were no longer statistically significant after adjusting for prematurity, cardiac lesion, and birth weight in a multivariate analysis.

**Conclusions** Our preliminary results are suggestive that pre-operative feeding strategies may modify the risk for NEC in infants with complex CHD, but are limited by small sample size. We are currently collecting data on approximately 200 more infants to meet our calculated sample size.

445 **EARLY FEEDINGS WITH AN EXCLUSIVE HUMAN MILK-BASED DIET ARE ASSOCIATED WITH IMPROVED OUTCOMES IN EXTREMELY PREMATURE INFANTS**

AB Hair,<sup>1</sup> S Mandal,<sup>2</sup> N Kikani-Agrawal,<sup>1</sup> KM Hawthorne,<sup>3</sup> SA Abrams<sup>3</sup>. <sup>1</sup>Baylor College of Medicine, Texas Children's Hospital, Houston, TX; <sup>2</sup>Internal Medicine, Augusta University- University of Georgia, Athens, GA; <sup>3</sup>Department of Pediatrics, Dell Medical School, The University of Texas at Austin, Austin, TX

10.1136/jim-2015-000035.447

**Purpose of Study** Early introduction of enteral feedings with human milk (HM) in conjunction with an exclusive HM-based diet (mother's milk, donor HM, and donor HM-derived fortifier) for extremely premature infants has not been studied. Our aim was to describe outcomes of extremely premature infants receiving a newly introduced feeding protocol with initiation of HM feedings in the first 48 hours of life with an exclusive HM-based diet.

**Methods Used** Prospective cohort study of consecutively followed infants between August 2010-December 2011 at Texas Children's Hospital with birth weight (BW)≤1250 g and <37 weeks gestational age (GA). Infants with congenital anomalies were excluded. All infants received a newly introduced feeding protocol which included starting enteral

feeds within 48 hours of life.

**Summary of Results** 104 infants met inclusion criteria with BW of  $913 \pm 182$  g and GA of  $27.6 \pm 2.0$  weeks (mean  $\pm$ SD). Baseline demographics and characteristics were similar between infants who received early feedings and those who did not. 52% of infants who received early feedings per protocol had decreased length of stay ( $83.1 \pm 33.9$  vs  $102.6 \pm 60.2$ ,  $p < 0.04$ ), decreased parenteral nutrition days ( $14.5 \pm 8.0$  vs  $20.7 \pm 14.7$ ,  $p = 0.007$ ), and decreased days to full feeds ( $15.9 \pm 9.7$  vs  $20.7 \pm 11$ ,  $p = 0.02$ ). Rates of late-onset sepsis and necrotizing enterocolitis were similar between groups.

**Conclusions** In this cohort study, initiation of early HM feedings as part of an exclusive HM-based diet was beneficial for infants  $< 1250$  g BW.

#### 446 POST DISCHARGE FEEDING REGIMENS AFFECT GROWTH VELOCITY IN VERY LOW BIRTH WEIGHT INFANTS

A Sitabkhan, AG Moreira, K Bonagurio, E Lavendar, A Gong, C Blanco. UTHSCSA, San Antonio, TX

10.1136/jim-2015-000035.448

**Purpose of Study** To investigate if post discharge growth is affected depending on the caloric enteral concentration prescribed at discharge in very low birth weight infants (VLBW) ( $< 1500$  g).

**Methods Used** A QI project was initiated to improve post-discharge growth velocity in VLBW infants. Growth parameters of VLBW Infants who followed in the Premature Infant developmental clinic (PREMIere) at University Hospital in San Antonio in 2011 were reviewed. Type of feedings at discharge and first clinic visit were classified as follow: breast milk (BM), elemental formula (ELE), mix of BM and post-discharge preterm formula (PRT), or PRT formula alone. Post discharge growth was compared between the various feeding type groups using SPSS.

**Summary of Results** 77 infants with BW of  $1123 \pm 226$  were followed at PREMIere; 59% of those infants were discharged on PRT, 21% on a mix of BM and PRT, 11% on BM and 8% on ELE formula. Birth and discharge anthropometrics were similar between feeding type groups. At the first clinic visit (post-discharge day =  $51.6 \pm 7$ ), infants who were on BM, PRT or BM+PRT feeds had transitioned to BM+PRT providing an average of 21 cal/oz by their first outpatient visit. Those discharged on ELE (20 cal/oz) remained on that feeding type. Growth velocity was significantly lower for the group on ELE when compared to BM, PRT or BM+PRT groups ( $27 \pm 8$  g/day for the ELE vs  $36 \pm 14$ ,  $33 \pm 10$  and  $34 \pm 11$  g/day respectively,  $p < 0.05$ ). Similar findings resulted from the exponential model for growth velocity. Length velocity was significantly lower in the ELE group with 0.09 cm/day whereas BM, PRT or BM +PRT groups had an increase of 0.14, 0.13, and 0.14 cm/day, respectively ( $p < 0.05$ ). FOC velocity was lower at 0.36 cm/week for the ELE group when compared to 0.66, 0.68, and 0.63 cm/week for the BM, PRT and BM+PRT groups respectively,  $p < 0.05$ . Similar results were found if infants were sub-classified by BW  $>$  or  $<$  1,000 grams.

**Conclusions** Growth rates were adequate for VLBW

infants discharged on BM, post-discharge formulas, or a mixture of the two. This is likely due parental mixing of EBM and PRT formula providing an average of 21 cal/oz. VLBW infants discharged on ELE formulas providing 20 cal/oz had sub-optimal global growth. We have implemented discontinuing or increasing caloric concentration of ELE formula prior to discharge in VLBW infants.

#### 447 VITAMIN D REDUCES HEPCIDIN CONCENTRATIONS INDEPENDENT OF INFLAMMATORY CYTOKINES IN HEALTHY ADULTS

E Smith, M Kearns, J Alvarez, S Zughair, V Tangpricha. Emory University, Atlanta, GA

10.1136/jim-2015-000035.449

**Purpose of Study** Disturbances in iron recycling may result from elevations in inflammatory cytokines and hepcidin, the major iron-regulatory hormone. Vitamin D is associated with reduced odds of anemia of inflammation, though its effect on iron recycling in healthy individuals is unclear. Our objective was to 1) examine the effect of high-dose vitamin D on hepcidin and inflammatory cytokine concentrations in healthy adults, and 2) determine whether changes in hepcidin were concomitant with or independent of changes in cytokines.

**Methods Used** This was a double-blind, placebo-controlled trial in healthy adults ( $n = 28$ ) randomized to receive an oral dose of 250,000 IU  $D_3$  or placebo. Between- and within-group differences in plasma hepcidin and inflammatory cytokine [interleukin (IL)-1 $\beta$ , IL-6, IL-8, and monocyte chemoattractant protein-1 (MCP-1)] concentrations at baseline and 1 week were determined using two-sample and paired t-tests, respectively.

**Summary of Results** At baseline, 25-hydroxyvitamin D [25 (OH)D], hepcidin, and inflammatory cytokine concentrations did not differ between vitamin D and placebo groups; 75% of subjects had plasma 25(OH)D concentrations  $< 20$  ng/mL. By 1 week, those who received vitamin  $D_3$  experienced a 73% reduction in plasma hepcidin (geometric mean ratio: 0.27,  $P = 0.005$ ) compared to no change with placebo ( $P = 0.11$ ). Cytokines did not change significantly in either group.

**Conclusions** High-dose vitamin D significantly reduced plasma hepcidin concentrations in healthy adults 1 week post-dosing; no change was observed in inflammatory cytokines. These findings suggest that in the absence of inflammatory conditions, vitamin D may have a role in regulating iron recycling by acting directly on hepcidin, independent of changes in inflammatory markers.

#### 448 MEDITERRANEAN DIET PATTERN ADHERENCE AND LEUKOCYTE TELOMERE LENGTH IN NHANES 1999 – 2002

C Carr,<sup>2,3,1</sup> L Bazzano,<sup>2,3</sup> T Harlan,<sup>2,1</sup>. <sup>1</sup>Goldring Center for Culinary Medicine, New Orleans, LA; <sup>2</sup>Tulane University School of Medicine, New Orleans, LA; <sup>3</sup>Tulane University School of Public Health and Tropical Medicine, New Orleans, LA

10.1136/jim-2015-000035.450

**Purpose of Study** Studies have shown considerable health benefits with adherence to a Mediterranean diet pattern. Increased cellular longevity and antiaging properties have been attributed to leukocyte telomere length (LTL) maintenance. We examined this association using the National Health and Nutrition Examination Survey (NHANES) 1999–2002, a representative sample of the US non-institutionalized general population.

**Methods Used** Using nutrition recall and food frequency questionnaire data, we abstracted a seven-point Mediterranean diet score with categories for alcohol consumption, polyunsaturated/saturated fat ratio, fiber, poultry and dairy, fruits and vegetables, grains and legumes, and fish. Points were awarded for moderate consumption of alcohol, poultry and dairy and for above-median values in the other categories. Scores were regressed against leukocyte telomere to single copy gene (T/S) ratio, controlling for history of hypertension, high cholesterol, diabetes, CHF, CAD, angina, MI, and stroke; recent changes to diet or exercise program; gender, age, race/ethnicity, family income, and current smoking. Data analysis was performed using SAS 9.4.

**Summary of Results** Of 7827 NHANES 1999–2002 participants with telomere assay data, 440 provided sufficient nutrition recall and food frequency questionnaire response data to be included in our study (mean age 53 +/- 20; 42% male; 62% white). Our data demonstrated a statistically-significant positive trend for the association of Mediterranean diet score with leukocyte T/S ratio ( $\beta=0.02$ ,  $p=0.05$ ).

**Conclusions** This is the first study to examine the association between Mediterranean diet pattern adherence and leukocyte telomere length in a representative sample of the US population. Our findings indicate that Mediterranean diet pattern adherence is positively associated with LTL, suggesting a potential role in successful aging.

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#### EXPLORING THE IMPACT OF HEALTHY NEIGHBORHOOD FOOD ACCESS ON CHILDREN'S DIET

L Futrell Dunaway,<sup>1</sup> T Carton,<sup>2</sup> AR Mundorf,<sup>1</sup> K Theall<sup>1</sup>. <sup>1</sup>Tulane University, New Orleans, LA; <sup>2</sup>Louisiana Public Health Institute, New Orleans, LA

10.1136/jim-2015-000035.451

**Purpose of Study** To examine the impact of food access on diet among a cross-sectional sample of children from a multilevel, community based study.

**Methods Used** As part of a study examining neighborhood influences on children's health disparities, 199 children ages 4 to 14 years and their families were recruited through local schools in an inner-city community in New Orleans, Louisiana. Data from a caregiver survey was geocoded and a multilevel data system of children nested within both household and neighborhood was created. The primary outcomes of interest were consumption of food (fruit, vegetables, sweets) and beverages (fruit juice, milk, soda). The primary exposure of interest was a small food store or supermarket within a given perimeter of the child's household.

**Summary of Results** Younger children and males were more likely to consume fruits while children, with mothers

with less than a high school education were more likely to consume sweets. Consumption of dinner at home more than 5 times per week was significantly correlated with increased fruit and vegetable consumption and decreased sweets consumption. At the neighborhood level, access to a small store within 500 m and supermarket within a 1000 m perimeter around the child's household were not significantly associated with children's food and beverages consumption. However, children who had access to fast food within 500 m were less likely to consume fruits and vegetables.

**Conclusions** Difference in food and beverage consumption in children was found for certain individual and maternal demographic variables and at the neighborhood level. Presence of a food store within a radius of the child's household was not significantly correlated with consumption, however there seem to be two significant factors affecting this relationship—the mothers work status and meals consumed at home. This study sheds light on the complex relationship between neighborhood food availability and dietary behavior among children and within households.

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#### A VISUAL TOOL TO REDUCE JUICE AND SUGAR-SWEETENED BEVERAGES ASSISTS PROVIDERS IN EDUCATING PATIENTS

C SanGiovanni,<sup>1</sup> L Mogilner<sup>2</sup>. <sup>1</sup>Medical University of South Carolina, Charleston, SC; <sup>2</sup>Icahn School of Medicine at Mount Sinai, New York City, NY

10.1136/jim-2015-000035.452

**Purpose of Study** Heavy consumption of juice and sugar-sweetened beverages has been associated with many adverse effects in children. Educating patients and families may be helpful in decreasing children's consumption of these beverages. This study tested the hypothesis that a tool visible to providers, patients and families would remind providers to discuss limiting juice and sugar-sweetened beverages and assist them in counseling families.

**Methods Used** Posters with information regarding the amount of sugar in popular beverages were hung in all exam rooms in a pediatric resident continuity clinic in East Harlem, New York. Eighteen months later, physicians were asked to estimate their counseling behaviors and use of this tool pre and post-intervention on a scale of 0 (not at all) to 4 (all the time). A paired t-test was performed to analyze providers' answers regarding how often they addressed limiting juice and sugar-sweetened beverages with patients and families pre and post intervention.

**Summary of Results** Thirty-nine providers including 31% PGY-1's, 26% PGY-2's, 18% PGY-3's, and 25% attendings completed the questionnaire, and 26 providers had practiced in the clinic prior to the educational intervention. There was a significant difference between providers' estimate of their pre and post intervention behaviors with a pre-intervention mean score of 1.54 and post intervention mean of 2.46 ( $p<0.01$ ). In addition, 23% of the providers reported the posters were "necessary in counseling patients/families" and 66.7% reported the posters were "very helpful in counseling patients/families" to limit

sugar-sweetened beverages. Lastly, 72% physicians reported patients/families asked “occasionally” about the information in the posters, 15.4% said patients/families asked “most of the time,” and 5% reported patients/families asked “all of the time.”

**Conclusions** A simple intervention of posting information about juice and sugar-sweetened beverages in a continuity clinic made a significant difference in a self-estimate of how often providers discussed limiting these beverages with patients. The posters assisted providers in counseling families but also prompted families to engage providers in this important discussion.

451 **SEVERE ALLERGIC COLITIS CAN PRESENT WITH ELEMENTAL FORMULA FEEDS IN INFANTS WITH SEVERE INTESTINAL FAILURE: A CASE SERIES**

A Sitabkhan, AG Moreira, N Mittal, R Jacob, R Tragus, C Blanco. *UTHSCSA, San Antonio, TX*

10.1136/jim-2015-000035.453

**Purpose of Study** To investigate if infants with severe intestinal failure presenting with bloody stools while on elemental formula develop allergic colitis secondary to the enteral fat source. The clinical details, histological findings and responses to treatment of this uncommon presentation are summarized.

**Methods Used** We report a series of infants with severe intestinal failure (defined as TPN dependence for >60 days and functional/anatomic short bowel) who developed allergic colitis despite feedings regimens of elemental formulas. All patients were evaluated for compassionate use of IV fish oil and had allergic colitis confirmed by colonoscopy at University Hospital between July 2011 and May 2015. Patient demographics, nutritional details, laboratory, and diagnostic results were collected. We compared the lipid source of each elemental formula utilized. Outpatient records were reviewed to evaluate outcomes up to 2 years post discharge for patients whose data was available.

**Summary of Results** Five infants with a gestational age of 32±6 weeks developed allergic colitis at a postnatal age of 158±96 days while on elemental formulas; 4/5 infants developed symptoms of bloody stools and feeding intolerance after weaning from maternal/donor breast milk. The initial histology reports while on elemental formulas containing plant-based lipids uniformly confirmed “moderately severe colitis with increased intraepithelial eosinophils”. Once the plant-based fat source was removed from the diet by utilizing custom made formulas, intestinal biopsies revealed resolution of allergic colitis. As expected, serum eosinophilia was absent in 4/5 children despite a histologic diagnosis of allergic eosinophilic colitis. Upon discharge, 2 of the 5 infants were able to tolerate fish or canola oils as a source of enteral fat. Though canola oil is plant-based, it is thought to have a lower potential for allergenicity when compared to sunflower, safflower, and soy derived oils.

**Conclusions** Infants with severe intestinal failure can develop allergic colitis even on elemental formulas. Plant-based lipids should be considered as a potential allergen in infants with severe intestinal failure who develop bloody stools

Perinatal Medicine I  
Concurrent Session  
2:00 PM  
Friday, February 19, 2016

452 **EFFECTS OF MATERNAL VITAMIN D SUPPLEMENTATION ON PLACENTAL GENE EXPRESSION**

EV Schulz,<sup>1</sup> L Cruze,<sup>2</sup> W Wei,<sup>1</sup> J Gehris,<sup>1</sup> C Wagner,<sup>1</sup> E Garrett-Mayer<sup>1</sup>. <sup>1</sup>Medical University of South Carolina, Charleston, SC; <sup>2</sup>MUSC, Charleston, SC

10.1136/jim-2015-000035.454

**Purpose of Study** Pregnancy is a critical developmental window in which maternal dietary supplementation with vitamin D appears to have a pronounced effect on fetal health outcomes. In a recent NICHD trial investigating serum levels of active, hormonal vitamin D during pregnancy, maternal levels were found to be twice the normally observed levels of non-pregnant women. To elucidate the purpose of this specialized vitamin D activity in pregnancy we investigated the role of maternal 25-hydroxyvitamin D [25(OH)D], the nutritional indicator of vitamin D status, in relation to placental maintenance and, specifically, expression of placental gene targets related to angiogenesis.

**Methods Used** A focused analysis of two placental genes related to angiogenesis was conducted in 43 subjects enrolled in a randomized controlled trial supplementing either 400 IU or 4400 IU of vitamin D per day during pregnancy. The placental mRNA was isolated from biopsies within one hour of delivery, followed by quantitative PCR. Associations between genes and 25(OH)D concentrations were estimated by linear regression fit using a Bayesian model.

**Summary of Results** We found that placental growth factor (PGF) and vascular endothelial growth factor (VEGF) gene expression are positively correlated with maternal vitamin D status. The corresponding correlation coefficients with 25(OH)D concentrations are 0.25 and 0.24 for PGF and VEGF, respectively. The posterior probability supporting a positive correlation between PGF and maternal vitamin D status is 0.95 and the posterior probability supporting a positive correlation between VEGF and maternal vitamin D status is 0.92.

**Conclusions** Our findings support a positive association between maternal vitamin D levels and gene expression of PGF and VEGF. This association may demonstrate a vitamin D supplementation impact on gene transcription in the placenta, suggesting the possibility to manipulate placental gene expression to improve placental health and maintenance.

453 **PLATELET ACTIVATING FACTOR REGULATES PRO-INFLAMMATORY SIGNALING IN HYPEROXIA-INDUCED LUNG INJURY**

A Yee, T Jilling, C Ren, N Ambalavanan. *University of Alabama at Birmingham, Birmingham, AL*

10.1136/jim-2015-000035.455

**Purpose of Study** To assess the role of platelet activating factor (PAF), a potent pro-inflammatory mediator, in neonatal hyperoxia-induced inflammation and inhibition of lung development (IAD) in mouse (a model of BPD). We previously found that hyperoxia increased expression of PAF receptor (PTAFR) and other components of the PAF biosynthetic pathway both *in vivo* in wild type (WT) mice as well as *in vitro* in mouse macrophages. We therefore hypothesized that mice with decreased PAF signaling (PTAFR KO) will have attenuated hyperoxia-induced inflammation and IAD, while the mice with increased PAF signaling (PLA2G7 KO lacking PAF acetylhydrolase which breaks down PAF) would have increased inflammation and IAD.

**Methods Used** WT, PTAFR KO, and PLA2G7 KO newborn mice were exposed to either room air (21% O<sub>2</sub>) or hyperoxia (85% O<sub>2</sub>) for 10 days (n=78). Pulmonary function testing (PFT) was done using flexiVent. Lungs were processed for RNA and protein isolation, or were inflation-fixed for histology. mRNA levels of cytokines, known mediators of BPD pathogenesis and participants of PAF signaling were quantified by quantitative PCR (qPCR). Lung development was evaluated using radial alveolar counts, mean linear intercepts, and automated morphometry. Data analysis was done using 2-way ANOVA.

**Summary of Results** PFT: Compliance was increased in PLA2G7 KO at 21% O<sub>2</sub> as compared to all other groups. Compliance was decreased, and similar in all groups at 85% O<sub>2</sub> as compared to 21% O<sub>2</sub>. PLA2G7 KO had the lowest resistance in both 21% and 85% O<sub>2</sub>. Histology: Compared to WT, alveolar development in 85% O<sub>2</sub> was similarly affected in PLA2G7 KO while improvement was noted in PTAFR KO. qPCR: 85% O<sub>2</sub> increased expression of PTGS2 (rate-limiting enzyme in prostaglandin synthesis) and CXCL1 (plays a role in inflammation and chemotaxis) significantly more in PLA2G7 KO and significantly less in PTAFR KO as compared to WT. PLA2G2E was also increased in 85% but there was no difference between the 3 genotypes. TNF- $\alpha$  and Col1a1 were not statistically different among groups.

**Conclusions** PAF contributes to hyperoxia-induced inflammation as seen with increased expression of pro-inflammatory markers (PTGS2 and CXCL1) in mice with increased PAF signaling (PLA2G7 KO) and attenuated in mice with decreased PAF signaling (PTAFR KO).

#### 454 THE ROLE OF SURFACTANT PROTEIN A IN THE PREVENTION OF NECROTIZING ENTEROCOLITIS

CZ Aron, JL Alcorn. University of Texas at Houston, Houston, TX

10.1136/jim-2015-000035.456

**Purpose of Study** Necrotizing enterocolitis (NEC) is a devastating and poorly understood gastrointestinal disease seen in premature neonates. Surfactant protein A (SP-A) is a collectin primarily in the lung that plays important roles in host defense and innate immunity, and has immunomodulatory properties. We have shown in a rat model of NEC that oral purified human SP-A significantly reduced NEC with reduced levels of intestinal pro-inflammatory cytokines and intestinal levels of toll-like receptor (TLR4),

which plays a key role in the pathogenesis of NEC. To assess the role of SP-A in GI protection, we studied SP-A null mice (SPA<sup>-/-</sup>) in an established mouse model of NEC to address the hypothesis that SPA<sup>-/-</sup> mice are more susceptible to GI disease when exposed to NEC stress.

**Methods Used** Wild type (WT) and SPA<sup>-/-</sup> mice (day 4–6) were separated from dams and gavaged four times daily with 150  $\mu$ l formula (FF group). To induce NEC-like stress, one group was exposed to hypoxia (5% O<sub>2</sub>, 10 min) and hypothermia (ice, 2 min) three times daily (FH group). One group, was also gavaged with 5  $\mu$ g purified SP-A daily (FHS group). Mice sacrificed day 5 and ileum harvested for histologic and molecular analysis of TLR4 by western analysis, and IL-1 $\beta$  by ELISA.

**Summary of Results** WT and SPA<sup>-/-</sup> pups had similar cases of NEC in the FH group (65%,54%). SPA<sup>-/-</sup> mice had more NEC than WT in the FF group (53%, 23%). SPA<sup>-/-</sup> mice gavaged with SP-A (FHS group) had reduced NEC (33%). Expression of TLR4 was 2 times higher in SPA<sup>-/-</sup> pups without NEC stressors compared to WT (p<0.001). With NEC stress TLR4 levels decreased 50% (p <0.02) in pups gavaged with SP-A when compared to FH group. Interestingly, intestinal IL-1 $\beta$  levels in WT mice (3.8 pg/mg) excluded from NEC stress were higher than SPA<sup>-/-</sup> mice (1.2 pg/mg) (p<0.003) at one week of age, then higher in SPA<sup>-/-</sup> mice (2.7 pg/mg) compared to WT (1.9 pg/mg) (p< 0.003) in week 4. With NEC stressors, expression of IL-1 $\beta$  levels in the FHS group showed a 50% reduction when compared to the FF and FH groups (p <0.02).

**Conclusions** Without SP-A, TLR4 levels and inflammatory markers such as IL-1 $\beta$  are increased in the neonatal GI tract. Furthermore, exogenous oral SP-A reduces cases of NEC, TLR4 levels and inflammation in a mouse model of experimental NEC. Our results suggest a role for SP-A in modulation of gastrointestinal inflammation in the neonate.

#### 455 OXIDATIVE STRESS IMPAIRS PLACENTAL EFFICIENCY IN A RODENT MODEL OF REDUCED UTERINE PERFUSION

CJ Lasley, N Ojeda. University of Mississippi Medical Center, Jackson, MS

10.1136/jim-2015-000035.457

**Purpose of Study** Epidemiological and experimental studies showed that reduced uterine perfusion resulted in growth-restricted offspring. However, the mechanistic pathways involved in this condition are not totally understood. We investigated whether oxidative stress affected placental efficiency in offspring exposed to reduced uterine perfusion.

**Methods Used** We used a rat model of growth-restricted offspring induced by reduced uterine perfusion at 14 days of gestation. A subset of animals received antioxidant treatment with Tempol, a free radicals scavenger, via drinking water, simultaneously with reduced uterine perfusion. At 19 days of gestation fetuses and placentas were excised by cesarean section followed by collection of blood and tissue for molecular assessment. Thiobarbituric acid reactive substances were used to measure placental lipid peroxidation which is a marker of oxidative stress. GraphPad software



was used for statistical analysis of variance among groups and correlation between variables with significance set at  $P < 0.05$ .

**Summary of Results** Reduced uterine perfusion resulted in growth-restricted fetuses with significantly lower fetal weight ( $1.30 \pm 0.11$  g), placental weight ( $0.55 \pm 0.02$  g), and placental efficiency (2.4  $\pm$  0.2 ratio), and higher placental lipid peroxidation ( $44.2 \pm 6.8$  pg/ul) compared to other groups ( $P < 0.05$ ). Antioxidant treatment completely reverted changes in lipid peroxidation, fetal and placental weight and placental efficiency in fetuses exposed to reduced uterine perfusion. Analysis of correlation showed negative correlation between fetal weight and placental lipid peroxidation (Spearman  $r = -0.6960$ ), and between placental efficiency and placental lipid peroxidation (Spearman  $r = -0.6936$ ) in growth-restricted fetuses and no correlations in other groups.

**Conclusions** These results suggest that oxidative stress is involved in fetal and placental changes observed in growth-restricted offspring exposed to reduced uterine perfusion. These results could help to develop new treatment strategies for pregnancies complicated with intrauterine growth restriction.

#### 456 INTRAPERITONEAL LIPOPOLYSACCHARIDE DISRUPTS EARLY NEURAL DEVELOPMENTAL PROGRAMS AND IMPAIRS BEHAVIORS IN NEONATAL RATS

A Bhatt, Y Pang, L Fan, H Zhu, X Dai. *University of Mississippi Medical Center, Jackson, MS*

10.1136/jim-2015-000035.458

**Purpose of Study** Perinatal Infection and/or inflammation are among the well-recognized risk factors of brain injury including white matter injury (WMI) resulting in neurodevelopmental disabilities in extreme premature infants. The primary neuropathology of WMI includes selective injury to oligodendrocyte (OL) progenitor cells, myelination deficit, and associated microglia activation. Utilizing multiple *in vitro* and *in vivo* models, we have investigated how bacteria endotoxin (lipopolysaccharide, LPS)-induced neuroinflammation causes OL development and myelination disturbances. The drawback of this model, however, is that the route of LPS administration is clinically less relevant. We aim to re-characterize neonatal brain injury using a more clinically relevant LPS route, i.e., by intraperitoneal (i.p.) injection.

**Methods Used** Rat pups at postnatal day 3 (P3) received intraperitoneal injection of LPS (1 mg/kg) or saline. We examined brain injury, inflammatory response, cell death, OL development and neurobehavioral outcome at different time points after LPS treatment.

**Summary of Results** LPS (i.p.) exposure on P3 resulted in a global activation of microglia ( $p < 0.01$  vs control,  $n = 6$ ) with unique morphological transformation, significant decrease in programmed cell death ( $p < 0.01$  vs control,  $n = 6$ ) in the P6 rat brain, significant increase of OLs in the corpus callosum ( $p < 0.01$  vs control,  $n = 8$ ) and robust neural progenitor cell proliferation in subventricular zone and the dentate gyrus of hippocampus ( $p < 0.05$  vs control,  $n = 8$ ) on P21. Additionally, deficits in communication and

cognition were noted in rats at P40 ( $p < 0.05$  vs control,  $n = 8$ ).

**Conclusions** Contrary to our initial hypothesis we did not observe any signs of cell injury and myelination deficit in the white matter of LPS i.p. injected rat pups, the findings which were eminent in the model of LPS i.c. injected pups. We speculate that change in phenotype of LPS-activated fetal microglia disrupts early neural developmental programs via stimulating excessive neurogenesis and oligodendrogenesis, reducing naturally occurring PCD, and altering neural differentiation, leading to abnormal circuitry maturation and ultimately impaired behaviors in rats.

#### 457 NEURODEVELOPMENTAL OUTCOME OF ELBWI TREATED WITH INTRAVITREAL BEVACIZUMAB

M Rydzewska, A Rifai, R Gulati, FG Eyal, M Zayek. *University of South Alabama, Mobile, AL*

10.1136/jim-2015-000035.459

**Purpose of Study** Posterior aggressive form of retinopathy of prematurity (ROP) is a common complication in the extremely-low birth infant (ELBW). Recently, intravitreal injection of bevacizumab (IVB) has been shown to be more effective than laser photocoagulation therapy for posterior form of ROP. Despite the fact that IVB could be a promising therapy and may preserve part of the peripheral retina, bevacizumab is anti-VEGF and may affect neurodevelopmental (ND) outcome. The aim of this study is to determine whether the use of IVB for the treatment of ROP in ELBW infants is associated with increased rates of adverse ND outcome.

**Methods Used** We retrospectively extracted medical data on 446 ELBW infants born from 2009 through 2014 with gestational age (GA)  $< 27$  weeks. Only 378 infants survived beyond 29 weeks PMA (postmenstrual age) and received a retinal exam. We compared the ND outcome of infants who received retinal therapy ( $n = 89$ ), laser vs. IVB, using  $\chi^2$  test and ANOVA.

**Summary of Results** The table below summarizes the characteristics, NICU and ND outcomes of infants in each

**Abstract 457 Table 1** Patient Demographics, Morbidities after the treatment and neurodevelopmental outcomes as evaluated by Bayley Scale of Infant Development at 18 mo

	Laser only	IVB
N	55	34
GA weeks	23 (22–24)	23 (22–25)
BW grams	551 (476–611)	492 (435–573)*
BPD mod-severe	50 (91)	34 (100)
Pulmonary hypertension	5 (9)	5 (15)
Death before discharge	2 (4)	2 (6)
N (followed at 18 month)	35	10
cognitive score $< 85$	18 (51)	5 (50)
language score $< 85$	23 (66)	6 (60)
motor score $< 85$	24 (68)	5 (50)
Cerebral palsy	16 (46)	5 (50)

\* $p < 0.05$ . Values are n (%) and median (interquartile range)

treatment group. 18-month assessment is not yet complete.  
**Conclusions** IVB for the treatment of threshold ROP was not associated with worse ND outcome. ND assessment is still being performed on the remaining infants.

458 **LEFLUNOMIDE ATTENUATES NEONATAL HYPEROXIC LUNG INJURY VIA BOTH ARYL HYDROCARBON RECEPTOR – DEPENDENT AND - INDEPENDENT MECHANISMS**

B Shivanna, S Zhang, A Patel, B Moorthy. *Baylor College of Medicine, Houston, TX*

10.1136/jim-2015-000035.460

**Purpose of Study** Hyperoxia contributes to the development of bronchopulmonary dysplasia (BPD) in human preterm infants. We observed that aryl hydrocarbon receptor (AhR) -deficient primary fetal human pulmonary microvascular endothelial cells (HPMEC) have an increased susceptibility to hyperoxic injury. Whether AhR activation is sufficient to protect HPMEC against hyperoxic injury is unknown. Leflunomide (LEF), a FDA approved immunomodulatory drug that is used to treat humans with rheumatoid arthritis, is known to activate AhR. Therefore, we tested the hypothesis that LEF protects HPMEC against hyperoxic injury via activation of the AhR.

**Methods Used** HPMEC were treated with varying concentrations of LEF and exposed to air or hyperoxia (95%) for up to 48 h, following which the cells were harvested to determine cell viability, hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) production, and AhR activation. Additionally, HPMEC were transfected with siRNA to knockdown AhR, following which the cells were treated with LEF and exposed to air or hyperoxia to determine the exact mechanisms by which LEF modulates hyperoxic injury.

**Summary of Results** LEF activated AhR in a dose dependent manner. Interestingly, LEF increased cell viability and decreased H<sub>2</sub>O<sub>2</sub> production both in air and hyperoxic conditions. Statistical analyses suggested that LEF had an interaction with hyperoxia for the dependent variables, cell viability and H<sub>2</sub>O<sub>2</sub> production. Our AhR knockdown studies suggested that although the protective effects of LEF against oxygen toxicity decreased in AhR-deficient conditions, the oxygen toxicity continued to be attenuated in AhR-deficient cells treated with LEF.

**Conclusions** LEF attenuates hyperoxic injury in fetal HPMEC via both AhR-dependent and -independent mechanisms. Our results indicate that LEF is a potential therapeutic drug for the management of BPD in human preterm infants.

459 **VARIABILITY OF THE FINNEGAN SCORING SYSTEM IN MONITORING INFANTS WITH NEONATAL ABSTINENCE SYNDROME**

A Christian, K Ibonia, P Westgate, E Gomez, H Bada. *University of Kentucky, Lexington, KY*

10.1136/jim-2015-000035.461

**Purpose of Study** To determine factors associated with the variability and severity of Finnegan scores in infants diagnosed with Neonatal Abstinence Syndrome (NAS).

**Methods Used** We reviewed our experience of using Finnegan scores for babies with NAS admitted to the neonatal intensive care unit (NICU). From the electronic medical records, we derived all Finnegan scores for each baby with NAS from July 1<sup>st</sup> to December 31<sup>st</sup> 2014. The following factors were analyzed as to their effect on the variability of Finnegan scores: daily patient census, time of day (noon to 7 PM, 7 PM to midnight, midnight to 7 AM and 7 AM to noon), day of the week (weekday versus weekend), and nurses assigning scores. Statistical methods include descriptive statistics and multivariate linear regression models accounting for within-baby correlation of scores.

**Summary of Results** A total of 9,198 observations (Finnegan scores) from 166 babies and 336 nurses were analyzed. The number of observations per baby ranged from 1 to 148 with a median of 55 and mean (SD) of 52 (40). The number of scores per nurse ranged from 1 to 180, with a median of 17, and mean (SD) of 27 (29). Patient census ranged from 39 to 93 with median of 76 and mean (SD) of 75 (11). 29% of scores were done during the weekend. Regression results showed that daily census, time of day, and day of week were not significant predictors of Finnegan scores. However, adjusting for these three factors, the mean Finnegan scores significantly differed across nurses ( $p < 0.0001$ ). Nursing explained 14% of the variability of the Finnegan Scores.

**Conclusions** The results call for more structure in training healthcare personnel and regular assessments of reliability in scoring of babies with NAS. We have recently accomplished training of personnel in Finnegan scoring with a future plan to analyze changes in variability of scoring post training.

460 **IMPACT OF HYPERGLYCEMIA AND PREMATURETY ON NEPHROGENESIS IN A BABOON MODEL**

D Callaway,<sup>1</sup> C Blanco,<sup>1</sup> J Jordan,<sup>1</sup> E Dick,<sup>2</sup> L McGill-Vargas<sup>1</sup>. <sup>1</sup>UTHSCSA, San Antonio, TX; <sup>2</sup>Texas Biomedical Research Institute, San Antonio, TX

10.1136/jim-2015-000035.462

**Purpose of Study** At the time of premature birth, nephrogenesis is incomplete and has been cited as a possible etiology for increased renal pathologies in adulthood. Furthermore, hyperglycemia following preterm birth has unknown consequences on kidney development. This is the first study to evaluate the combined effects of hyperglycemia and prematurity on nephrogenesis.

**Methods Used** Baboons were delivered prematurely (67% gestation; n=9) or at term (n=6) and survived for 2–3 weeks. Preterm animals were classified by glucose control during the first 5 days of life: preterm normoglycemic (PtN; target serum glucose 50–100 mg/dL) and preterm hyperglycemic (PtH; target serum glucose 150–250 mg/dL). Vitals and serum chemistry were assessed daily. Kidneys from both preterm groups and term controls were assessed histologically for glomeruli number, maturity, size, and morphology. Kidney lysates were evaluated for

oxidative damage with a marker for lipid peroxidation, 4-hydroxynonenal (4-HNE).

**Summary of Results** Despite elevated mean glucose levels in PtH animals compared to PtN ( $168.2 \pm 9.33$  vs  $69.5 \pm 3.18$ ,  $p < 0.0001$ ) during the first week of life, no glucosuria was present in either group. There were no persistent differences in vital signs or serum chemistry to suggest significant distress or acute kidney injury. Histological examination of kidneys revealed decreased glomeruli numbers and increased renal corpuscle area in preterm groups compared to term. With regards to glomerular maturity, PtH kidneys in comparison to PtN had a 30% reduction in nephrogenic zone width ( $p < 0.0001$ ) and 240% increase in stage II and III mature glomeruli ( $p < 0.05$ ). Immunoblots demonstrated 60–75% higher levels of 4-HNE in PtH kidneys compared to both PtN and term ( $p < 0.05$ ).

**Conclusions** Premature baboons have a reduced number of mature nephrons but larger renal corpuscle area compared to term baboons. PtH compared to PtN baboons demonstrated accelerated glomerular maturation without any sustained clinical differences. However, 4-HNE was significantly increased in the PtH group, indicating that hyperglycemia of prematurity increases oxidative stress within the kidney tissue and could contribute to the development of adult renal pathologies in surviving preterm infants.

## Pulmonary and Critical Care Concurrent Session

2:00 PM

Friday, February 19, 2016

### 461 REDUCTION OF CENTRAL LINE ASSOCIATED BLOOD STREAM INFECTIONS (CLA-BSI) AFTER ADOPTION OF CENTRAL LINE INSERTION AND MAINTENANCE PROCEDURES

TG Carroll,<sup>1</sup> L Perron<sup>2</sup>. <sup>1</sup>University of Oklahoma Health Science Center, Oklahoma City, OK; <sup>2</sup>The Children's Hospital at OU Medical Center, Oklahoma City, OK

10.1136/jim-2015-000035.463

**Background** Central venous lines (CVL) are an important component in the treatment of pediatric patients. However, CVLs are associated with complications, most importantly central line associated bloodstream infections (CLA-BSI). CLA-BSI's are a major cause of mortality, morbidity, increased length of stay and unreimbursed health care costs. Over the last 7 years, the Children's Hospital Association (CHA) has developed strict evidence-based insertion and maintenance guidelines for CVLs that have reduced member hospitals CLA-BSI rates from 6.6 per 1000 line days to 1 per 1000 line days. This reduction has led to 4300 CLA-BSI's prevented, 515 deaths prevented and over 150 million dollars saved amongst member institutions. This quality improvement project evaluated if the strict adoption of the CHA Pediatric Intensive Care Unit (PICU) CLA-BSI Collaborative CVL insertion and maintenance guidelines would reduce the overall rate of CLA-BSI in the Children's Hospital (TCH) at OU Medical Center PICU.

**Methods Used** Over a six-month period beginning in October 2012, CHA protocols were in-serviced to physicians and staff. The process required ordering and stocking 2 central line carts, insertion checklists, and protocols for weekly CVL dressing and tubing changes. CHA protocols required strict insertion and maintenance guidelines that were implemented and audited for compliance

**Summary of Results** In 2011, prior to implementation of CHA guidelines, TCH PICU had 2,684 central line days and 9 CLA-BSI's, which is equivalent to a rate of 3.4 CLA-BSI per 1000 line days. In 2014, after strict implementation of the CHA CLA-BSI collaborative CVL insertion and maintenance protocols, the CLA-BSI rate dropped to 3 CLA-BSI's total or 0.9 per 1000 line days. This reduction occurred despite increase in CVL usage by 25% in 2014 compared to 2011. This improvement dropped un-reimbursable health care costs in the TCH PICU from \$352,000 in 2011 to \$117,000 in 2014.

**Conclusions** Given the significant morbidity and mortality associated with CLA-BSI in the PICU, the implementation of the CHA protocols has benefited TCH patients greatly.

### 462 HOUSEHOLD PROXIMITY TO WATER AND RISK OF NONTUBERCULOUS MYCOBACTERIA IN CHILDREN WITH CYSTIC FIBROSIS

J Bouso,<sup>1,2</sup> J Burns,<sup>1</sup> O Elidemir<sup>2,1</sup>. <sup>1</sup>Florida State University, Pensacola, FL; <sup>2</sup>Nemours Children's Clinics, Pensacola, FL

10.1136/jim-2015-000035.464

**Purpose of Study** Nontuberculous mycobacteria (NTM) is an emerging group of pathogens that while ubiquitous in nature has a particular affinity for patients with cystic fibrosis (CF). Although NTM acquisition may present as asymptomatic colonization, it can also lead to life-threatening disease. Delineating risk factors within the CF population will not only help categorize those more likely to acquire NTM, but may also influence life choices in families of CF patients if such risk factors are modifiable. It is well known that open water is a reservoir for NTM and that rates of infection correlate directly with levels of humidity. The aim of our study was to determine if there is an association between household proximity to water and NTM acquisition. We hypothesized that CF patients who live closer to water would be more likely to acquire NTM.

**Methods Used** An IRB approved retrospective chart review was completed of all CF patients at the CF Foundation accredited center of Nemours Children's Clinic in Pensacola, Florida. Inclusion criteria required at

**Abstract 462 Table 1** Closest distance from household address to water (oceans, bays, rivers, streams, lakes, ponds)

NTM status	N	Mean Distance (m)	Std. Dev. (m)	Std. error mean (m)
Negative	35	742.25	566.39	95.73
Positive	6	248.31	128.70	52.54

p<0.01

least two AFB sputum cultures and a consistent home address during the study period of 2012–2015. The straight-line distance from each patient's home to the nearest natural water source was determined using ArcMap®, a Geographic Information System. The mean closest distance to water was compared for NTM positive vs NTM negative patients by non-parametric Mann Whitney U test.

**Summary of Results** Of the 41 patients who met inclusion criteria, 6 tested positive for NTM with 100% of these patients growing *Mycobacterium avium complex*. The mean household distance to water for patients with NTM (248.31 m) was significantly less when compared to those negative for NTM (742.25 m);  $p=0.004$ .

**Conclusions** In our geographic area, children with CF who live closer to water are more likely to acquire NTM. Therefore, living further from natural water sources may be beneficial for patients with CF. Future studies in other geographic regions are needed to determine if these results are generalizable.

#### 463 EFFECT OF MOBILE HEALTH TECHNOLOGY ON POSITIVE AIRWAY PRESSURE ADHERENCE IN PATIENTS WITH SLEEP APNEA

KJ Pak,<sup>1</sup> L Seoane,<sup>1,2</sup> J Bakker,<sup>3</sup> S Bertisch,<sup>4</sup> C Pham,<sup>1</sup> N McNaughton,<sup>2</sup> J Park,<sup>2</sup> K Severinsen,<sup>2</sup> LA Bazzano<sup>5,1</sup>. <sup>1</sup>Ochsner Clinic Foundation, New Orleans, LA; <sup>2</sup>University of Queensland, Brisbane, QLD, Australia; <sup>3</sup>Brigham & Women's Hospital, Boston, MA; <sup>4</sup>Beth Israel Deaconess Medical Center, Boston, MA; <sup>5</sup>Tulane University, New Orleans, LA

10.1136/jim-2015-000035.465

**Purpose of Study** Mobile health strategies are cost-effective in improving healthy behaviors such as smoking cessation, but literature regarding effects on CPAP adherence is limited. This study, investigates whether texting improves CPAP compliance.

**Methods Used** Patients with newly diagnosed sleep apnea (<6 months) were randomized into either the usual treatment (n=25) or intervention group (n=25). Individuals completed questionnaires including SEMSA (Self-Efficacy Measure for Sleep Apnea), Epworth Sleepiness Scale (ESS) and FOSQ (Functional Outcomes of Sleep Questionnaire) at baseline, 4 weeks and then 8–12 weeks. The intervention involved surveillance texts to address various issues (mask fit, irritation, sleep disturbance, claustrophobia, self-efficacy, machine troubleshooting), and texts were sent at baseline, day 2, then every week until week 8. Additional texts targeting individual barriers per questionnaire responses were sent at the different time points. Data were analyzed by two-way analysis of variance.

**Summary of Results** Device adherence (% change in nights used  $\geq 4$  hours) compared to initial time point) was significantly greater in patients receiving texts (+57.6%, +54.7%) versus those with usual care (+3.4%, -17.3%) at the 2<sup>nd</sup> and 3<sup>rd</sup> time points, respectively ( $p=0.05$ ). Post-hoc subgroup analysis of patients with baseline non-compliance, showed significantly improved adherence with texts (+142.8%, +148.9%) compared to those with usual treatment (+3.9, -36.6) ( $p=0.03$ ). Mean SEMSA

self-efficacy scores were greater with intervention at the three time points (control=3.1, 3.0, 3.4; intervention=3.4, 3.5, 3.5) ( $p=0.002$ ). ESS scores, however, were higher with texts (control=11.31, 7.50, 7.63; intervention= 14.3, 12.0, 11.5) ( $p=0.003$ ). FOSQ scores were not significantly different.

**Conclusions** Supportive text messages significantly improved compliance over 8–12 weeks. Targeted texts may help with self-efficacy, but texts did not reduce ESS significantly as compared to control.

#### 464 ALVEOLAR MACROPHAGES FROM HIV-1 TRANSGENIC RATS DEMONSTRATE ABNORMAL BUT REVERSIBLE POLARIZATION

B Staitieh,<sup>1</sup> E Egea,<sup>1</sup> X Fan,<sup>1</sup> WA Neveu,<sup>1</sup> DM Guidot<sup>1,2</sup>. <sup>1</sup>Emory University, Atlanta, GA; <sup>2</sup>Atlanta VA, Decatur, GA

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**Purpose of Study** Classically activated, or M1 alveolar macrophages, require GM-CSF signaling and are effector cells of the innate immune system that perform key functions such as phagocytosis and pathogen killing. Alternatively activated, or M2 alveolar macrophages, are associated with wound-healing. Macrophage activation is known to be a dynamic process, but diseases such as HIV infection, which is associated with impaired GM-CSF signaling, polarize the macrophage population toward an M2 state. It is unknown if this abnormal polarization is fixed or potentially reversible in individuals with HIV.

**Methods Used** We first isolated alveolar macrophages from HIV-1 transgenic rats and assessed the canonical M1 and M2 polarization markers iNOS and Arginase 1, respectively. We next assessed GM-CSF-Receptor- $\beta$  gene expression by PCR. Finally, we assessed expression of both polarization markers and GM-CSF-Receptor- $\beta$  after treating HIV-1 transgenic rat alveolar macrophages with GM-CSF *ex vivo*. In addition, we assessed the ability of GM-CSF treatment to restore phagocytic function in HIV-1 transgenic rat alveolar macrophages.

**Summary of Results** Alveolar macrophages from HIV-1 transgenic rats were skewed toward the M2 state and GM-CSF-Receptor- $\beta$  expression was decreased. In response to treatment with GM-CSF *ex vivo*, the polarization balance of the macrophage population closely resembles that of the wild type littermates. In addition, both GM-CSF-Receptor- $\beta$  expression and phagocytic function were restored by GM-CSF treatment.

**Conclusions** Our results suggest that the skewing of alveolar macrophages during chronic HIV-1 transgene expression toward the M2 state may be due to a decrease in GM-CSF signaling. Consistent with this interpretation, treatment with GM-CSF restores both polarization balance and M1 functionality, indicating that the skewing in chronic HIV infection may be reversible depending on the underlying milieu in the alveolar space. Further experiments are necessary to determine the mechanisms underlying the decrease in GM-CSF signaling and to better understand the implications of the abnormal M2 polarization for host immunity in individuals living with HIV.

465 **HIV-RELATED VIRAL PROTEINS IMPAIR NRF2 FUNCTION AND INCREASE OXIDATIVE STRESS IN ALVEOLAR MACROPHAGES**

E Egea,<sup>1</sup> X Fan,<sup>1</sup> B Staitieh,<sup>1</sup> DM Guidot<sup>1,2</sup>. <sup>1</sup>Emory University, Atlanta, GA; <sup>2</sup>Atlanta VA, Decatur, GA

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**Purpose of Study** Individuals living with HIV are at markedly increased risk for pneumonia, even when adherent to anti-retroviral therapy. HIV is associated with oxidative stress, glutathione (GSH) deficiency, and macrophage immune dysfunction within the alveolar space. HIV-related viral proteins, including gp120 and Tat, are toxic to cells and can induce oxidative stress even in the absence of the intact virus, but their mechanisms of action are poorly understood. We hypothesize that HIV-related proteins increase oxidative stress in the alveolar macrophage by suppressing the signaling of Nrf2, a key mediator of anti-oxidant defenses.

**Methods Used** NR8383 cells (a rat alveolar macrophage cell line) were treated for 3 days with gp120 (100 ng/ml) or Tat (10 ng/ml). Using flow cytometry, we then measured oxidative stress with CellRox Deep Red, and reduced free thiols levels, a surrogate marker for GSH, with Thioltracker. Finally, gene and protein expression of Nrf2 and two downstream Nrf2-ARE effectors, Glutamate-cysteine ligase catalytic subunit (GCLC) and NAD(P)H dehydrogenase [quinone] 1 (NQO1) were determined by qRT-PCR (Bio-Rad) and Western blot, respectively.

**Summary of Results** HIV-related viral proteins increased oxidative stress, decreased GSH levels, and impaired the expression of Nrf2 and its downstream effectors GCLC and NQO1 in alveolar macrophages.

**Conclusions** Our results suggest that exposure to HIV-related viral proteins increases oxidative stress in alveolar macrophages and that this increase can be explained, at least in part, by decreased GSH and inhibition of the Nrf2-ARE axis. Importantly, only a small fraction of alveolar macrophages are infected with virus in patients living with HIV, and therefore our results suggest that the defects in alveolar macrophage function that we previously identified in these individuals may be due to the direct effects of these viral proteins and not to viral replication *per se*.

466 **ALCOHOL INDUCES LUNG FIBROBLAST SENEESCENCE VIA INDUCTION OF DNMTS.**

WA Neveu,<sup>1</sup> ST Mills,<sup>1</sup> DM Guidot,<sup>1,2</sup> V Sueblinvong<sup>1</sup>. <sup>1</sup>Emory University, Atlanta, GA; <sup>2</sup>Atlanta VA, Decatur, GA

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**Purpose of Study** We previously determined that alcohol induces TGFβ1 and primes the lung for fibroproliferative disrepair following acute lung injury. Co-treatment of alcohol-fed mice with s-adenosylmethionine (SAME) attenuates this effect. We have shown that primary lung fibroblasts (PLF) from old mice have decreased Thy-1 expression, and Thy-1 expression can be suppressed by

TGFβ1-induced Thy-1 promoter hypermethylation. We hypothesized that alcohol induces fibroproliferation through TGFβ1-mediated Thy-1 promoter hypermethylation in lung fibroblasts, causing a decrease in Thy-1 expression. We sought to determine whether alcohol regulates Thy-1 promoter hypermethylation through activation of DNA methyltransferases (DNMTs) and effects of SAME on phenotype of alcohol-treated lung fibroblast.

**Methods Used** Mouse PLF were cultured ± alcohol (60 mM) ± SAME (250 μM) for 24 hrs at which time Thy-1, DNMT1, DNMT3a, and DNMT3b gene expression, DNMT activity, and Thy-1 promoter methylation by qMethyl PCR were determined. Thy-1 protein expression was quantified after 72 hrs of culture in alcohol. Lungs from alcohol-fed rats (36% of total calories in a liquid diet) ± SAME (0.4% in water) for 8 weeks were analyzed for expression of the senescence markers p16, p19, SirT1, and SirT6.

**Summary of Results** Alcohol treatment suppressed Thy-1 gene and protein expression while induced DNMT1 and DNMT3b gene expression, global DNMT activity, and Thy-1 promoter hypermethylation. Concomitant treatment with SAME did not attenuate DNMT activity, it restored Thy-1 protein expression. Chronic alcohol exposure induced a senescent phenotype in the rat lung as shown by upregulation of p16, SAME attenuated this effect. SAME induced SirT6 gene expression which has been associated with inhibition of TGFβ1-mediated fibrosis.

**Conclusions** Alcohol induces a senescent phenotype in lung fibroblasts as reflected by decreased Thy-1 expression, and is associated with an increase in DNMT activity and Thy-1 promoter hypermethylation. SAME treatment restores Thy-1 expression independent of DNMT activation while inhibiting p16 expression in the lung. We speculate that alcohol-induced epigenetic modification of Thy-1 may have important implications in the 'alcoholic lung' and merits further investigation into the underlying mechanisms as they may represent novel therapeutic targets.

467 **INFECTIOUS COMPLICATIONS IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE RECEIVING BIOLOGIC THERAPY**

CD Ochoa, P Rajaram, S Tanukonda, RT Sadikot. Emory University, Atlanta, GA

10.1136/jim-2015-000035.469

**Purpose of Study** Biologic agents are increasingly used for the management of inflammatory bowel disease (IBD). A small but significant increase in the rate of infection has been demonstrated in patients on anti-TNF alpha therapy. This has been inconsistently demonstrated in the IBD population. The aim of this study is to describe the epidemiological data and characteristics of patients with IBD admitted to a major VA referral center.

**Methods Used** A retrospective analysis of IBD patients prescribed anti-TNF alpha therapy was conducted after obtaining IRB approval. Eligibility criteria included biopsy proven IBD and initiation of anti-TNF alpha therapy. ICU, floor and emergency department visits were reviewed to determine if treatment was initiated for suspected or

culture proven infection. Demographic data, additional therapies, number of hospitalizations, source of infection and comorbid conditions were reviewed.

**Summary of Results** We identified 55 patients with documented IBD initiated on anti-TNF alpha therapy. The median age of the population was 53. 91% of the cohort were men, 47% African American and 53% Caucasian. The most common comorbid conditions included diabetes, hypertension and respiratory disease. The average duration of therapy was 47.3 months. The overall rate of infection was 12 per 100 patient years of treatment (26 unique events). The rate of infection leading to admission was 6.5 per 100 patient years of therapy. The most common infections identified were respiratory (8 events) followed by genitourinary and gastrointestinal (both with 7 events). Frequently isolated organisms included *E. Coli* and *C. Difficile*. The rate of outpatient infection was similar at 5.5 events per 100 patient years of therapy. 6 patients were found to have recurrent infection, though no variable was independently associated with this outcome. 49% of the cohort received steroid therapy concurrently with anti-TNF alpha therapy. Those with infectious complications were likely to have diabetes and COPD as comorbid conditions (20% vs. 30% and 2.9% vs. 15%, respectively).

**Conclusions** This study found that IBD patients prescribed anti-TNF alpha therapy had infections at a rate higher than previously reported. These patients were likely to receive concurrent steroid therapy and carry the diagnoses of diabetes and COPD.

#### 468 E-CIGS FOR SMOKING CESSATION: META-ANALYSIS AND SUMMARY OF PROSPECTIVE STUDIES

M Orellana-Barríos, J Payne, RM Medrano-Juarez, S Yang, K Nugent.  
TTUHSC, Lubbock, TX

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**Purpose of Study** The use of electronic cigarettes (e-cigs) is increasing, but their use as a smoking cessation aid is controversial. E-cig related citations are increasing, but the number of randomized clinical trials (RCTs) or prospective studies (PSs) is small with variable methodology. This study constitutes a review of the literature on e-cigs use for smoking cessation, identifying RTCs for a meta-analysis and summarizing observational data via a narrative summary.

**Methods Used** A systematic PubMed search was performed for English-language articles, published between 2007 and Aug 2015 using the search terms within titles/abstracts: “Electronic cigarette\*”, “e-cig\*”, “electronic nicotine d\*”, “Electric cigarette\*”, “Electric nicotine d\*”. One author performed 2 searches (Jan 2015, Aug 2015) yielding 721 and 504 related citations, respectively. Another author reviewed the list and identified articles for inclusion based on titles/abstracts. Another author extracted the data. Ten citations were screened as RCTs; 6 were screened as PSs. Two articles were included in the meta-analysis and 4 articles in the PSs narrative summary.

**Summary of Results** The 2 RCTs had varied study arms, but both had subjects on nicotine or non-nicotine e-cigs. The combined OR for cessation was 2.02 (95% CI: 0.97–

4.22;  $p = 0.06$ ,  $I^2 = 0.00$ ) in favor of nicotine containing e-cigs. The combined 6-month intention-to-treat cessation rate was 8.79% and 4.62% for nicotine and non-nicotine e-cigs, respectively. The 4 PSs had significant heterogeneity in their methods, the type of e-cigs used, time to follow up, and populations (all adults). The average combined abstinence rate was 29.1% (6–18 months rates). The cessation rates are not statistically different among study groups ( $p = 0.213$ ). Only one study included a control group. All prospective studies have been performed in Italian populations.

**Conclusions** There are few comparable RCTs and PSs related to e-cigs use for smoking cessation, despite increasing number of citations. One RCT has compared e-cigs to other smoking cessation aids. There is no statistical difference in the rates of cessation between nicotine versus non-nicotine e-cigs. The reported cessation rates in PSs are higher than reported in RCTs. More RCTs comparing e-cigs to other cessation methods are needed.

#### 469 PPAR $\gamma$ MODULATES PINK1 IN HYPOXIA-EXPOSED HUMAN PULMONARY ARTERY SMOOTH MUSCLE CELLS

A Chaudhry, TC Murphy, CM Hart, DE Green. Emory University, Atlanta, GA

10.1136/jim-2015-000035.471

**Purpose of Study** Pulmonary hypertension (PH) is a progressive disorder that causes significant morbidity and mortality. Pulmonary artery smooth muscle cell (PASMC) proliferation, a key feature in the cellular pathogenesis of PH, has been recently linked to abnormalities in mitochondrial dynamics and respiration. Our lab recently demonstrated that the peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) ligand, rosiglitazone (RSG), attenuated PASMC proliferation by abrogating hypoxic reductions in the dual specificity phosphatase, PTEN (phosphatase and tensin homolog). PTEN regulates the mitochondrial serine/threonine kinase, PINK1 (PTEN-induced kinase) which preserves mitochondrial integrity and homeostasis through autophagic removal of damaged mitochondria. Therefore, the current study examines the hypothesis that hypoxia stimulates HPASMC proliferation through reductions in PTEN and PINK1 and that PPAR $\gamma$  activation attenuates proliferation by attenuating reductions in PTEN and PINK1.

**Methods Used** To model pathophysiological stimuli for HPASMC proliferation, selected HPASMC were exposed to hypoxia (1% O<sub>2</sub>) for 72 hours. PTEN and PINK1 protein and mRNA levels were measured using Western Blotting and qRT-PCR, respectively. Selected HPASMC were also transfected with an adenoviral PPAR $\gamma$ -expression plasmid (AdPPAR $\gamma$ , 10 MOI)  $\pm$  activation with 10 mM RSG. PTEN was silenced using siRNA and PINK1 mRNA levels were measured. HPASMC proliferation was measured with cell counting.

**Summary of Results** Hypoxia reduced PINK1 protein and mRNA levels. SiRNA-mediated depletion of PTEN reduced PINK1 levels and enhanced proliferation in normoxia-exposed HPASMC. In contrast, AdPPAR $\gamma$ -transfected HPASMC demonstrated increased

levels of PTEN and PINK1 in both normoxic and hypoxic environments.

**Conclusions** PPAR $\gamma$  plays a pivotal role in maintaining vascular homeostasis by regulating PTEN and PASMC proliferation. Hypoxia reduces PPAR $\gamma$  and PTEN causing reductions in the mitophagy protein, PINK1, and HPASMC proliferation. In contrast, increasing PPAR $\gamma$  attenuates reductions in PTEN and PINK1 and HPASMC proliferation. Ongoing studies will determine if reductions in PINK1 stimulate HPASMC proliferation by modifying mitochondrial dynamics or mitophagy.

## Renal, Electrolyte and Hypertension I

### Concurrent Session

2:00 PM

Friday, February 19, 2016

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#### AUGMENTATION OF INTRARENAL ANGIOTENSINOGEN PRODUCTION INDUCED BY CHRONIC ANGIOTENSIN II AND HIGH SALT INTAKE IN MICE LACKING TNF-ALPHA RECEPTOR TYPE 1 OR TNF-ALPHA RECEPTOR TYPE 2

EP Mehaffey, A Castillo, G Navar, DS Majid. *Tulane University School of Medicine, New Orleans, LA*

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**Purpose of Study** Chronic angiotensin II (AngII) treatment increases TNF- $\alpha$  generation in the kidney and enhances intrarenal angiotensinogen (AGT) formation. It has also been shown in-vitro that TNF- $\alpha$  suppresses AGT production in cultured human kidney cells. These conflicting findings may indicate differential activation of TNF-alpha receptors type 1 (TNFR1) and type 2 (TNFR2) signaling pathways. We tested the hypothesis that chronic elevation in AngII levels coupled with high salt (HS) intake reduces TNFR1 activity but enhances TNFR2 activity that induces cellular responses leading to increased formation of intrarenal AGT. **Methods Used** We assessed the renal and systemic responses to chronic infusions with AngII (25 ng/min; implanted minipump) with HS (4% NaCl) diets for 4 weeks in mice lacking TNFR1 receptors (TNFR1KO; n=7), mice lacking TNFR2 (TNFR2KO; n=6) and wild-type (WT; n=6) mice. Mean systemic blood pressure (SBP) was measured by tail-cuff plethysmography and 24-hour urine collections were done in metabolic cages throughout the treatment period. The urinary excretion rate of AGT was measured as a reflection of intrarenal generation of AGT using ELISA at baseline and at 2 and 4 week periods. Urinary sodium and potassium (UNaV, UKV) were measured with flame photometry.

**Summary of Results** Each group of mice had an increase in SBP after 4 weeks. The increase in SBP in response to AngII +HS was greater in TNFR1KO mice compared to WT mice (115 $\pm$ 3 vs 102 $\pm$ 2 mmHg, p<0.05), while the TNFR2KO had no difference from WT. uAGT increased in both WT mice (6 $\pm$ 3 to 46 $\pm$ 16 ng/24 hrs, p<0.05) and TNFR1KO mice (6 $\pm$ 2 to 167 $\pm$ 75 ng/24 hrs, p<0.05), but a greater increase was observed in TNFR1KO mice (0.05<p<0.1). TNFR2KO mice had no significant increase in uAGT (8 $\pm$ 7 to 65 $\pm$ 44 ng/24 hrs). UNaV increased equally in WT (118

$\pm$ 13 to 883 $\pm$ 121), TNFR1KO mice (96 $\pm$ 15 to 942 $\pm$ 86), and TNFR2KO mice (94 $\pm$ 8 to 733 $\pm$ 195) while no group experienced a change in UKV.

**Conclusions** The results suggest that TNFR1 expression mitigates the hypertensive response to chronic AngII infusion with high salt intake, likely by suppressing intrarenal AGT formation, while TNFR2 activity contributes to elevate intrarenal AGT.

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#### PRORENIN RECEPTOR IN COLLECTING DUCT MAINTAINS RENAL FUNCTION AND THE DEVELOPMENT OF ANGIOTENSIN II-DEPENDENT HYPERTENSION

V Reverte Ribo,<sup>1</sup> CB Rosales,<sup>1</sup> MR Gallaty,<sup>1</sup> D Seth,<sup>1</sup> AA McDonough,<sup>2</sup> M Prieto<sup>1</sup>. <sup>1</sup>Tulane University, New Orleans, LA; <sup>2</sup>Keck School of Medicine, Los Angeles, CA

10.1136/jim-2015-000035.473

**Purpose of Study** Prorenin, the inactive form of renin, is augmented in the collecting duct (CD) during Ang II-dependent hypertension. Binding of the prorenin receptor (PRR) to prorenin in the CD may increase local Ang II formation and ultimately sodium (Na<sup>+</sup>) reabsorption. To examine the functional relevance of the PRR on renal Na<sup>+</sup> homeostasis, we generated a novel mouse model with cell-type PRR specific deletion in the collecting duct (KO).

**Methods Used** Renal function was examined at 12–14-wk of age in anesthetized CT (N=8) and KO (N=6) male mice. Glomerular filtration rate (GFR) and renal blood flow (RBF) were determined by inulin and PAH acid clearances, respectively. To evaluate the contribution of PRR in the CD in the development of Ang II-dependent hypertension, we measured SBP and DBP by telemetry in CT (N=4–6) and KO (N=4–6) male mice during chronic Ang II infusion (400 ng/kg/min, for 14 d).

**Summary of Results** BW was similar between both KO and CT mice. Kidney weight (0.3 $\pm$ 0.04 g vs. 0.40 $\pm$ 0.02 g), glomeruli number (35.8 $\pm$ 2.7 glom/slide vs. 47.2 $\pm$ 2.3 glom/slide) and renal papillas were decreased (P<0.05) in KO compared with CT mice. KO mice exhibited half-fold increase urine flow (8.9 $\pm$ 1.4 vs. 5.8 $\pm$ 10.7 uL/min/Kw g) which was associated with a 38.5 % reduction in urine osmolarity (581 $\pm$ 65 vs. 939 $\pm$ 49 mmol/Kg). MAP (71 $\pm$ 4 vs. 84 $\pm$ 1 mmHg), GFR (0.5 $\pm$ 0.1 vs. 0.9 $\pm$ 0.1 ml/min/kw g) and urine Na<sup>+</sup> and K<sup>+</sup> (UNa<sup>+</sup>V: 0.8 $\pm$ 0.2 vs. 1.3 $\pm$ 0.2 umol/min/kw g and UK<sup>+</sup>V: 1.0 $\pm$ 0.4 vs. 1.5 $\pm$ 0.2 umol/min/kw g, respectively). RBF did not differ from controls. Sodium fractional excretion (FENa<sup>+</sup>) was higher (P<0.05) in KO mice compared with CT (1.6 $\pm$ 0.4 vs. 0.9 $\pm$ 0.2%). Although baseline 24 hours BP was similar in both CT (N=4) and KO (N=4) mice, the SBP in response to chronic Ang II infusion in KO mice was 12 mmHg lower compared with CT mice (P<0.05). Ang II infusion increased alpha-ENaC full length in CT and KO mice but to a lower extent in KO mice (1.8 $\pm$ 0.2 vs. 2.9 $\pm$ 0.3 alpha -ENaC/ b-actin). Alpha and gamma-ENaC cleaved forms were similar increased (P<0.05) during Ang II infusion in CT and KO mice.

**Conclusions** The PRR plays a role to maintain the renal function and in the development of Ang II-dependent hypertension.

472 **ADVANCED GLYCATION END PRODUCTS STIMULATE ANGIOTENSINOGEN EXPRESSION IN RENAL PROXIMAL TUBULE CELLS**

JM Garagliano, A Derbenev, A Zsombok, G Navar, R Sato. *Tulane SOM, New Orleans, LA*

10.1136/jim-2015-000035.474

**Purpose of Study** Elevated plasma and tissue concentrations of advanced glycation end products (AGEs) are seen in hyperglycemic individuals and are implicated in renal dysfunction in diabetes mellitus (DM). In addition, AGEs and their receptor are involved in paracrine activation of other pathophysiological systems. The intrarenal renin-angiotensin system, including proximal tubular angiotensinogen (AGT), is activated in DM contributing to the development of nephropathy. However, the effect of AGEs on AGT expression in proximal tubular cells (PTC) has not been determined.

**Methods Used** To establish augmentation of intrarenal AGT and AGE levels in DM, urinary AGT and AGE levels in streptozotocin (200 mg/kg)-induced DM mice were determined by ELISAs. The stimulating effect of AGEs on AGT expression was tested using cultured rat PTC treated with 0–200 µg/ml AGE-BSA for 24 hours. AGT mRNA, intracellular AGT protein, and secreted AGT levels were measured by real-time RT-PCR, western blot analysis, and ELISA, respectively.

**Summary of Results** Urinary AGT and AGE levels were concomitantly greater in DM mice compared to control mice (AGT: 21.6±5.5 ng/day vs. 190.1±57.8 ng/day, AGE: 139.1±21.6 ng/day vs. 332.8±102.7 ng/day). Direct treatment of PTC with AGE-BSA increased AGT mRNA (3.43±0.11-fold compared to control), intracellular AGT protein (3.60±0.38-fold), and secreted AGT levels (2.11±0.18-fold). Non-glycated BSA serving as a negative control did not alter AGT levels. Expression of AGE receptor in cultured PTC was demonstrated by western blot analysis and immunocytochemistry. Adding recombinant soluble AGE receptor, which competes with AGE receptor on plasma membrane, to culture medium attenuated the AGE-induced AGT augmentation, suggesting that AGE-BSA stimulates AGT expression via activation of AGE receptor. Enhanced phosphorylation of ERK1/2, but not p38 MAP kinase, was observed in AGE-BSA-treated PTC.

**Conclusions** The results indicate that both AGEs and uAGT are increased in DM mice and that AGEs directly stimulate AGT expression in PTC. ERK1/2 may serve as a signal transducer in this axis. The findings suggest that elevated AGEs contribute to intrarenal AGT augmentation in DM and development of diabetic nephropathy. The findings provide a rationale for targeting AGE-AGT axis to treat or prevent diabetic nephropathy.

473 **ANGIOTENSINOGEN IS UPREGULATED UNDER HIGH GLUCOSE CONDITIONS IN RENAL PROXIMAL TUBULAR CELLS**

M Cypress, R Sato, G Navar. *Tulane University, New Orleans, LA*

10.1136/jim-2015-000035.475

**Purpose of Study** Increased activity of the intrarenal renin-angiotensin system (RAS) contributes to the development of diabetic nephropathy. Upregulation of angiotensinogen (AGT) in the proximal tubule plays a central role in intrarenal RAS activation. AGT is upregulated in proximal tubular cells (PTC) under high glucose conditions, via reactive oxygen species (ROS). However, the detailed mechanisms have not been delineated. Glucose transporters expressed in the early proximal tubule segments are responsible for most of the glucose reabsorption in the kidney. Sodium-glucose cotransporter 2 (SGLT2) has recently been identified as one pharmacological target in the treatment of diabetes. Thus, to determine the role of SGLT2-dependent glucose transport on AGT expression, an experimental model describing AGT expression under high glucose conditions in early PTC is required.

**Methods Used** Immortalized mouse PTC derived from the early proximal tubular segment were used. PTC were treated with 5 mM (normal), 15 mM, or 25 mM D-glucose for up to 24 hours. As an osmotic control, PTC were treated with an equivalent dose of D-mannitol. Sodium pyruvate was used to determine the role of glycolysis in AGT upregulation. PTC were pretreated with 2.5 mM tempol, an antioxidant, to demonstrate that high glucose-induced AGT expression is mediated by ROS. AGT mRNA and protein levels were quantified using qRT-PCR and western blot analysis, respectively.

**Summary of Results** AGT protein levels were increased by 15 mM (4.43±0.23-fold compared to control) and 25 mM (4.61±0.18-fold) glucose. 25 mM glucose augmented AGT mRNA levels (31.1±3.5-fold). AGT augmentation was observed at 6 hours, and increased further at 12 hours. AGT expression was not increased by mannitol, indicating that increased osmolarity did not affect AGT upregulation. Pyruvate also enhanced AGT expression (10.74±1.03-fold). The addition of tempol attenuated AGT augmentation (4.38±0.01-fold) during high glucose, suggesting that glycolysis and ROS play critical roles in high glucose-induced AGT expression.

**Conclusions** The findings of this study demonstrate that AGT expression is increased in early PTC under hyperglycemic conditions mediated by glycolysis and ROS. The establishment of this experimental model will be used to determine the contribution of SGLT2-dependent glucose transport on AGT expression in PTC.

474 **INNATE IMMUNITY REGULATED BY TOLL-LIKE RECEPTORS ACTIVATE INFLAMMATORY PATHWAYS IN MYELOMA KIDNEY**

A Khan,<sup>1</sup> N Seyrek,<sup>2</sup> V Batuman<sup>1,3</sup>. <sup>1</sup>Tulane University, School of Medicine, New Orleans, LA; <sup>2</sup>Acibadem University School of Medicine, Istanbul, Turkey; <sup>3</sup>Veterans Affairs, New Orleans, LA

10.1136/jim-2015-000035.476

**Purpose of Study** Acute kidney injury (AKI) in multiple myeloma (MM) is generally mediated by the toxic and inflammatory effects of monoclonal free light chains (LC) on renal proximal tubule epithelial cells (RPTECs). Although implicated in the pathogenesis of multiple myeloma, the role of Toll-like receptors (TLRs) in



LC-induced nephropathy has not been previously characterized.

**Methods Used** Confluent human RPTECs were exposed to 25  $\mu$ M of human urinary K-LC for 24 hr, supernatant media and cells were collected to study K-LC induced pathogenesis at expression and production levels.

**Summary of Results** K-LC significantly injured RPTECs and arrested cell growth as evidenced by cell morphology and significant release of inflammatory cytokines and chemokines (IL-6,  $p < 0.0001$ ; TNF- $\alpha$ ,  $p < 0.0001$  and MCP-1,  $p = 0.028$ ) in media compared to untreated RPTECs as determined by ELISA. The mRNA expression of kidney injury biomarkers (KIB) NGAL was increased by 424 fold ( $p < 0.0001$ ) and KIM-1 by 3.2 fold ( $p < 0.0001$ ) in RPTECs exposed to K-LC compared to untreated RPTECs. After exposure to K-LC, the mRNA expression of AKI-prominent TLRs (TLR2, TLR3, TLR4, TLR6 and TLR9) were significantly upregulated in RPTECs; TLR6 showed the highest increase (5.7 fold) followed by TLR2 (3.5 fold). In this study, TLRs followed both MyD88- and TRIF-dependent pathways as mRNA expression of both adaptor proteins was significantly upregulated but TRIF was higher (2.2 fold) than MyD88 (0.5 fold). In downstream TLRs signaling pathways, the expression of pro-inflammatory cytokines (IL-6, 35.7 fold; TNF- $\alpha$ , 21.5 fold and IL-18, 0.21 fold), chemokines (MCP-1, 23.3 fold), pro-fibrotic (TGF- $\beta$ 1, 1.5 fold) and pro-apoptotic genes (P53, 0.17 fold and Bcl2, 1.3 fold) were also significantly upregulated by K-LC in RPTECs.

**Conclusions** K-LC is highly nephrotoxic and NGAL could be a diagnostic KIB for MM. Innate immunity mediated by TLR2 and TLR6 dimers play a major pathogenic role in the inflammatory and apoptosis signaling pathways in MM kidney. TLR2 and TLR6 may prove to be promising drug targets for the development of new therapeutics to ameliorate LC-induce kidney injury in MM.

#### 475 CALCIUM-SENSITIVE DICARBOXYLATE TRANSPORT IS REGULATED VIA GQ IN OK CELLS

R Walker, J Coleman-Barnett, LL Hamm, K Hering-Smith. *Tulane University, New Orleans, LA*

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**Purpose of Study** Citrate (Cit) prevents stones by chelation of calcium in the nephron. Urinary excretion of Cit is regulated by proximal tubule reabsorption, much of which is via the apical sodium-dependent dicarboxylate cotransporter (NaDC1). We previously demonstrated novel apical Ca-sensitive dicarboxylate (CaSDT) transport in the opossum kidney proximal tubule cell line (OK) & while not fully defined is likely not NaDC1. Reducing extracellular Ca from 1.2 mM to  $< 60 \mu$ M results in increased Cit & succinate (Suc) transport in OK cells. Previously we have shown activation of the calcium-sensing receptor (CaSR) with spermine (Sp) inhibited transport in both low ( $< 60 \mu$ M) & normal (NL, 1.2 mM) Ca. Also increasing intracellular Ca with thapsigargin (TG) yields results similar to Sp. Activation of PKC with PMA inhibited transport in low Ca only, implying that CaSDT is regulated by the CaSR through the  $G_q$ /PKC pathway. The purpose is to

investigate possible ligand biased signaling through the  $G_q$  and/or  $G_i$  pathways.

**Methods Used**  $^{14}$ C-Suc uptakes were performed in OK cells in NL & low Ca buffer. All measurements are in pmol/well. ELISA assays were performed in OK cells to measure cAMP levels in response to NL & low Ca as well as treatment with Sp & IBMX.

**Summary of Results** CaSRs activate PKC through  $G_q$ , but also inhibit adenylate cyclase (AC) through  $G_i$ . To inhibit  $G_i$ , cells were incubated with Pertussis toxin (PTX, 100 ng/ml) overnight before Suc uptake. Uptake was slightly increased in NL ( $0.088 \pm 0.01 - 0.094 \pm 0.01$ ,  $p = 0.01$ ), but not low ( $0.14 \pm 0.01 - 0.15 \pm 0.01$ ,  $p = 0.3$ ). To mimic  $G_i$ , cells were incubated with AC inhibitor, MDL-12,330A (50  $\mu$ M) 30 min before Suc uptake. MDL inhibited uptake in both NL ( $0.09 \pm 0.01 - 0.05 \pm 0.01$ ,  $p < 0.01$ ) & low Ca ( $0.13 \pm 0.01 - 0.08 \pm 0.01$ ,  $p < 0.01$ ). If MDL (via AC inhibition) results in inhibition of transport, addition of 8-Br-cAMP (8Br) should stimulate transport. Cells were incubated with 100  $\mu$ M 8Br 30 min before Suc uptake. No increase in uptake occurred in NL ( $0.12 \pm 0.005 - 0.11 \pm 0.006$ ) or low Ca ( $0.17 \pm 0.01 - 0.18 \pm 0.01$ ). ELISA assays revealed no significant change in cAMP levels in response to changes in Ca, addition of Sp, or IBMX.

**Conclusions** Despite evidence provided by MDL, the lack of effect of 8Br and PTX and the ELISA results indicate that there is likely no regulation through the  $G_i$  pathway. Stimulation of CaSR inhibits CaSDT likely via the  $G_q$  pathway in OK cells.

#### 476 CHARACTERISTICS AND MORTALITY RATES IN DIALYSIS PATIENTS WITH HISTORY OF NEPHRECTOMY

T Welsh,<sup>1</sup> J Waller,<sup>2</sup> MF Kheda,<sup>3</sup> S Baer,<sup>4,3</sup> R Colombo,<sup>3</sup> S Nahman,<sup>1,4</sup> L Huber<sup>1,4</sup>. <sup>1</sup>Medical College of Georgia at Georgia Regents University, Augusta, GA; <sup>2</sup>Georgia Regents University, Augusta, GA; <sup>3</sup>Medical College of Georgia, Augusta, GA; <sup>4</sup>Charlie Norwood VA Medical Center, Augusta, GA

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**Purpose of Study** Nephrectomy (Nx) is frequently performed for causes such as cystic disease or renal malignancy. Bilateral Nx (BNx) in ESRD patients eliminates residual renal function, the loss of which has been negatively linked to survival. Thus the goal of this work was to assess the effect of Nx on mortality in ESRD.

**Methods Used** Nx status, demographics and comorbidities were queried in United States Renal Data System incident dialysis patients from 2005–2010 (N=676,638). Survival analysis was performed by Cox Proportional Hazards model to determine the adjusted hazard ratio (HR).

**Summary of Results** During the study period, among those with no missing data there were 225 (0.19%) BNx and 1283 (1.06%) unilateral Nx (UNx), age  $63 \pm 13$  and  $69 \pm 11$  years respectively. 5% of the no Nx (NoNx) population (N=23,897) was used as a control group, mean age  $63 \pm 15$ . Those with BNx were less likely to have: diabetes (25% BNx, 44% UNx, 57% NoNx), CAD (20%, 37%, 30%), stroke (7%, 11%, 12%), and hemodialysis (72%, 86%, 90%). Those with BNx were more likely to be or have: Caucasian race (86%, 83% 66%), cystic disease

(28%, 6%, 1%), renal cancer (50%, 60%, 0.2%), and renal transplant (27%, 12%, 3%). Death rates were 49% BNx, 59% UNx, 55% NoNx. When compared to NoNx, both BNx (HR=0.84, 95%CI 0.69–1.02) and UNx (HR=0.73, 95%CI 0.67–0.79) had decreased HR for death.

**Conclusions** Nx was associated with a lower rate of hemodialysis, fewer comorbidities, and superior survival, suggesting that in this population, residual renal function is less important than dialysis mode and/or overall state of health.

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#### "BINDER REMINDERS" FOR PERSISTENT HYPERPHOSPHATEMIA IN HEMODIALYSIS PATIENTS: A FELLOW'S QUALITY IMPROVEMENT PROJECT

D Jammalamadaka, JJ White. *Georgia Regents University, Augusta, GA*

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**Purpose of Study** Despite regular quality improvement (QA) processes, control of mineral metabolism remains poor. One root cause is patient non-adherence to phosphate binders. Evolving data suggest SMS/text reminders improve medication adherence in a wide range of chronic illnesses. Here, we report our initial experience with text reminders on phosphate control in HD patients.

**Methods Used** 40 patients with phosphorus >5.5 mg/dL for 2 of last 3 months and possessing cell-phones with texting capabilities were studied. We randomly assigned 20 to receive the phrase "Binder Reminder" at mealtimes x 7 days prior to their monthly lab draw. The remaining 20 received usual care. Group assignment and messaging was performed by a nephrology fellow, not part of the multidisciplinary team. Patients were excluded if they declined participation, missed any dialysis sessions during the 7 day period, or if they were unable to obtain their binders. Phosphate level after intervention was the primary outcome.

**Summary of Results** Our initial QA project utilizing SMS/text messaging appears to have no effect on short-term phosphorus control in a group of hemodialysis patients with chronic hyperphosphatemia. A major drawback is the small number of patients and the number excluded (33%).

**Conclusions** This study does provide useful preliminary data for the planning of a proper pilot project, highlights the importance of contemporary control groups in QA to exclude the Hawthorne effect, and, given its simplicity, may be a model for fellow-driven QA projects and education.

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#### THE HAS-BLED SCORE AS A PREDICTOR FOR MORTALITY IN DIALYSIS PATIENTS WITH ATRIAL FIBRILLATION: CHALLENGES AND OPPORTUNITY FOR FUTURE STUDY

J Wong,<sup>1</sup> J Waller,<sup>1</sup> M Diamond,<sup>1</sup> S Bushik,<sup>1</sup> A Sayed,<sup>1</sup> MF Kheda,<sup>2</sup> NS Nahman,<sup>1</sup> R Sorrentino,<sup>1</sup> W Maddox<sup>1</sup>. <sup>1</sup>Georgia Regents University, Augusta, GA; <sup>2</sup>Southwest Georgia Nephrology Clinic, Albany, GA

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**Purpose of Study** Previously, the HAS-BLED score has been shown to predict bleeding in end stage renal disease (ESRD) patients with atrial fibrillation (AF). It is unclear whether it may also be used to predict mortality.

**Methods Used** Using the United States Renal Data System (USRDS) all incident dialysis patients from 2006–2010 who had a diagnosis of atrial fibrillation or flutter were evaluated for risk factors used to determine the HAS-BLED score as well as additional clinical risk factors based on ICD-9 codes from USRDS CMS hospital claims data. Anticoagulation was determined using Medicare Part D claims. Time to death from incident date of dialysis was the primary outcome of interest and a Cox Proportional Hazards model was constructed to determine the adjusted hazard ratio of the HAS-BLED score controlling for other risk factors. All statistical analysis was performed using SAS 9.4 and statistical significance was assessed using a significance level of 0.05.

**Summary of Results** The crude hazard ratio (HR) for the HAS-BLED score was 1.029 (95%CI=1.019–1.040). However, the adjusted HR (aHR) for the HAS-BLED score was 0.97 (95%CI=0.96–0.98) indicating a decrease in mortality as the score increases. Among the variables present in the HAS-BLED score, only elderly age (65 or greater) was associated with an increase aHR for mortality and several showed a lower aHR.

**Conclusions** The HAS-BLED score is a poor predictor for mortality in this patient population, likely owing to the protective effects of some individual risk factors. Further study to devise a new scoring schema in this population is warranted.

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#### EARLY MORTALITY IN DIALYSIS PATIENTS ANTICOAGULATED FOR ATRIAL FIBRILLATION

S Bushik, J Waller, R Elmor, R Sorrentino, MF Kheda, W Maddox, NS Nahman, M Diamond. *Georgia Regents University, Augusta, GA*

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**Purpose of Study** Mortality is high during the first 90 days of hemodialysis. Atrial fibrillation (AF) is an important co-morbidity that may contribute to mortality early in dialysis. AF also causes embolic stroke and is treated with life-long oral anticoagulation (OAT). We have previously shown early increased mortality in HD patients receiving OAT without significant stroke reduction (JASN, 25:609A, 2014). It is unclear why OAT increased early mortality in these patients. To address this question, we queried the USRDS for unique risk factors for mortality in this cohort.

**Methods Used** All incident adult HD cases from the USRDS for 2005–2008 were queried for demographics, access type, risk factors before dialysis, and mortality. Data were derived from ICD9 and CPT codes, or Form 2728. Proportional hazards models were used to estimate the hazard ratio (HR) for death within 90 days.

**Summary of Results** 34,522 incident HD patients with AF were identified, 6664 (19.3%) of whom died within 90 days of the initiation of dialysis. For the entire group, demographics showed: 83.1% Caucasian, mean age 75.4 years (SD=9.0), and 41.5% female. When controlling for diabetes, cardiomyopathy, TIA, pulmonary hypertension,

aortic stenosis, CHF, MI, coagulation defects, obesity, cardiac device, age and access type the HR for death in the OAT group was 1.10 (95% CI 1.04 - 1.16). The 1-, 2- and 3-month mortality rates were 6%, 15% and 22% in OAT and 5%, 12% and 19% in non-OAT, respectively. Bleeding was not significantly associated with mortality in this model ( $p=0.59$ ).

**Conclusions** OAT therapy in HD patients with AF may contribute to the increased death rate observed during the first 90 days of dialysis. Significant bleeding was not associated with increased mortality. We would speculate that the use of OAT inhibits other Vitamin K-dependent carbonylation that lead to increased mortality in the HD population independent of bleeding. This level of clinical detail is beyond the scope of an administrative dataset like the USRDS, but suggests that future studies investigating OAT in HD patients focus on factors other than hemorrhage risk in mortality.

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### SURVIVAL OF ESRD PATIENTS DIAGNOSED WITH IDIOPATHIC HEART FAILURE

J Patel, S Nahman, A Chen, S Li, AE Berman, M Diamond, L Huber, MF Kheda, FM Yang. *Georgia Regents University, Augusta, GA*

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**Purpose of Study** The prognosis of patients with pre-dialysis IHF after the institution of dialysis is unknown. On this basis, we used the USRDS to compare survival between IHF patients diagnosed prior to ESRD with patients developing IHF after the institution of dialysis.

**Methods Used** All incident adult end-stage renal disease cases from the USRDS from 1967–2012 were queried for a diagnosis of IHF before or after the incident date of dialysis. IHF was defined by the presence of any ICD-9 HF code (428.0 - 428.9), and the absence of all other cardiovascular diagnoses. Descriptive statistics and co-morbidities by group were calculated, and survival analysis performed using Cox regression.

**Summary of Results** 50,052 patients were identified with IHF. 46% and 54% were diagnosed with IHF before (pre-dialysis) or after (post-dialysis) the incident date of dialysis, respectively. When compared to post-dialysis, pre-dialysis were older (73% > age 65 vs. 33%), White (61% vs. 59%), diabetic (45% vs. 6%), and female (52% vs. 47%, all  $p<0.001$ ), and exhibited a hazard ratio (HR) for death of 1.82 (95% confidence limits 1.773–1.861,  $p<0.001$ ). Diabetes prior to dialysis and age > 44 years also exhibited increased HR for death (1.11 and 1.62, respectively). Non-white race was protective for death in all patients with IHF.

**Conclusions** In ESRD patients, a diagnosis of IHF is common either before or after the incident date of dialysis. When compared to post-dialysis a diagnosis of IHF before dialysis is associated with decreased survival. This may be the result, at least in part, of pre-existing heart disease in an older, diabetic population. IHF diagnosed after dialysis includes younger patients likely with volume overload and an intact ejection fraction; thus manifesting with more readily reversible conditions. These results imply that IHF

before and after the incident date of dialysis may represent two distinct disease entities, and suggests that unique management strategies for each syndrome may be indicated.