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A-8 PROTEIN KINASE D1-CD36 SIGNALING AXIS
PROMOTES ARTERIOLAR DIFFERENTIATION

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Endothelial cell (EC) heterogeneity is critical to vascular endothelial differentiation and cardiovascular disorders. Endothelial differentiation into arterial, venous or capillary (microvascular) EC phenotypes in specific tissue microenvironment will determine whether to form arteries (arteriogenesis), veins (venogenesis), or capillaries (angiogenesis). Adult ECs demonstrate differentiation plasticity (Opansky *et al.* 2016, *Circulation*; Ren *et al.* 2016, *ATVB*). Capillary EC differentiation into arterial ECs may facilitate the development of arterioles and be essential for recovering blood supply under ischemic conditions (Ren *et al.* 2016, *ATVB*; Ren *et al.*, *Circulation* 2016). We observed that MAPK/Erk1/2, a downstream signaling of protein kinase D1 (PKD-1) pathway, played a key role in the arterial cell differentiation and promoted arteriogenesis under ischemia conditions (Ren, *et al.*, 2010, *JCI*). In microvascular ECs (MVECs), a lipid signaling mediator (lysophosphatidic acid)-induced PKD-1/Erk1/2 signaling was involved in transcriptional repression of angiogenic regulator CD36 gene. This CD36 downregulation facilitated transcriptional reprogramming of MVECs, which subsequently expressed arteriogenic genes, contributed to microvascular remodeling, and was implicated in the capillary arterIALIZATION (formation of small arteries from capillaries). We thus hypothesized that LPA/PKD-1-CD36 signaling axis is critical to arteriolar differentiation. To test this hypothesis, we transduced MVECs with wild-type or constitutively active PKD-1 by lentiviral infection. Using real time quantitative RT-PCR, we observed that forced PKD-1 expression significantly promoted the expression of mRNA proarteriogenic genes including ephrinB2 and DLL4. The mRNA levels of Hey1, a transcription factor involved in arterial differentiation, also increased over 10 fold more than in the control. Treatment of MVECs overexpressed PKD-1 with a selective PKD inhibitor abolished PKD-1-induced arteriogenic expression. Prolonged EC exposure to GS4012, a small chemical molecule that repairs arterial defects in transgenic zebrafish and mouse models, also increased the mRNA expression of arteriogenic gene ephrin B2 and DLL4 via stimulation of PKD-1 signaling. To investigate the effect of inhibiting CD36 signaling, we transduced CD36 shRNA by lentiviral infection to effectively knock down endogenous CD36 expression in MVECs. Intriguingly, knocking down CD36 expression significantly

stimulated the expression of arteriogenic genes, and mRNA levels of Neuropilin 1, Hey2 and DLL4 increased 5 to 60 fold over the control. Functionally, overexpression of PKD-1 promoted branching morphogenesis in both two and three dimensional MVEC culture. Our studies indicate that PKD-1-CD36 signaling axis is essential to arteriolar differentiation via regulation of arteriogenic gene expression in ECs. Targeting this signaling axis could provide an approach to regulating de novo arteriogenesis.

A-9 NOVEL PEPTIDE B7-33, A SINGLE-CHAIN DERIVATIVE OF THE RELAXIN HORMONE, PROTECTS CYTOTROPHOBLASTS FROM ANTI-ANGIOGENIC MILIEU IN CELLULAR MODELS OF PREECLAMPSIA

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Background Preeclampsia (PreE) is a hypertensive pregnancy disorder, which occurs in approximately 10% of all gestations. Recently, a digitalis-like factor, marinobufagenin (MBG) has been implicated as a causative factor in preE. We demonstrated that MBG inhibits the proliferation, migration, and invasion of cytotrophoblast (CTB) cells. We also showed that hyperglycemia impairs CTBs function via stress signaling. Relaxin is a peptide hormone that allows vasodilation and plays an important role in the process of parturition. The literature suggests potential therapeutic role of H2 relaxin in preeclampsia (PreE), however, there is a controversy on hypotensive action of the peptide. Due to the complex insulin-like structure of relaxin (A- and B-chains, 53 amino acids, 3 disulfide bonds), a novel H2 relaxin B-chain-only peptide variant B7-33 (27 amino acids without any disulfide bonds) has recently been developed. This single-chain peptide displayed equivalent efficacy to the natural H2 relaxin in several functional assays both *in vitro* and *in vivo*. Importantly, B7-33 was shown to have H2 relaxin-like RXFP1 specific effects, particularly in endogenously expressing RXFP1 cells, thus we hypothesized that B7-33 could be an alternative and cost-effective treatment option for PreE compared with H2 relaxin.

Methods Human CTBs were treated with DMSO (vehicle) or 0.1, 1, 10 or 100 nM of MBG for 48 h and were co-treated with B7-33 (25 nM) with MBG exposure, while some cells were treated with 5, 10, 25 and 50 nM B7-33 alone. CTBs were also treated with 100, 150, 200, 300, or 400 mg/dL glucose for 48 h and were co-treated with B7-33 (25 nM) with glucose exposure. Levels of vascular endothelial growth factor (VEGF), placental growth factor (PLGF), soluble fms-like tyrosine kinase-1 (sFlt-1), and soluble endoglin (sEng) were measured in culture media using ELISA kits. Cell lysates were utilized to evaluate the

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mTOR, pAKT and MMP-9 expression by western blotting. Statistical comparisons were performed using analysis of variance with Duncan's post hoc test.

Results Secretion of sFlt-1 and sEng were increased while VEGF and PlGF were decreased in CTBs treated with ≥ 1.0 nM MBG and ≥ 150 mg/dl of glucose (* $p < 0.05$ for each). B7-33 co-treatment significantly rescued CTBs from both MBG-induced and hyperglycemia-induced anti-angiogenic profile ($p < 0.05$ for each). There is no effect of B7-33 on sFlt-1, sEng and PlGF; however, it increases expression of VEGF, while CTBs were treated only with B7-33. B7-33 also causes increased expression of mTOR and pAKT in CTBs.

Conclusions B7-33 mitigates the MBG-induced and hyperglycemia-induced dysfunction of CTBs by attenuating anti-angiogenic phenotype similar to that seen in PreE. This study supports the importance of continuing research of B7-33 in preE prevention.

A-10 THE MISSED INFERIOR SINUS VENOSUS DEFECT LEADING TO RIGHT HEART FAILURE

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Introduction Sinus venous atrial septal defects (SV-ASD) are communication between the atria caused by malpositioning of SVC or IVC insertion. They are often associated with partial anomalous pulmonary venous return (PAPVR). Late diagnosis and surgical repair increases morbidity and mortality. Our case is about a female with remote history of ASD repair, who presented with heart failure symptoms and chronic atrial fibrillation. She was found to have an inferior SV-ASD on further diagnostic testing.

Case presentation 66 year old female, with a history of repaired ASD at age 10 and symptomatic bradycardia with pacemaker (PPM) placement, presented with exertional dyspnea and lower extremity swelling and persistent hypoxemia. TTE showed enlarged right ventricle, but no ASD. Device interrogation showed atrial fibrillation with ventricular pacing, currently being treated with propafenone. Ablation therapy was planned. CT chest with contrast was done for pre-procedure workup. It demonstrated a 2.5x2.3 cm inferior SV-ASD, severely dilated IVC measuring 4.4 cm, and redundant inter-arterial septum representing the prior patch repair. Cardiac MRI illustrated SV-ASD with Qp/Qs (pulmonary to systemic flow) of 2.7, moderately dilated right ventricle and moderately reduced right ventricular systolic function. Based on these findings, surgical SV-ASD closure was performed.

Discussion Our case illustrates that when a patient with a history of ASD repair in childhood presents with right-sided heart failure, further lesions leading to right sided volume loading should be considered. TTE remains the first choice for imaging, but TEE has been shown to increase detection of SV-ASD and PAPVR. Newer imaging modalities like cardiac MRI or CT should be considered

the gold standard for defining complex anatomy in congenital heart disease. Cardiac MRI is also an excellent tool for chamber size quantification and shunt fraction calculations. Treatment remains surgical closure.

Conclusion In a patient with previous ASD repair presenting with symptoms of heart failure, atrial fibrillation, and unexplained right atrial and ventricular enlargement, SV-ASD, or other volume loading lesions should be considered. Input from cardiologists trained in congenital heart diseases should be considered in the management and long term follow up of this complex patient population.

B-1 RISK OF VENTRICULAR ARRHYTHMIAS IN LONG QT SYNDROME PATIENTS ON ANTI-EPILEPTIC DRUGS

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Objective Since many anti-epileptic drugs (AEDs) affect ion channel function we investigated whether AED usage alters the risk of cardiac arrhythmias in patients with corrected QT (QTc) interval prolongation.

Methods Using the Rochester-based Long QT Syndrome (LQTS) Patient Registry, the study included patients with a history of taking AEDs, plus QTc prolongation (n=293) or LQTS genotype negative family members with normal QTc durations (Control, n=64). We assessed the recurrent rate/risk of ventricular arrhythmias (aborted cardiac arrest, sudden cardiac death, ventricular tachyarrhythmia) in each patient on vs. off AEDs, and stratified by LQTS genotype (LQTS1, LQTS2, & LQTS genotype unknown) and class of AED (Na⁺ channel blocker and GABA modifier AEDs).

Results In contrast to Controls, participants with QTc prolongation had a 1.8-fold higher rate of arrhythmias on vs. off AEDs. The multi-variate time-dependent adjusted risk of arrhythmias was higher when participants with QTc prolongation were on AEDs (HR 1.43, 95% CI 1.17–1.74, $p < 0.001$). However, LQTS1 patients exhibited a decreased risk when on AEDs (HR 0.37, 95% CI 0.15–0.95, $p = 0.038$). The risk did not differ when each group of participants were on or off GABA modifier AEDs. In contrast, there was an increased risk when participants with QTc prolongation, specifically LQTS2 participants, were on Na⁺ channel blocker AEDs, but decreased risk in LQTS1 participants ($p = 0.003$, interaction.) This effect was attenuated by concurrent beta blocker therapy ($p < 0.01$, interaction).

Conclusions Pharmacogenomic analyses indicate specific classes of AEDs exhibit LQTS genotype/phenotype-specific effects on the risk of ventricular arrhythmias.

Results Set the stage for future prospective and mechanistic studies to validate whether AEDs with predominantly Na⁺ channel blocking action are deleterious in LQTS2 patients, and protective in LQTS1 patients.

B-2 MALIGNANT HYPERTHERMIA-ASSOCIATED MUTATION OF LEAKY RYR1 INDUCES MITOCHONDRIAL DAMAGE IN THE HEART

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Human families carrying the ryanodine receptor type 1 (RyR1) mutations mainly show skeletal muscle disorders including malignant hyperthermia (MH). Importantly, it is also reported in the clinical case studies that the members of MH families frequently show sudden cardiac death (SCD) in the conscious condition without anesthesia. However, the molecular mechanism underlying cardiac phenotypes in MH is completely unknown. We previously reported that a low level of RyR1 (but not RyR2) is expressed in the mitochondria (termed “mitochondrial RyR1”: mRyR1), but not in the sarcoplasmic reticulum (SR) in the rat and mouse hearts, which serves as an important mitochondrial Ca²⁺ influx pathway in addition to the mitochondrial Ca²⁺ uniporter (MCU) in the heart. Using knock-in mice carrying a MH-related RyR1 mutation Y522S (YS), we found that YS hearts exhibit disrupted mitochondrial morphology as well as compromised mitochondrial functions with a significantly higher cellular oxidative state compared to the wild-type (WT) hearts. Moreover, *ex-vivo* YS heart developed significantly higher number of multiple ventricular extrasystoles by β -adrenergic stimulation compared those observed in the WT hearts. Therefore, we next hypothesize that YS-RyR1s form “leaky channel” at mitochondria and induce mitochondrial Ca²⁺ overload, which alters the cellular Ca²⁺ handling and oxidative levels in cardiomyocyte. Using isolated mitochondria loaded with Ca²⁺ or membrane-potential sensitive dyes under the confocal microscope, we found that YS mitochondria have higher basal mitochondrial Ca²⁺ concentration, depolarized mitochondrial membrane potential compared to WT mitochondria. In addition, YS cardiomyocytes exhibit higher basal cytosolic Ca²⁺ concentration as well as slower cytosolic Ca²⁺ clearance compared to WT. Finally, pretreatment of RyR1 blocker dantrolene cancelled these changes in YS mitochondria and cardiomyocytes and normalized their Ca²⁺ handling profiles similar to the levels found in WT. In summary, these results indicate that chronic mitochondrial Ca²⁺ overload via leaky mutant mRyR1 damages cardiac mitochondrial functions and structures, which may alter cytosolic Ca²⁺ handling, induce cellular oxidation, and increase the arrhythmogenic events in MH.

B-3 ACUTE HEART FAILURE SYNDROMES IN PATIENTS WITH BODY MASS INDEX>30

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Introduction The Framingham Heart Study identified obesity as a major risk factor for heart failure, with excessive body weight adversely affecting ventricular function.

Hypothesis In this study, we aim to study the effect of obesity in the outcome of different phenotypes of heart failure (HF) in patients who were admitted to the hospital for an acute HF syndrome (AHFS).

Methods A retrospective chart analysis of all patients who were admitted to the hospital for an AHFS between 2005 and 2015. Patients were divided into two groups: obese (BMI ≥ 30 kg/m²) and normal (BMI <25). Patients with BMI from 25 to 29 were excluded. We assessed the left ventricular ejection fraction and subsequently divided the patients into two groups: HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). We studied the 30-day readmission rate, mortality rate and length of stay (LOS).

Results Of 2090 patients who were admitted to the hospital for AHFS, 362 patients (17.3%) had BMI ≥ 30 vs 1232 (59%) had BMI <25. Among AHFS patients and BMI ≥ 30 , 61% had HFpEF and 39% had HFrEF. Approximately 54% of AHFS patients with BMI ≥ 30 were male vs 55% of AHFS with BMI <25 ($P=0.9$). The average age of AHFS in patient with BMI ≥ 30 was 61 years vs 70 years in AHFS and BMI <25 ($P<.001$). Additionally, 61% of AHFS and BMI ≥ 30 had HFpEF vs 48% in HFpEF patients and BMI <25 group (OR: 1.7, $P<0.001$). The 30-day readmission rate, mortality rate and LOS did not differ between AHFS with BMI ≥ 30 and BMI <25 ($P=0.6$, 0.07 and 0.06). Among AHFS and HFrEF, average age in patients with BMI ≥ 30 was 57 years vs 65 years in BMI <25 ($P<0.001$). In the same group (AHFS and HFrEF), 30-day readmission was 19% in patients BMI <25 versus 10% in patients with BMI ≥ 30 (OR: 2.1, $P=0.01$). The mortality rate and LOS did not differ between the two groups ($P=0.8$ and 0.9). Among AHFS and HFpEF, average age of patients with BMI ≥ 30 was 65 years versus 74 years in patients with BMI <25. In the same group (AHFS and HFpEF), patients with BMI ≥ 30 had a higher 30-day readmission rate of 23.4% versus 15.3% in BMI <25 group (OR: 1.6, $P=0.01$). The mortality rate and LOS did not differ between the two groups ($P=0.7$ and 0.9). Subgroup analysis of HFrEF versus HFpEF among patients with AHFS and BMI ≥ 30 , patients with HFpEF had a 30-day readmission rate of 20% versus 10% in HFrEF (OR: 2.2, $P=0.01$). The mortality rate and LOS did not differ ($P=0.5$ and .09). After we divided the patients with AHFS and BMI ≥ 30 in to two groups; BMI ≥ 30 –39 and BMI ≥ 40 , 64% of the patients with BMI ≥ 40 found to have HFrEF vs 13% among BMI 30–39 (OR: 6.2, $P<0.001$). The 30-day readmission rate was 11.5% in BMI ≥ 40 vs 5% in BMI ≥ 30 –39 group (OR: 2, $P=0.02$). **Conclusion** Patients with HF and BMI ≥ 30 seem to develop AHFS at an earlier age. The majority of patients with AHFS and BMI between 30 and 39 have HFpEF while patients with BMI ≥ 40 have HFrEF. The 30-day readmission rate was higher in patients with HFpEF and BMI ≥ 30 . Finally, there is a direct proportion between 30-day readmission rate and increasing the BMI.

B-4 ROLE OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION IN EARLY INCIDENCE OF CORONARY ARTERY DISEASE

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Background Data on the effect of CD4 count and HIV-viral load on cardiovascular disease is not consistent. Most studies suggest that lower CD4 count and higher HIV-viral load are associated with greater cardiovascular risk. In this study, we evaluated the early incidence of symptomatic CAD in HIV-infected patients and correlated that to multiple variables- CD4 counts, viral load, age, sex and anti-retroviral medications.

Methods Retrospective analysis of 9,320 patients who were admitted from 2006–2014 for chest pain and underwent for coronary angiography. One hundred and five patients had documented HIV-Infection. We compared those patients with matched control group and multiple variables such as: CD4 count, viral load, sex, age and Anti-retroviral medications (ART).

Results Patients with HIV-infection had more prevalence of CAD than non-HIV patient (OR: 2.2, 95% CI: 1.2–3.8, $p=0.007$). Out of 9,320 patient with chest pain, 105 patients had HIV infection, 75 (71.5%) found to have symptomatic CAD. The average age of CAD in HIV-infected patients was 54 vs 63.3 years old in non-HIV ($p<0.001$). Out of 75 patients with CAD, 15 (20%) presented with STEMI, 33 (44%) with NSTEMI and 27 (36%) with stable angina. Sub-group analysis revealed, the HIV-infected patients had more non-obstructive CAD when compared with non HIV-infected with CAD (OR: 2, 95% CI: 1.1–3.7, $p=0.04$). Among HIV patients, average CD4 counts of HIV-infected patients with CAD were 504 vs 327 in HIV-infected without CAD ($p=0.01$). Furthermore, 52% of HIV patients with CAD had detectable viral load versus 27% of HIV-infected patient without CAD (OR: 3, 95% CI: 1.17–7, $p=0.02$). Of 75 patients with HIV-infection and CAD, 65 (87%) were on ART vs 12 out of 30 (40%) HIV-infected patients without the evidence of CAD (OR: 9.7, 95% CI: 3.6–26, $p<0.0001$).

Conclusions Our study confirmed the higher prevalence of symptomatic CAD in HIV-infected patients. However, our data does not support the notion that higher CD4 count and antiretroviral therapy associated with lower risk of CAD. However, we found detectable viral load associated with higher incidence of CAD. Further study needed to understand the effect of HIV-infection and antiretroviral treatment on CVD risk.

B-5 ELIGIBILITY FOR PCSK9 INHIBITOR TREATMENT IN 1090 HYPERCHOLESTEROLEMIC PATIENTS REFERRED TO A REGIONAL CHOLESTEROL TREATMENT CENTER WITH LDL CHOLESTEROL ≥ 70 MG/DL DESPITE MAXIMAL TOLERATED CHOLESTEROL LOWERING THERAPY

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Background Lowering of LDL cholesterol (LDLC) has been revolutionized by PCSK9 inhibitors, Alirocumab (Praluent) and Evolocumab (Repatha). PCSK9 inhibitors have approved indications as adjunct to diet and maximally tolerated lipid lowering therapy (MTLLT) for patients with heterozygous familial hypercholesterolemia (HeFH), homozygous familial hypercholesterolemia, or clinical atherosclerotic cardiovascular disease (CVD) where LDLC lowering is insufficient despite MTLLT.

Objective We have applied FDA approved and commercial insurance eligibility criteria for PCSK9 inhibitor use in 1090 patients serially referred to our Cholesterol Diagnosis and Treatment center (within the last 3 years), who, after ≥ 2 months of MTLLT, retained follow up LDLC ≥ 70 mg/dl. We documented the percentage of patients with HeFH and/or CVD who met FDA insurance criteria for PCSK9 inhibitor therapy using LDLC goal-based guidelines.

Methods We included 1090 consecutively referred patients with LDLC ≥ 70 mg/dl after ≥ 2 months of MTLLT, and characterized them by FDA indications and commercial insurance eligibility for PCSK9 inhibitor use.

Results Of the 1090 patients with LDLC ≥ 70 mg/dl after ≥ 2 months of maximally tolerated MTLLT, 353 (32%) had HeFH and/or CVD events. Of these 353 patients, 140 (13% of the cohort of 1090) had HeFH and/or CVD, with LDLC > 100 mg/dl on MTLLT, meeting both FDA and commercial insurance criteria for PCSK9 inhibitor therapy. Fifty-one patients (5%) were statin intolerant only without HeFH or CVD events.

Conclusion Of 1090 patients referred for diagnosis and treatment of high LDLC, with LDLC ≥ 70 mg/dl after ≥ 2 months on MTLLT, 140 (13%) had HeFH and/or CVD, with LDLC > 100 mg/dl, meeting both FDA and commercial insurance criteria for PCSK9 inhibitor therapy. Extrapolating from our referral cohort where 13% of hypercholesterolemic patients would be eligible by FDA-commercial insurance criteria for PCSK9 inhibitors, it is possible that at least 6 million Americans would be candidates for PCSK9 inhibitor therapy, where specialty-priced drugs would need to be used for treatment of a common public-health problem.

B-6 ISOLATED CARDIAC AMYLOIDOSIS: A RARE CARDIOMYOPATHY

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Background Cardiac involvement is commonly seen as part of systemic amyloidosis. However, isolated cardiac amyloidosis is a rarely reported entity. It is characterized by extracellular amyloid infiltration throughout the heart causing restrictive cardiomyopathy. Patients most commonly present with symptoms and signs of heart failure. Here we present an unusual case of isolated cardiac amyloidosis in a patient with acute heart failure. This case is also distinctive for the reason that our patient was an elderly female whereas isolated cardiac amyloidosis has been described mostly in older men.

Case A 70 years old African American female with a history of hypertension presented to us with the chief complaint of dyspnea at rest and bilateral pedal edema for 1 week. Physical exam showed elevated jugular venous pressure, gallop rhythm on cardiac auscultation, bibasilar crackles and pedal edema. The limb leads on EKG showed low voltage complexes. Transthoracic echocardiography demonstrated severe concentric left ventricular hypertrophy with EF of 30%, severe diastolic dysfunction with restrictive MV inflow pattern, severe biatrial enlargement and speckled appearance of the myocardium. Workup for systemic causes of amyloidosis including serum and urine protein electrophoresis and immunofixation, serum free light chain analysis and abdominal fat pad biopsy were negative. Cardiac MR showed difficulty nulling the myocardium to identify the correct inversion recovery time and diffuse late gadolinium contrast enhancement suggestive of cardiac amyloidosis. Endomyocardial biopsy was performed and the sample was positive for Congo red staining. Mass spectroscopy of the specimen showed Wild-type transthyretin-related amyloidosis (ATTRwt).

Conclusion Isolated cardiac amyloidosis is a rare syndrome. Moreover, symptomatic cardiomyopathy due to ATTRwt has been reported predominantly in men (85%), making this case even more interesting. This diagnosis should be kept in mind when encountering patients of heart failure with preserved ejection fraction. It is important to recognize cardiac amyloidosis at an early stage owing to emergence of new therapies and improvement in survival.

B-7 CARDIOTONIC STEROIDS ALTER THE MONOLAYER PERMEABILITY AND JUNCTIONAL PROTEINS IN LYMPHATIC ENDOTHELIAL CELLS

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Objective Preeclampsia (preE) is a hypertensive disorder unique to pregnancy. Cardiotoxic steroids (CTSs) such as marinobufagenin (MBG), cinobufotalin (CINO), and ouabain (OUB) are Na⁺/K⁺ ATPase inhibitors. MBG is elevated in a rat model and patients with preE and caused a vascular leak syndrome in vivo and in vitro. Edema is a common syndrome of preE. To assess whether CTSs are involved in the leakage of lymphatic endothelial cells (LECs) lining during preE, we evaluated the effect of these CTSs on monolayer permeability of LECs in culture.

Methods LECs isolated from a rat mesenteric collecting lymphatic vessel were treated with DMSO (vehicle), CTSs (1, 10 or 100 nM). Some LECs were pretreated with 1 μM L-NAME (N-Nitro-L-Arginine Methyl Ester) before

treatment with 100 nM MBG or CINO. Monolayer permeability of CTS-induced LECs was measured by using a fluorescent dye that was quantified on a fluorescence plate reader. The expression of β-catenin and VE-cadherin in the CTS-treated LECs was measured by immunofluorescence. Western blot was performed to measure β-catenin and VE-cadherin protein levels as well as MLC-20 phosphorylation.

Results MBG (≥ 1 nM) and CINO (≥ 10 nM) increased (p<0.05) the monolayer permeability of LECs compared to DMSO while OUB had no effect. Pretreatment of LECs with 1 μM L-NAME attenuated (p<0.05) the monolayer permeability of LECs treated with either 100 nM of MBG or CINO. The β-catenin expression in LECs was downregulated (p<0.05) by both MBG and CINO treatment. However, CTSs had no effect on the LECs tight junctions. VE-cadherin was downregulated (p<0.05) by CINO and MLC-20 phosphorylation was upregulated (p<0.05) by MBG.

Conclusions We have demonstrated that bufadienolides, MBG and CINO, caused an increase in the monolayer permeability of LECs which was attenuated by L-NAME pretreatment. The data suggest that CTSs exert their effect via nitric-oxide dependent signaling pathway and that CTSs may be involved in the vascular leak syndrome in the LEC lining in preE.

C-2 CHRONIC INOTROPE INFUSION: A VIABLE OPTION FOR LOW OUTPUT HEART FAILURE

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Introduction The use of inotropes in low cardiac output heart failure (HF) has been controversial. While widely used clinically, randomized trials have had conflicting data. There is insufficient evidence to support long-term inotrope use secondary to the increased mortality seen in patients with advanced heart failure. We present an interesting case of a female with low cardiac output heart failure who has been on a stable regimen of chronic dobutamine and milrinone treatment for over 2 years.

Case description Our case is about a 78 year old female with an extensive past medical history, including ischemic cardiomyopathy post bypass surgery, systolic HF (NYHA Class III), atrial fibrillation, ventricular tachycardia and subsequent biventricular pacemaker, venous thrombosis, mitral valve replacement, end stage renal disease with hemodialysis 3 days a week. Given all of her co-morbidities, she was deemed to not be a candidate for LVAD or transplant. She continued to have multiple admissions for congestive HF. Treatment options were limited due to hypotension, and she was unable to tolerate ace inhibitors, hydralazine, isosorbide dinitrate and spironolactone. She was started on continuous dobutamine infusion and intermittent milrinone infusion with hemodialysis sessions. The patient has now been on this regimen for over 2 years, and has been

tolerating well, with decreased hospital admissions for congestive heart failure.

Discussion While the use of inotropic agents chronically continues to be controversial, it is important to note that many of these studies were performed on patients without low output HF limited by hypotension. Recent studies have shown that for patients with low output HF, milrinone and dobutamine, the two inotropes approved for use in the U. S., can improve NYHA class, may reduce the number in hospitalizations, and may not affect overall mortality. Our case demonstrates a situation where the use of chronic inotropes has been clearly beneficial for our patient.

Conclusion Outpatient chronic inotrope infusions may be an effective form of therapy for selected patients with severe, low output congestive failure who are unable to take conventional HF medications secondary to hypotension.

C-3 VENTRICULAR FIBRILLATION: A RHYTHM COMPATIBLE WITH LIFE IN LVAD PATIENTS

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Introduction Left Ventricular Assist Devices (LVADs) are common in patients with end stage heart failure (HF), both as a bridge to heart transplantation (BTT) or as destination therapy (DT). Ventricular tachycardia (VT) and Ventricular fibrillation (VF) are common causes of mortality in HF patients and occur in up to 20% of the patients even after LVAD placement. VF is a fatal arrhythmia resulting in death in the absence of circulatory support. We report a case of sustained VF with preserved hemodynamics in one such patient.

Case report A 64-year-old male with an ischemic cardiomyopathy presented to the hospital with substernal chest pain at rest. Patient had ICD placed for primary prophylaxis against sudden cardiac death years prior. Four months prior to admission, patient had a continuous-flow Heart-Mate II LVAD placed as BTT for end stage HF. On day of admission, patient started having substernal chest pain at rest radiating to the left arm with discharge of his ICD. On route to the hospital, patient received six shocks by his ICD. In the ER, patient was alert, conversant and asymptomatic, with VF as his presenting rhythm. Blood pressure on admission showed Mean Arterial Pressure (MAP) of 65. Amiodarone was administered in addition to sedation, with subsequent successful external defibrillation with a 360-J biphasic shock giving return to normal sinus rhythm. He did return to VT within 5 minutes of the original defibrillation. Intravenous lidocaine was added to amiodarone and just prior to external defibrillation his ICD discharged with successful termination of the VT.

Discussion This case demonstrates that ventricular fibrillation, an otherwise fatal arrhythmia, can be tolerated well in

patients with an LVAD allowing appropriate management of the arrhythmia. Despite the fact that LVAD can maintain hemodynamics during both VT and VF, these arrhythmias are still associated with potential complications like end organ damage from hypoperfusion as well as thrombus formation and right heart failure. Another point highlighted by this case is the failure of his device to detect VF and deliver appropriate therapy. This brings to question if there is something wrong with the detection algorithms of the ICD for VF.

C-4 IS DEMENTIA A BARRIER TO RECEIVING CORONARY ARTERY BYPASS GRAFT SURGERY IN PATIENTS PRESENTING WITH ACUTE MYOCARDIAL INFARCTION? INSIGHTS FROM NATIONAL INPATIENT SAMPLE

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Background Patients with dementia who present to hospitals with acute myocardial infarction (AMI) traditionally receive less aggressive care. Studies have shown that these patients are at a higher risk of in-hospital mortality when they do not receive invasive coronary procedures including coronary artery bypass graft (CABG). It is not clear from current data if dementia is a barrier to receiving CABG in patients with dementia who present with AMI.

Methods We searched the National Inpatient Sample (NIS) 2013 using International Classification of Diseases (ICD-9-CM) codes for patients older than 18 years with dementia (290.xx, 294.xx, 310.0, 331.xx) who presented with AMI (410.xx). We used propensity score to establish matched cohorts to control for baseline imbalances in patients with and without dementia. We used Chi squared test and ANOVA to compare categorical and continuous variables respectively. We performed multivariate binary logistic regression to identify adjusted odds-ratio (AOR) between the groups.

Results We identified a total of 839,070 (weighted) patients with AMI admitted in 2013. A total of 72,975 (8.7%) patients had dementia. A total of 55,205 (6.6%) coronary artery bypass graft surgeries (CABG) were performed in the same admission. CABG rates were 7.1% and 1% in non-dementia and dementia groups. We identified a total of 72,945 patients in each group after propensity score matching (PSM). A total of 3,355 (2.3%) CABGs were identified in matched cohorts. CABG rates were 3.6% and 1% in non-dementia and dementia groups after PSM. Adjusted odds ratio (AOR) for undergoing CABG in dementia cohort was 0.309 (CI=0.257–0.373; p<0.0001) compared to non-dementia cohort.

Conclusion Patients with dementia are much less likely to receive CABG as compared to their matched cohort without dementia.

C-5 TRANSIENT GLOBAL AMNESIA (TGA): MINOR INCONVENIENCE OR EARLY WARNING SIGN OF MYOCARDIAL INFARCTION?

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Introduction Transient global amnesia is a clinical diagnosis characterized by the sudden and reversible onset of anterograde amnesia accompanied by repetitive questioning. Although relatively benign, underlying life-threatening medical conditions (e.g., myocardial infarction, dissecting aortic aneurysm, arrhythmias) have been associated with transient global amnesia and should be considered to prevent catastrophic outcomes.

Case description A 69-year-old female with history of migraines presented with an acute episode of altered mental status and confusion with repetitive queries. Upon arrival to the emergency department, she was found to be hypertensive to 171/79 mm Hg. Neurological exam revealed poor short-term memory with anterograde amnesia and continued perseveration of the same questions/statements. Otherwise alert and oriented with no aphasia or cognitive deficits. Physical examination revealed no focal neurological or epileptic signs or symptoms. A brain computed tomography without contrast showed diffuse cerebral atrophy, otherwise no acute findings or prior infarcts. Biological parameters and diagnostic tests ruled out metabolic disorders (i.e., hypoglycemia, hypocalcemia), infection, fluid/electrolyte derangement as underlying etiology of her acute presentation and the lack of disturbance of consciousness and altered cognition excluded delirium. Clinical picture was consistent with TGA. Her troponin was elevated to 0.79 ng/mL. Electrocardiogram revealed T-wave inversions in the anteroseptal leads and mild ST-segment elevations in the inferior leads leading to diagnosis of non-ST-elevation myocardial infarction. A transthoracic echocardiogram estimated global left ventricular ejection fraction at 25% with severe left ventricular systolic dysfunction and delayed diastolic relaxation. A coronary angiogram performed later demonstrated non-obstructive coronary artery disease. Nearly 24 hours after the initial presentation; she appeared to be making new memories and returning to baseline. Troponin down trended and repeated electrocardiograms were unchanged from admission. She was safely discharged with routine post myocardial infarction treatment and follow-up.

Discussion A sympathetic efflux can occur as early as three hours after an acute myocardial infarction and we are speculating that this post infarction surge contributed to the manifestations of transient global amnesia. This **Case report** as well as the others mentioned in the literature have important clinical implication as early recognition of TGA or anyone presenting with acute alerted mental status or confusion, especially ones with cardiovascular risk factors, should be evaluated carefully for potential underlying medical co-morbidities.

C-6 EFFICACY OF ALIROCUMAB AND EVOLOCUMAB IN LOWERING LOW-DENSITY LIPOPROTEIN CHOLESTEROL TO LESS THAN 70 MG/DL IN 107 HIGH-RISK HYPERCHOLESTEROLEMIC PATIENTS

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Background Reduction of low-density lipoprotein cholesterol (LDLC) to <70 mg/dL is optimal in high-risk patients with cardiovascular disease (CVD). In 107 high-risk, high LDLC patients (70 intolerant to any statin dose-sequence), only 3 (3%) had entry LDLC <70 mg/dL on a maximal tolerated LDLC lowering regimen. In these 107 patients, our specific aim was to assess efficacy of alirocumab (ALI) and evolocumab (EVO) in lowering LDLC to <70 mg/dL.

Methods We followed 107 patients for a median 24 weeks on ALI 75 mg (n=33), ALI 150 mg (n=30), or EVO 140 mg (n=44) every 2 weeks. Of the 107 patients, 43 had heterozygous familial hypercholesterolemia (HeFH), 38 CVD, and 26 both HeFH and CVD.

Results Median entry LDLC was 149 mg/dL for all patients, 181 for HeFH only, 132 for CVD only, and 161 for both HeFH and CVD. For the full cohort, 73 of 107 patients (68%) achieved LDLC <70 mg/dL on treatment. Of the 43 patients with HeFH only, 51% achieved LDLC <70 mg/dL on ALI or EVO. Of the 38 with CVD only, 87% achieved LDLC <70 mg/dL. In 26 patients with both HeFH and CVD, 69% achieved LDLC <70 mg/dL. Of 33 patients on ALI 75 mg, 24 (73%) achieved LDLC <70 mg/dL. Of 30 patients on ALI 150 mg, 21 (70%) achieved LDLC <70 mg/dL. Of 44 patients on EVO 140 mg, 28 (64%) achieved LDLC <70 mg/dL.

Conclusion Optimal LDLC reduction to <70 mg/dL was achieved in 73 of 107 (68%) in our cohort with EVO or ALI, demonstrating the central importance of ALI and EVO in high-risk patients who otherwise do not achieve LDLC <70 mg/dL with maximal tolerated LDLC lowering regimens.

C-7 ATHEROTHROMBOSIS IN 153 PATIENTS WITH PREMATURE CORONARY ARTERY DISEASE

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Specific aim In 153 patients who sustained premature cardiovascular disease (CVD) events \leq age 45, we evaluated the contribution of thrombosis to atherosclerosis-atherothrombosis. **Methods:** Measures of thrombophilia-hypofibrinolysis were obtained in 153 patients with CVD \leq age 45 compared to 110 healthy normal controls and 110 patients who had venous thromboembolism (VTE without CVD). **Results:** Of the 153 CVD patients, 121 (79%) had sustained myocardial infarction, 70 (46%) had coronary artery stenting, and 53 (35%) had coronary

artery bypass grafts. The patients' first CVD event occurred at age 20 to ≤ 25 in 4 patients, 25–30 in 19, 30–35 in 24, 35–40 in 51, and 40 to ≤ 45 in 55. At study entry, mean (standard deviation) and 25th, 50th, and 75th percentile levels for LDL cholesterol were 130 (61) and 89, 126, and 162 mg/dL; for triglycerides were 349 (640) and 122, 193, and 346 mg/dL; and for HDL cholesterol were 39 (11) and 31, 37, and 44 mg/dL, respectively. Of the 153 patients, 56 (37%) smoked, 58 (38%) had hypertension, and 56 (37%) were diabetic. Patients with premature CVD differed from normal healthy controls for high Factor VIII (10/44 [23%] vs 7/103 [7%], $p < 0.01$), high homocysteine (31/151 [21%] vs 5/107 [5%], $p = 0.0002$), low Protein C (8/43 [19%] vs 6/96 [6%], $p = 0.034$), low free Protein S (5/42 [12%] vs 2/96 [2%], $p = 0.027$), high ACLA IgM (11/129 [9%] vs 2/109 [2%], $p = 0.041$), and Lupus Anticoagulant (4/27 [15%] vs 2/110 [2%], $p = 0.014$). There were no ($p > .05$) differences between cases and VTE controls excepting free Protein S which was more often low in VTE controls (24/85 [28%] vs 5/42 [12%], $p = 0.045$). Conclusions: In 153 hyperlipidemic patients with premature CVD \leq age 45, familial and acquired thrombophilias were pervasive including high Factor VIII, high homocysteine, low Protein C, high ACLA IgM, and Lupus Anticoagulant. Thrombophilia appears to be an important etiology for premature atherosclerotic-atherothrombotic CVD. Moreover, thrombophilia in the premature CAD patients was comparable to VTE controls without CVD, emphasizing the pervasive nature of thrombophilia and atherothrombosis in patients identified by premature CVD.

C-8 IS HEAT HARD ON THE HEART?

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10.1136/jim-2017-000448.17

Introduction Heat stroke is an acute thermoregulatory failure that often results from exposure to high temperatures and progresses to multi-organ failure. The most common cardiac manifestations include tachycardia and non-specific ECG changes. ST-segment elevation in heat stroke is rare and is speculated to be due to myocardial ischemia. We present a case of ST-segment elevation in a patient with heat stroke and multi-organ failure with normal cardiac function.

Case Report A 50 year old male was admitted for severe non-exertional hyperthermia associated with multi-organ failure. He was found unconscious with a rectal temperature of 43°C, acute respiratory failure, acute tubular necrosis, severe rhabdomyolysis, disseminated intravascular coagulation and shock liver. His initial pertinent laboratory results included a potassium of 6.1 mEq/L, creatinine 4.52 mg/dL and creatinine kinase 340,000 U/L. His cardiac enzymes were up trending with a maximum troponin of 5.45 ng/mL. His urine toxicology was negative. His electrocardiogram (EKG) showed ST-segment elevation and T wave inversions in leads V4-V6. The echocardiogram, however, revealed a normal ejection fraction with no wall motion abnormality. Endotracheal intubation was performed to protect the airway and the patient was started

on “arctic sun” external cooling system. Furthermore, the patient was started on continuous renal replacement therapy and vasopressors to maintain perfusion. He improved symptomatically and the EKG changes resolved quickly as the body temperature improved over the next 48 hours. Once the patient had recovered, a nuclear stress test was performed, which showed no signs of ischemia.

Discussion Myocardial injury may occur during heat stroke, resulting in the release of cardiac enzymes and ST-segment elevation. Such findings might behave as diagnostic pitfalls by mimicking the presentation of coronary artery occlusive disease. To the best of our knowledge, no previous studies have reported cardiac enzyme elevation and ST-segment elevation without wall motion abnormalities on echocardiography. In our patient, the EKG changes resolved in the absence of any specific treatment for acute coronary syndrome. Because of these findings and a normal nuclear stress test, acute myocardial infarction was ruled out. Conditions other than acute myocardial infarction may cause ST segment elevation on EKG, which raises the question whether ST segment elevation in patients with heat stroke in the absence of coronary artery occlusion is simply an aberrant EKG finding or truly a reflection of myocardial damage.

Conclusion This case reveals that the multi-organ failure seen in heat stroke does not spare the heart. However, such damage is likely to be transient and not necessarily due to myocardial infarction.

C-9 MINOR CONSTITUENTS REMOVED RICE BRAN OIL AND SESAME OIL AS COMPARED TO NATIVE OILS CHANGES THE ARACHIDONIC ACID LEVELS AND LPS INDUCED ACUTE RETINAL INFLAMMATION IN RATS

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Retinal lipids are rich in polyunsaturated fatty acids, which are susceptible to oxidation initiated by oxygen free radicals. The minor constituents present in dietary oils such as Rice bran oil (RBO) and Sesame oil (SESO) scavenge oxygen free radical and exhibit anti-inflammatory property. The unsaponifiable fraction (UF) of RBO and SESO contain minor constituents like gamma oryzanol (γ -ORY) and sesamin respectively. The beneficial effects of γ -ORY/ sesamin on retinal inflammation has not received adequate attention. To evaluate this UF from RBO-Native (N) and SESO-N were removed by column chromatography and designated as UF-RBO and UF-SESO, respectively. These oils were supplemented at 10Wt% levels in AIN-93 diet and fed to rats for a period of 60 days. The retinal lipids of rats fed MCR oils showed higher levels of total cholesterol, triacylglycerols and phospholipids when compared to rats fed oils containing UF. The fatty acid composition of retinal lipids showed an increased level of arachidonic acid (20:4) ($P < 0.05$) in rats fed MCR oils as compared to rats given native oils. The rats fed MCR oils generated higher levels of prostaglandin (PGE_2), thromboxane (TXB_2), leukotriene B_4 (LTB_4) and LTC_4 by up-regulating the expressions of cyclooxygenase (COX)-2 and 5-lipoxygenase

(LOX). The expression of PPAR γ was down-regulated in rats fed MCR oils. However when UF was added back to MCR oils and fed to rats the expression of PPAR γ was up-regulated with a down-regulation of COX-2 and 5-LOX. Hence, minor constituents present in the dietary oils such as RBO and SESO influenced LPS induced acute retinal inflammation by modulating eicosanoid metabolism.

C-10 PERICARDITIS SECONDARY TO COXSACKIE B VIRUS INFECTION PRESENTING AS CARDIAC TAMPONADE

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Introduction Coxsackieviruses belong to the family Picornaviridae and the genus Enterovirus, which also includes poliovirus and echovirus. Enteroviruses are among the most common and important human pathogens. Coxsackie B is a group of six serotypes of Coxsackievirus which can trigger illnesses ranging from mild gastrointestinal distress to severe pericarditis and myocarditis. If not treated promptly Coxsackie B virus induced pericarditis can lead to life threatening cardiac tamponade.

Case summary A 25-year-old male patient with history of seizure disorder with his last episode being seven years ago and on no medications for seizures presented with hypotension with mean arterial pressures ranging 50–55 mm Hg, tachycardia with heart rates ranging 110–120 bpm, chest pain, fevers, chills which had been going on for around a week. Initial encounter in the emergency room was concerning for cardiac tamponade with labs showing mild leukocytosis, elevated creatinine at 2.5, elevated AST at 205, ALT 133, Total CK at 267 with normal CKMB and Troponin I, INR 2.6 and ESR of 290. His ECG showed sinus tachycardia without any changes in the PR or the ST segments. Echocardiography was done showing pericardial fluid with tamponade physiology confirming the suspicion. He underwent emergent pericardiocentesis and had a Jackson-Pratt (JP) drain placement. The pericardial fluid had increased white blood cells at 5000 per cubic millimeter but didn't grow any pathogens on the gram stain and culture. The differential diagnosis included infectious etiologies, Collagen vascular diseases and malignancy. A comprehensive workup was performed which showed negative ANA, RF, RPR, HIV, Viral hepatitis panel, Chlamydia, EBV, CMV, Ehrlichia, Histoplasma, Aspergillus, Mycoplasma tuberculosis with pending Coxsackie A and B titers. He was started on anti-inflammatory therapy with Aspirin and Colchicine and given significant clinical improvement after the JP drain removal he was discharged home with close follow up scheduled. Four days after discharge, the patient came back to the emergency room with hypotension, tachycardia and shoulder pain. He was found to have cardiac tamponade on physical exam confirmed by a trans-thoracic echocardiogram; but this time, with a posteriorly located loculated pericardial effusion. He was emergently taken to the operative room for a pericardial window formation. The pericardial sack was found to have fibrinous fluid with multiple adhesions which had to be lysed intraoperatively. During this hospital stay, the serologies from his previous admission came back positive for Coxsackie B virus and were negative

for Coxsackie A virus. He was managed in intensive care unit initially and was discharged after a three week hospital stay where he was managed with supportive care and aggressive cardiac rehabilitation.

Conclusion Coxsackie B virus can cause full-fledged pericarditis leading to cardiac tamponade which can in some cases even lead to fibrinous pericarditis needing pericardial window formation.

C-11 HEAD TO HEAD EFFICACY COMPARISON OF ALIROCUMAB 75 AND 150 MG VS EVolocumab 140 MG IN REAL WORLD PATIENTS

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Background In 107 high-risk patients, 60% with cardiovascular disease (CVD), and with median low-density lipoprotein cholesterol (LDLC) 149 mg/dL despite maximum tolerated lipid lowering therapy (MTLT), we compared and contrasted efficacy-safety of Alirocumab (ALI 75 mg, 150 mg) and Evolocumab (EVO 140 mg).

Methods We followed 107 patients for a median 24 weeks, 33 on ALI 75 mg, 30 on ALI 150 mg, and 44 on EVO 140 mg bi-weekly. After adjustment for age, race, gender, body mass index, treatment duration, entry LDLC, heterozygous familial hypercholesterolemia (+/-), statin intolerance (+/-), and previous CVD (+/-), absolute and % changes in LDLC were compared for the ALI and EVO doses. Treatment side effects were also compared.

Results Of the 107 patients, 70 could not tolerate any statin. LDLC reduction from baseline MTLT was 45% for ALI 75 mg, 64% for ALI 150 mg, and 63% for EVO 140 mg ($p < 0.0001$ for all). Absolute and % LDLC lowering was greater on ALI 150 mg than 75 mg ($p = 0.0013$, $p = 0.0018$), and greater on EVO 140 mg than ALI 75 mg ($p = 0.017$, $p = 0.005$). No differences were observed between any groups for treatment-associated side effects ($p > 0.05$).

Conclusion EVO 140 mg and ALI 150 mg did not differ in LDLC reduction, however ALI 75 mg had lower absolute and % LDLC reduction than ALI 150 mg or EVO 140 mg. Side effect profiles did not differ. All 3 groups represent paradigm shifts in LDLC lowering, particularly for patients with statin intolerance who comprised 65% of our 107 high-risk hypercholesterolemic patients.

C-12 IS MITRAL STENOSIS ASSOCIATED WITH GI BLEEDING, A TWIST ON HEYDE

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Introduction Heyde's syndrome is the link between aortic stenosis and angiodysplasia leading to Gastrointestinal (GI)

bleed. There have been multiple cases and theories leading to this phenomenon, including the loss of von Willebrand factor (vWF) through shear factor of a stenotic valve. This association is further validated by the cessation of GI bleed after aortic valve replacement. The question posed is, if aortic stenosis can lead to GI bleeding through loss of vWF or other mechanisms, would mitral stenosis cause a similar presentation?

Methods A single center, retrospective chart analysis was done on patients, age 18 and over, with evidence of mitral stenosis on echocardiogram for any signs of GI bleeding. The outpatient clinic notes and admission notes, along with colonoscopies to detect the presence of angiodysplasia were reviewed for GI bleeding. Patient's with concomitant aortic stenosis were excluded.

Results 162 patients were found to have mitral stenosis over the study period. Mitral stenosis group were 35% males and 65% female. Average age was 61 years old. Approximately 4% had mitral stenosis secondary to rheumatic heart disease and 45% due to calcified annulus. Of 162 patients with mitral stenosis, 7 (4.3%) patients had evidence of gastrointestinal bleed versus 16 (10%) of non-mitral stenosis group ($p=0.06$). Patients with mitral stenosis and GI bleed were found to have arteriovenous malformation (AVM) (35%), gastric or duodenal ulcer (35%), colon cancer (3%) and diverticulitis (37%).

Conclusion Mitral stenosis does not have an increase incidence of GI bleeding when compared to the control group, though the P value was not statistically significant. vWF is thought to be decreased because of increased shear force through a stenotic valve. Flow through the stenotic mitral valve is orders of magnitude lower than the flow through a stenotic aortic valve given the force of contractility in the atria compared to the ventricle, therefore is unlikely to cause decrease in vWF to lead to GI bleeds.

Endocrinology/Metabolism

A-11 ENDOTHELIN CONVERTING ENZYME 1 EXPRESSION IN THE MOUSE PLACENTA

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Objective Endothelin converting enzyme 1 (ECE1) is one of the key enzymes involved in the proteolytic processing of Endothelin 1 (ET1), a potent vasoactive peptide and mediator of vascular adaptation. ET1 is thought to be important in the pathogenesis of preeclampsia, intrauterine growth restriction (IUGR), and preterm labor. Its role in vascular adaptation is also critical in normal placental development. While much is known about ET1 and its role in pregnancy conditions, less is known about ECE1 and its role in regulating production of ET1. ECE1 is a membrane bound extracellular enzyme; therefore knowing its distribution in the placenta is essential to understanding its role. The objective of this study was to describe placental localization and spatial distribution of ECE1 in the mouse placenta at 12.5 days of gestation.

Study Design Using immunohistochemical analysis and immunofluorescence, ECE1 expression in the mouse

placenta was studied. Using a novel mouse model with heterozygous mice harboring beta-galactosidase knocked into the *Ece1* locus, we were able to use beta galactosidase activity to identify cells expressing the *Ece1* gene. By having the knock in allele present in either the dam or the sire, we can distinguish ECE1-expressing cells of fetal and maternal origin. Placentas obtained from mice at 12.5 days post coitus were stained for beta galactosidase. Immunofluorescence was performed for ECE1 and Platelet/endothelial cellular adhesion molecule 1 (PECAM).

Results Beta galactosidase staining was demonstrated at the maternal fetal interface of mouse placentas derived from dams harboring the knock-in allele. Immunofluorescence studies show co-localization of ECE1 and PECAM within the same cells (see image). These Results are currently being extended to 18.5-day placentas and by performing immunofluorescence for cytokeratin.

Conclusion Our Results indicate that in 12.5-day mouse placentas, ECE1 is only expressed in PECAM positive cells. Cytokeratin staining will distinguish endothelial from trophoblast cells. A better understanding of this enzyme's role will elucidate its potential as a target for prognosis and therapy in pregnancy disease states involving pathologic vascular adaptation and tone, such as preeclampsia and IUGR.

A-12 SHORT-TERM METHIONINE DEPRIVATION IMPROVES METABOLIC BIOMARKERS OF OBESITY

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Obesity has become an epidemic in the United States and worldwide. Obesity, along with its associated metabolic disorders including hyperglycemia and dyslipidemia, predisposes patients to two major types of chronic diseases, diabetes and cardiovascular diseases and thus poses an imminent threat to our economy and healthcare system. New strategies to combat obesity are urgently needed. Recent studies in mice and humans have found that dietary methionine restriction produces many beneficial effects on metabolic health including reducing adiposity, improving glycemic control and promoting lipid homeostasis. However, the difficulty of adhering to a methionine-restricted diet for a long term limits its translational potential as an approach to treat obesity. To address this problem, we propose short-term methionine deprivation as a rapid and more effective alternative to treat obesity and its associated metabolic disorders. To determine the impact of methionine deprivation on metabolic health, we placed C57BL/6J mice on a methionine-free diet for 5 weeks. We observed that methionine deprivation results in progressive weight loss, and body composition analysis revealed that 5 weeks of methionine deprivation led to a profound reduction in fat mass, with less pronounced decreases in lean and total body mass, indicating that methionine deprivation is an effective approach to reduce adiposity. Calorimetry-based metabolic chamber experiments after 2 weeks of diet feeding indicated that mice fed

OMet diet have increased food consumption and heat production (normalized to body weight), decreased voluntary movement, and an improved metabolic flexibility as reflected by a greater shift between the daytime respiratory exchange ratio (RER) and nighttime RER. Analysis of glycemic control by glucose, insulin and pyruvate tolerance test indicated that methionine deprivation is effective in improving glucose tolerance and hepatic insulin sensitivity. To evaluate the potential of short-term methionine deprivation as a strategy to treat obesity, we examine the metabolic effects of short-term methionine deprivation in a high-fat-diet-induced obesity. 5 weeks of methionine deprivation not only significantly reduces the adiposity induced by high-fat-diet feeding, but also corrects other metabolic abnormalities associated with obesity including hyperglycemia, hyperinsulinemia, dyslipidemia. At the transcriptional level, we found that short-term methionine deprivation produces a coordinated transcriptional remodeling of genes involved in lipid metabolism, reflected by downregulation of lipogenesis and upregulation of fatty acid oxidation in the liver and a simultaneous upregulation of lipogenesis and fatty acid oxidation in adipose tissue. Molecular signaling analysis revealed downregulation of eIF2 α signaling and mTORC1 signaling in both liver and muscle. Collectively, our study demonstrates that short-term dietary deprivation of methionine produces many similar, but more profound metabolic benefits as long-term methionine restriction. As such, we propose that this dietary strategy might be used as an adjunct in combination with drugs to treat obesity and obesity-related disorders such as type 2 diabetes.

A-13 OBESITY DRIVES THE DECLINE IN LARGE HDL SUBSPECIES AMONG MALE ADOLESCENTS

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Background We have shown that adolescents with type 2 diabetes have an altered HDL subspecies profile, characterized by a depletion of large apoE rich HDL particles. We have also shown a significant inverse relationship between this profile and arterial stiffness suggesting that the loss of these particles is associated with early atherosclerosis. In this study, we sought to evaluate known risk factors (that contribute to the depletion of large HDL subspecies in adolescents.

Methods To evaluate the contributions of obesity, insulin resistance and diabetes to loss of large HDL particles, we studied five adolescent groups (n=20 per group) with highly specific phenotypes. Insulin resistance was defined by fasting insulin levels and HOMA-IR. Adolescent groups were: lean insulin sensitive (normal body mass index (BMI) with no insulin resistance); lean insulin resistant (normal BMI with insulin resistance), obese insulin sensitive (obese BMI with no insulin resistance), obese insulin resistant (obese BMI with insulin resistance), and with type 2 diabetes (obese with insulin resistance and type 2 diabetes by

the American Diabetes Association criteria). Stored plasma from each participant was fractionated using gel filtration chromatography to isolate HDL subspecies.

Results The mean age of the cohort was 17.9 \pm 1.6 years. Groups did not differ in age and race (50% Caucasian, 50% African American, all male). Large rich HDL subspecies declined significantly across each group from lean insulin sensitive, to lean insulin resistant, to obese insulin sensitive, to obese insulin resistant to type 2 diabetes ($p<0.0001$). An inverse relationship was also seen for small HDL particles ($p<0.0001$). Medium size particles did not differ across groups. These data were confirmed by nuclear magnetic resonance (NMR)spectroscopy. Obesity explained ~50%, insulin resistance ~25%, and diabetes ~10% of the decline in large particles between lean insulin sensitive to type 2 diabetes participants. Twenty percent remained unexplained.

Conclusions Obesity appears to drive the decline in large atheroprotective HDL particles in male adolescents. However, contributions of insulin resistance and type 2 diabetes are evident. Whether weight loss reverses this profile and has the potential to improve cardiovascular risk remains to be determined.

A-14 THROMBOTIC EVENTS AFTER STARTING TESTOSTERONE THERAPY IN 83 PATIENTS FOUND TO HAVE FAMILIAL AND ACQUIRED THROMBOPHILIA

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In 84 patients (76 men, 8 women) who sustained 101 venous thromboembolic events (VTE) after starting testosterone therapy (TT), our specific aim was to assess for familial and acquired thrombophilia. We compared thrombophilia in the 84 cases versus 110 (53 men, 57 women) patient controls having unprovoked VTE without TT (VTE controls, no TT). Of the 84 patients, 62 had deep venous thrombosis-pulmonary embolism (DVT-PE), 18 had osteonecrosis (1 also had DVT-PE), 4 had ocular thrombosis (1 also had DVT-PE and osteonecrosis), and 2 had an ischemic stroke. After starting TT, the VTE events occurred at a median of 6 months, 25 and 75th percentiles 2 and 12 months. Cases on TT differed from VTE controls (no TT) for factor V Leiden heterozygosity (22 of 82 [27%] vs 14/110 [13%], $p=0.016$) and for the lupus anticoagulant (11 of 76 TT cases [14%] vs 4/91 VTE controls [4%], $p=0.03$). After a first thrombotic event and continuing TT, 11 cases had a second thrombotic event, despite adequate concurrent anticoagulation, 6 of whom, still anticoagulated, had a third thrombosis. Before starting TT, screening for familial and acquired thrombophilia, particularly Factor V Leiden and the lupus anticoagulant, should identify men and women at high risk for VTE with an adverse risk-benefit ratio for TT. When TT is given to patients with familial and acquired thrombophilia, thrombosis may occur and recur in thrombophilic men and women despite anticoagulation.

A-15 COMPARISON OF β -CELL FUNCTION BETWEEN ADULTS AND ADOLESCENTS WITH DYSGLYCEMIA

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Progressive impairment in β -cell function has been described with progression from normoglycemia to dysglycemia to type 2 diabetes (T2D) using direct measurements and model-based approaches. We have evaluated qualitative and quantitative differences in this impairment between adults and adolescents along the clinical spectrum of glucose tolerance. Direct and model-based measures of β -cell function were calculated using standard 75 g oral glucose tolerance tests. We applied minimal models using SAAM II modeling software to derive total, static (ϕ iS) and dynamic (ϕ iD) components of β -cell function. **Results** from 50 adolescents (mean \pm SD BMI 39.0 \pm 8.2 kg/m², 12–18 y) and 122 adults (BMI 30.2 \pm 7.1 kg/m², 22–66 y) were analyzed, with paired β -cell function and insulin sensitivity data available in 39 adolescents and 94 adults. Both groups showed a decline in direct and modeled measures of β -cell function across stages of dysglycemia. Indices of insulin production and insulin sensitivity differed by clinical stage, and by age group (e.g. insulinogenic index IGI $p=0.001$; HOMA-IR $p=0.044$). Dysglycemic adolescents showed higher IGI than adults (5.8 \pm 3.76 vs. 1.45 \pm 1.9, $p<0.001$), and greater dynamic insulin secretion (ϕ iD, 2215 \pm 1613 vs. 1051 \pm 736, $p=0.001$; ϕ iS 139 \pm 160 vs. 77 \pm 59, $p=0.05$), with greater HOMA-IR (11.01 \pm 7.46 vs. 4.03 \pm 2.86, $p=0.005$) and nonsignificantly lower modeled Si. Disposition indices for modeled secretion components were nonsignificantly lower in dysglycemic adolescents. No group differences in β -cell function were apparent in established T2D. Among adolescents but not adults, IGI was associated with LDL-C ($r=0.46$ $p=0.004$) and triglycerides ($r=0.40$, $p=0.007$). Adolescents with dysglycemia exhibit higher levels of insulin production, in the setting of greater insulin resistance, than comparably dysglycemic adults. Group differences were no longer apparent in established T2D.

A-16 TREATMENT OF SEVERE HYPERTRIGLYCERIDEMIA (500 TO \geq 2000 MG/DL) IN 405 PATIENTS

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Specific aim In 405 patients with severe hypertriglyceridemia (HTG) (500– \geq 2000 mg/dL) our specific aim was to identify variables contributing to HTG and assess success of TG lowering therapy.

Methods Four-hundred and five patients with HTG (500 to \geq 2000 mg/dL) were assessed in order of referral for diagnosis and treatment. Initial lifestyle modifications were fat free diet if TG was >2000 mg/dL, $<15\%$ calories as fat if TG was 1000–2000 mg/dL, and $<20\%$ of calories as fat if TG was ≥ 500 <1000 mg/dL, with a polyunsaturated to

saturated ratio of >2 to 1 as well as calorie restriction if BMI was ≥ 30 . Maintenance fat intake was targeted at $<25\%$ of calories. Hemoglobin A1C was targeted to $<7\%$. Fibric acids and 4 g/day of branded long chain marine omega-3 fats were given, except in those patients in TG groups ≥ 1500 mg/dL where omega-3 fats of 6–8 g/day were given. Nicotinic acid was not used. Alcohol was restricted to zero. Estrogens and (where possible) corticosteroids were discontinued. TG at entry and on Rx (mg/dL), 25th, 50th, 75th percentiles, duration of therapy, and changes on therapy ($^{\#}p<0.0001$) were as follows: Group TG: 500–1000 1000–1500 1500–2000 ≥ 2000 mg/dL
 n=212 74 54 65 Entry TG 635, 683, 820 1129, 1250, 1390 1630, 1714, 1830 2280, 2812, 3534 TG on Rx 187, 285, 467 $^{\#}$ 183, 354, 562 $^{\#}$ 183, 318, 502 $^{\#}$ 208, 423, 879 $^{\#}$
 Duration Rx (mo) 10, 26, 55 11, 25, 58 9, 32, 78 15, 30, 66 On therapy, TG levels were lowered ($p<0.0001$) in each TG group. On therapy, TG was to an optimal target ≤ 200 mg/dL in 28% of patients. Additionally, 44% of patients had TG reduced to 200–500 mg/dL and 17% had a TG reduction to 500–1000 mg/dL. As a result of treatment, $\sim 90\%$ of patients had TG reduced below the level of risk for pancreatitis (>1000 mg/dL). Major contributors to TG >500 mg/dL were poorly controlled diabetes, present in 43–58% of patients, and alcohol excess (>21 beverages/week), present in 9–28% of patients. In the 4 TG groups at entry, 51%, 48%, 63%, and 67% were diabetic, hemoglobin A1C was $\geq 7\%$ in 43%, 58%, 36%, and 47%, fasting blood glucose >126 in 40%, 47%, 45%, and 47%, and alcohol excess (>21 drinks/week) in 19%, 18%, 28%, and 9%. Currently available therapy successfully lowers TG in patients with severe hypertriglyceridemia, and largely prevents pancreatitis. However, new and more effective medications are needed to bring TG <200 mg/dL in a majority of patients with initial TG ≥ 500 mg/dL.

A-17 TREATMENT OF SEVERE HYPERTRIGLYCERIDEMIA (500 TO \geq 2000 MG/DL) IN 636 PATIENTS

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Specific aim In 636 patients with severe hypertriglyceridemia (HTG) (500– ≥ 2000 mg/dL) our specific aim was to identify variables contributing to HTG and assess success of TG lowering therapy.

Methods Six-hundred and thirty-six patients with HTG (500 to ≥ 2000 mg/dL) were assessed in order of referral for diagnosis and treatment. Initial lifestyle modifications were fat free diet if TG was >2000 mg/dL, $<15\%$ calories as fat if TG was 1000–2000 mg/dL, and $<20\%$ of calories as fat if TG was ≥ 500 <1000 mg/dL, with a polyunsaturated to saturated ratio of >2 to 1 as well as calorie restriction if BMI was ≥ 30 . Maintenance fat intake was targeted at $<25\%$ of calories. Hemoglobin A1C was targeted to $<7\%$. Fibric acids and 4 g/day of branded long chain marine omega-3 fats were given, except in those patients in

TG \geq 1500 mg/dl groups where omega-3 fats of 6–8 g/day were given. Nicotinic acid was not used. Alcohol was restricted to zero. Estrogens and (where possible) corticosteroids were discontinued. TG at entry and on Rx (mg/dl), 25th, 50th, 75th percentiles, duration of therapy, and changes on therapy ($^{\#}p < 0.0001$) were as follows: Group TG: 500–1000 1000–1500 1500–2000 \geq 2000 mg/dl
 n=414 103 55 64 Entry TG 560,601,684 1083,1164,1350 1630,1697,1830 2279,2798,3638 TG on Rx 183, 282, 462 $^{\#}$ 188, 364, 635 $^{\#}$ 183, 305, 483 $^{\#}$ 206,414,881 $^{\#}$ Duration Rx (mo) 10, 26, 54 11,24,47 9,32,78 14,31,68 On therapy, TG levels were lowered ($p < 0.0001$) in each TG group. On therapy, TG was to an optimal target \leq 200 mg/dL in 28% of patients. Additionally, 46% of patients had TG reduced to 200–500 mg/dL and 17% had a TG reduction to 500–1000 mg/dL. As a result of treatment, 91% of patients had TG reduced below the level of high risk for pancreatitis (>1000 mg/dL). Major contributors to TG >500 mg/dl were poorly controlled diabetes, present in 37%–54% of patients, and alcohol excess (> 21 beverages/week), present in 14–30% of patients. In the 4 TG groups at entry, 51%, 46%, 63%, and 67% were diabetic, hemoglobin A1C was \geq 7% in 44%, 54%, 37%, and 42%, fasting blood glucose >126 in 39%, 48%, 44%, and 47%, and alcohol excess (>21 drinks/week) in 18%, 22%, 30%, and 14%. By step-wise multiple regression with explanatory variables gender, age, TG and glucose at entry, entry glucose <126 mg/dl or ≥ 126 mg/dl, change in glucose on therapy, and duration of treatment, the greater the change in glucose on treatment, the higher the glucose at entry, the longer the treatment period, and the higher the entry TG, the greater the reduction in TG (partial $R^2=1\%$, $p < 0.0001$; partial $R^2=1.3\%$, $p < 0.0001$; partial $R^2=0.9\%$, $p=0.002$; partial $R^2=60\%$, $p < 0.0001$). Currently available therapy successfully lowers TG in patients with severe hypertriglyceridemia, and largely prevents pancreatitis. However, new and more effective medications are needed to bring TG <200 mg/dl in a majority of patients with initial TG ≥ 500 mg/dl.

A-18 DIABETIC PAPILOPATHY

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Introduction Diabetic papillopathy (DP) is a rare condition that occurs in 1.4% of patients with type 1 and type 2 diabetes mellitus (DM). Patients present clinically with unilateral or bilateral optic disc edema and variable visual loss. Its cause is poorly understood. DP can occur in patients irrespective of metabolic control or severity of diabetic retinopathy. Most authors believe DP is a form of ischemic optic neuropathy. To date there are no specific diagnostic criteria for DP and it remains a diagnosis of exclusion. In addition, while DP has a generally favorable prognosis, there is no validated treatment. Success with intravitreal or periocular corticosteroids and anti-vascular

endothelial growth factors has been reported in a few case series. As internists, it is important to be aware of DP and recognize it early because it can mimic ominous processes such as infection, inflammation, metastatic infiltration, malignant hypertension, and raised intracranial pressure. This encounter intends to highlight approach to a patient with DP for internists prior to referral to ophthalmology. Our case also serves to raise awareness of DP as a potential albeit rare ocular complication associated with DM.

Case Description A 19 year old male patient with uncontrolled type 1 DM presented to the emergency room (ER) with sudden onset blurry vision in his right eye. He denied any visual symptoms in the left eye. The visual deficit was painless. Patient also denied having any other neurological symptoms especially headache, diplopia, painful eye movements, weakness, numbness or tingling in his extremities. His last hemoglobin A1c (HbA1c) measured one month prior was 14.1% when he had been admitted with diabetic ketoacidosis (DKA). Patient did not remember his last eye examination. Physical examination revealed a visual acuity of 20/50 OD and 20/20 OS with normal intraocular pressure. Pupils were equal and reactive to light bilaterally. Extraocular muscle movements were painless. Confrontation testing of the visual field showed right inferonasal field deficit. Funduscopic examination demonstrated significant bilateral optic disc swelling, OD $>$ OS and considerable peripapillary hyperemia. Macula appeared normal on both sides. Computed tomographic (CT) scan of the head was obtained which showed no signs of raised intracranial pressure. Blood pressure, complete blood count and basic metabolic panel was within normal limits. Urgent ophthalmology consult was requested. Slit lamp examination was performed which was consistent with funduscopic findings and exhibited bilateral optic disc edema with peripapillary retinal changes, including heme and cotton wool spots. There was no evidence of **Background:** diabetic retinopathy. Magnetic resonance imaging (MRI) and magnetic resonance venography (MRV) of the head was ordered and it was unremarkable. Further investigations including serum angiotensin-converting enzyme, anti-nuclear antibody, vitamin B12, folate, erythrocyte sedimentation rate, C reactive protein, human immunodeficiency virus 1/2 immunoassay, Bartonella antibody, and fluorescent treponemal antibody tests were normal. Fluorescein angiography demonstrated disc staining consistent with DP. With the diagnosis of bilateral diabetic papillopathy, regular follow up was scheduled. Patient was counseled on the importance of improvement of glycemic control and the potential need for lumbar puncture if his vision deteriorated. At 1 month follow up, patient's visual deficit and DP had improved.

Conclusion In **Conclusion**, DP should be considered in the differential diagnosis of papilledema in patients with DM. Furthermore, it is important for internists to be aware of the full spectrum of ocular diabetic complications in order to recognize and manage them at an early stage given the significant disease burden.

A-19 COMPARING QUALITY OF LIFE IN GCK-MODY, HNF1A-MODY, TYPE 1, AND TYPE 2 DIABETES

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Background Maturity Onset Diabetes of the Young (MODY) is young onset, autosomal dominant diabetes solely due to highly penetrant single gene mutations in genes important to beta cell function. It accounts for ~2% of all diabetes. Mutations in two genes, HNF1A and GCK, account for ~90% of all MODY. MODY due to HNF1A and GCK is clinically actionable. Treatment is not needed for GCK-MODY and HbA1c doesn't change. First-line therapy for HNF1A-MODY is inexpensive sulfonylureas pills. The associated decreased costs and medical surveillance and expected decrease in burden of diabetes care may have positive effects on quality-of-life (QOL) compared to polygenic forms of diabetes. However, QOL has not been rigorously investigated in MODY in general, with only one study carried out in a Polish population. To our knowledge, analysis of QOL in a US MODY population and comparisons to polygenic forms of diabetes have not been carried out. Aim. We sought to define and compare QOL in US patients with GCK-MODY and HNF1A-MODY. We further aimed to compare QOL between GCK-MODY, HNF1A-MODY, Type 1 Diabetes and Type 2 Diabetes.

Methods Cross-sectional study with convenience sample of patients, ages 18–50 years, with Type 1 and Type 2 diabetes seen in the University of Chicago Kovler Diabetes Center and subjects enrolled in the University of Chicago Kovler Monogenic Diabetes Registry with GCK-MODY or HNF1A-MODY. Subjects were administered the ADDQoL-19, a validated, reliable 21-item tool (with 19 individual domain items) to assess diabetes-related QOL. Surveys were scored according to the survey-specific methods. Briefly, two overview items were scored individually. Individual Domains were given a weighted impact score and each subject was given an Averaged Weighted Impact Score (AWI). AWI scores could range from +3 to –9, with more negative scores signifying more impact of QOL. AWI was compared between GCK- and HNF1A-MODY and for all diabetes types.

Results The overall AWI for GCK-MODY was –1.05 +/- 1.4. The lowest Domain Weighted Impact Scores were in Freedom to drink (–2.35) and Freedom to eat (–2.65) and Feelings about the future (worries, hopes) (–3.06). The overall AWI for HNF1A-MODY was –1.61 +/- 1.01, signifying a higher impact on QOL compared to GCK-MODY. The lowest Domain Weighted Impact Scores were in Physical Activity (–2.11), Finances (–3.32), Family life (–2.95), Freedom to eat (–3.42) and Feelings about the future (worries, hopes) (–4.58). There was a statistically significant difference in AWI scores between GCK-MODY, HNF1A-MODY, Type 1 Diabetes and Type 1 Diabetes with AWI scores of –1.05, –1.61, –2.21 and –3.49, respectively. These differences were driven by GCK-MODY

differing from both Type 1 and Type 2 Diabetes and Type 1 and Type 2 Diabetes differing from one another. In regression analysis controlling for age, sex, ethnicity, diabetes duration and insulin treatment, diabetes type remained a predictor of AWI score.

Discussion MODY QOL in our study was similar to that found in the Polish study of QOL in MODY (GCK QOL AWI –1.05 vs. –0.95; HNF1A QOL AWI –1.61 vs. –1.52). While there was fairly minimal effect on QOL in GCK, freedom to eat/drink were affected despite GCK-MODY needing no treatment, including no special diet. QOL was less affected in HNF1A-MODY than in T1DM and T2DM, and there was no apparent effect of insulin in our study. Surprisingly, T1DM QOL was less affected than T2DM, which may be attributed to differences in socioeconomic status in the studied population, which were not controlled for in this study. Use of a convenience sample limits generalizability of our study. Additionally, patients with Type 2 Diabetes differed from other groups with regards to age and ethnicity. With these limitations, we show improved QOL in MODY compared to polygenic diabetes, further supporting the importance of accurate diagnosis of monogenic forms of diabetes.

B-8 ADIPOSE CREB3L3 MEDIATES OBESITY-INDUCED METABOLIC DYSFUNCTION

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A “metabolically healthy obese” subpopulation makes up an estimated 10–30% of the total obese population. While the preserved metabolic health of these individuals is attributed to having more subcutaneous fat accumulation, smaller adipocytes, reduced visceral fat inflammation, and low ectopic fat accumulation, the cellular mechanisms underlying this phenotype remain unclear. We have discovered that the fat-specific ablation (KO) of cyclic-AMP Responsive Element Binding Protein 3-like-3 (CREB3L3), a transcription factor that we have found to be selectively downregulated in obese subcutaneous fat, creates a phenotype strikingly similar to metabolically healthy obesity when KO mice are fed a high-fat diet (HFD). The KO mice become more obese than floxed wildtype (WT) controls, with significantly larger visceral epididymal and subcutaneous inguinal fat depots, but do not exhibit any signs of metabolic dysfunction. These mice do not exhibit the impaired glucose tolerance or insulin sensitivity expected with their larger body weight. Surprisingly, despite significant enlargement of their epididymal fat depot and adipocytes, these mice have a downregulation of visceral inflammatory markers. While the KO mice have significantly larger visceral adipocytes, the subcutaneous adipocytes are significantly smaller, and both the KO epididymal and inguinal fat depots trend towards having more total adipocytes. Despite their enhanced adiposity, KO mice do

not have increased circulating free fatty acids, triglycerides, cholesterol, or hepatic lipid accumulation. This reduction in circulating lipids despite the KO mice being more obese suggests that ablation of CREB3L3 in adipose tissue can reduce circulating lipids, which was confirmed in our chow-fed KO mice. Taken together, our data suggest that the ablation of CREB3L3 in adipose tissue can preserve metabolic homeostasis during obesity by improving lipid handling and reducing visceral inflammation.

B-9 MALE AND FEMALE SEX HORMONES DETERMINE METABOLIC EFFECTS OF HEPATIC MTORC2

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Rapamycin is an immunosuppressant and anticancer drug that extends lifespan in model organisms including mice, but side effects including metabolic disruption may limit its wide-scale use for diseases of aging. We have previously found that many side effects of rapamycin may be mediated by “off-target” disruption of the mechanistic target of rapamycin complex 2 (mTORC2), and that deletion of Rictor, an essential protein component of mTORC2, specifically in the liver.

Results in hepatic insulin resistance, disrupted glucose homeostasis and decreased male, but not female, lifespan. Here, we investigated the interaction of sex hormones and hepatic mTORC2 with respect to metabolic health and lifespan. We gonadectomized pre-pubertal male and female mice in which Rictor is specifically deleted in the liver (LRKO) and their wild-type littermates. Ovariectomy impaired glucose and pyruvate tolerance, while castration had no effect on glucose homeostasis. Deletion of Rictor strongly impaired glucose and pyruvate tolerance in male mice, regardless of surgery treatment. Intriguingly, Rictor deletion impaired glucose and pyruvate tolerance in female mice undergoing sham surgery, but had no further effect on ovariectomized mice. On the other hand, we observe that while sham operated LRKO mice accumulate less fat mass and die at faster rate than WT sham littermates, castrated LRKO respond similar than castrated WT littermates. These **Results** suggest that while female sex hormones are required for mTORC2 modulation of hepatic insulin signaling and glucose homeostasis, testosterone would sensitize male mice to loss of hepatic Rictor.

B-10 REVERSIBLE OSTEO NECROSIS OF THE KNEES ASSOCIATED WITH HOMOCYSTEINEMIA

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Thrombophilia can be etiologic for primary osteonecrosis, not secondary to high dose-long term steroids or alcoholism. Heritable thrombophilias like Factor V Leiden, the G20210A Prothrombin gene mutation, methylenetetrahydrofolate reductase (MTHFR) mutations, high Factors VIII and XI, can promote development of osteonecrosis, and environmental thrombophilia –promoting factors like oral contraceptives, estrogens, and testosterone hormonal therapy, smoking, etc. have a synergistic effect. A 32-year-old Caucasian female presented 5 years ago, with chief complaints of bilateral knee pains and inability to walk. She also had irregular periods, hair thinning, recent weight gain (70–80 lbs. from baseline over 1 year), intermittently irregular menstrual cycles, brownish discoloration in arm pits and nape of neck and 1 first trimester spontaneous abortion. A former smoker (8 pack years), she was taking oral contraceptives. She had been infertile and had a right oophorectomy. She was found to have hypothyroidism, polycystic ovarian syndrome, Vitamin D deficiency and insulin resistance. Her MRI showed bilateral multiple small (6 mm) osteonecrotic bone infarcts in distal femoral and medial tibial metaphysis with associated intra-articular effusion. Thrombophilia studies revealed MTHFR compound C677T-A1298C heterozygosity with resultant high homocysteine. Oral contraceptives were stopped, and to deal with the high homocysteine, she started L methyl folate 5 mg daily, Vitamin B6 50 mg daily, and Vitamin B12 2 mg daily, and to deal with the polycystic ovary syndrome, 2.55 g metformin daily. Over the next 1 month, she had symptomatic relief in her knee pains. She lost 21 lbs. over the period of the next 1 year. Currently, 5 years after the initial diagnosis, she has no knee pain. When osteonecrosis is associated with familial homocysteinemia and compound MTHFR heterozygosity, and accelerated by thrombophilic estrogen-progestin oral contraceptives, stopping the contraceptives and treatment with L-methylfolate-B6-B12 may resolve symptoms and stop progression of the disease, thus avoiding the otherwise usual total knee replacement within 2 years of diagnosis when not treated.

B-11 DECREASED CONSUMPTION OF SPECIFIC MACRONUTRIENTS PROMOTES METABOLIC HEALTH AND LONGEVITY

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Calorie restriction is the nutritional ‘gold standard’ in lifespan extension, and also improves metabolic health in many model organisms. This intervention is extremely difficult to sustain, especially in a population struggling with both obesity and readily available food sources. While CR limits the intake of all macronutrients, it’s unclear what macronutrient drives these benefits. An attractive alternative to restricting all calories is to limit only certain macronutrients, changing the ratio of macronutrient intake. A low protein, high carbohydrate diet increases lifespan and improves metabolic health in both rodents and humans.

However, the specific amino acid composition of protein intake may have more of an impact on metabolism than previously thought. Our lab has recently shown that a diet restricted in branched chain amino acids (BCAAs; leucine, isoleucine, and valine) improves glycemic control and metabolic health in young, wild-type mice. In addition, we have determined that reduced consumption of BCAAs does not induce fibroblast growth factor 21 (FGF21), a hormone produced in fasting and protein restriction. We have since expanded our research to explore the effects of BCAA restriction in metabolically disadvantaged mice fed a diabetogenic diet. After prolonged exposure to a high fat, high sugar diet, we find that intervening with a low BCAA diet rapidly reverses diet induced obesity, improving glucoregulatory control and inducing weight loss via decreasing adiposity. Mice sustain these effects when fed BCAA restricted diets for a prolonged period of time after intervention. Importantly, the effects of BCAA restriction occur in the context of a normal or even high fat diet. Our **Results** suggest that a reduction in dietary BCAAs promotes metabolic health in previously diabetic phenotypes, and may represent a highly translatable option to insulin-resistant obesity.

Epidemiology/Health Outcomes/Quality Improvement/Bio-informatics

A-20 CHARACTERISTICS OF PATIENTS LEAVING AGAINST MEDICAL ADVICE: INSIGHTS FROM NATIONAL INPATIENT SAMPLE 2013

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Background Patients who leave the hospital against medical advice (AMA) are at an increased risk for mortality and readmission. **Methods** We searched and analyzed the national inpatient sample (NIS) of 2013 for patients who were discharged AMA. We used Chi squared test and ANOVA to compare categorical and continuous variables respectively. We performed multivariate binary logistic regression to identify adjusted odds-ratio (AOR) for AMA. **Results** There were a total of 26,238,138 hospitalizations in 2013 out of which 317,680 patients (1.21%) left AMA. The mean LOS and total charges was 2.48 days and \$23,365.34 in patients leaving AMA compared to 4.65 days and \$42,422.87 in patients not leaving AMA. Females were 59% less likely to leave AMA. As compared to caucasians, asians were 45% and hispanics were 30% less likely to leave AMA. As compared to medicare patients, self insured patients were 115% and medicaid patients were 47% more likely to leave AMA. Private insurance patients were 46% less likely to leave AMA when compared to medicare. Patients in higher income group were less likely to leave AMA. The top 10 primary diagnoses for leaving AMA are alcohol withdrawal (3.3%), pneumonia (2.5%), acute pancreatitis (2.4%), COPD exacerbation (2.2%),

septicemia (2.2%), drug withdrawal (2.1%), diabetic ketoacidosis due to type 1 diabetes (1.9%), chest pain not otherwise specified (1.7%), acute kidney injury (1.5%) and cellulitis leg (1.3%). All p values were <0.001. **Conclusion** Our study shows some characteristics of patients leaving AMA.

A-21 DETRIMENTAL SIGNALING INVOLVED IN PLACENTAL PATHOPHYSIOLOGY DURING PREECLAMPTIC PREGNANCIES

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Objective Preeclampsia (preE) is a disease of new onset hypertension and proteinuria after 20 weeks gestation. It has a significant link to alterations of placental function leading to vasoconstriction, hypoxia and oxidative stress that can initiate stress and apoptotic signaling pathways. These signals have the potential to cross the placental barrier and leave a persistent defect in the circulation of the growing fetus that may lead to pathological responses later in life. This study was conducted to assess detrimental signaling in placentas from patients with and without preeclampsia.

Methods We collected placentas and umbilical cord samples from 40 normal pregnant (NP) and 30 preeclampsia (preE) consenting patients after deliveries in an IRB approved prospective study. Patients considered to have the diagnosis of preeclampsia were required to have persistent blood pressures >140/90 and proteinuria of >300 mg in a 24 hour urine specimen. After delivery, samples of both the placenta and umbilical cord were collected and evaluated for various signals. p38 mitogen-activated protein kinase (p38 MAPK) phosphorylation, pro-apoptotic Bcl-2-associated X (Bax), anti-apoptotic Bcl-2, caspase-9, pro-inflammatory cyclooxygenase-2 (Cox-2), and (pro) renin receptor (PRR) were evaluated by Western blot and immunohistochemistry. Comparisons were made using Student's t test.

Results p38 phosphorylation (Placenta: 1.5 fold, Cord: 1.7 fold), ratio of Bax/Bcl-2 (Placenta: 1.2 fold, Cord: 1.5 fold), caspase-9 (Placenta: 1.5 fold, Cord: 1.8 fold), Cox-2 (Placenta: 0.8 fold, Cord: 2.5 fold), Erk 1/2, and PRR expression were up-regulated (p<0.05) in preE compared to normal pregnant patients.

Conclusions Detrimental signaling is augmented in preeclampsia and this alters the intrauterine environment by activating injurious cellular signaling that may then be transported to the fetus and have important implications later in life.

A-56 COMPUTATIONAL MODEL OF ANTIDEPRESSANT RESPONSE HETEROGENEITY AS MULTI-PATHWAY NEUROADAPTATION

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Current hypotheses cannot fully explain the clinically observed heterogeneity in antidepressant response. The therapeutic latency of antidepressants suggests that therapeutic outcomes are achieved not by the acute effects of the drugs, but rather by the homeostatic changes that occur as the brain adapts to their chronic administration. We present a computational model that represents the known interactions between the monoaminergic neurotransmitter-producing brain regions and associated non-monoaminergic neurotransmitter systems, and use the model to explore the possible ways in which the brain can homeostatically adjust to chronic antidepressant administration. The model also represents the neuron-specific neurotransmitter receptors that are known to adjust their strengths (expressions or sensitivities) in response to chronic antidepressant administration, and neuroadaptation in the model occurs through sequential adjustments in these receptor strengths. The main result is that the model can reach similar levels of adaptation to chronic administration of the same antidepressant drug or drug combination along many different pathways, arriving correspondingly at many different receptor strength configurations, but not all of those adapted configurations are also associated with therapeutic elevations in monoamine levels. When expressed as the percentage of adapted configurations that are also associated with elevations in one or more of the monoamines, our modeling Results largely agree with the percentage efficacy rates of known antidepressants and antidepressant combinations. Our neuroadaptation model provides an explanation for the clinical reports of heterogeneous clinical outcomes among patients chronically administered the same antidepressant drug regimen.

B-12 CAN STUDENTS ACCURATELY ASSESS THEIR OWN CLINICAL PERFORMANCE?

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Purpose/Hypothesis Self-assessments are commonly used in various disciplines of the health care field. The validity of self-assessment tools have been critiqued in previous literature and is an important factor to consider, as most decisions related to quality of patient care relies heavily on both aspiring and practicing clinicians' confidence in their abilities. In the present study, we sought to identify the differences between student physical therapists' self-assessment scores and the instructor assessment scores. In addition, we also collected narrative feedbacks from student physical therapists and instructors to examine the factors that need to be included when developing a successful self-assessment tool and to improve the validity of a self-assessment tool.

Number of Subjects Forty-two second year Doctor of Physical Therapy students (SPTs).

Materials/Methods The SPTs developed and led individual balance training programs for community-dwelling older individuals with balance deficits. The balance training program met three times per week for four weeks to help improve balance and reduce the risk of falls among community-dwelling older adults with balance deficits. The SPTs were put into groups of two. Each student group treated the participant for the whole session (45 minutes) once a week. The following areas of student performance were assessed: 1) Selection of appropriate intervention, 2) Appropriate use of sensory cues, 3) Appropriate interaction with the participants, 4) Provide rationale for treatment, 5) Provide Patient/family education. The students were required to rate their performance in those areas each week. In addition to the rating, students reflected on their strengths and areas for improvement. Formal assessment conducted by physical therapy faculty were also performed in the same areas at Week 1 and Week 4. Paired t-test was conducted to determine the differences in student self-assessment scores and instructor feedback scores. All values were considered significant at $p < 0.05$.

Results The Results of the study suggest higher initial self-assessment scores as compared with initial instructor feedback scores at Week 1. In comparison between the instructors and students' comments, we found that students were able to identify their weaknesses in patient care, however, unlike the instructors' feedback were unable to identify how to accurately correct their weaknesses.

Conclusions Bias-inducing variables, such as overconfidence and decision making process of CIs has the potential to significantly affect differences in initial self-assessment scores by student PTs compared to instructor feedback scores. This research suggests that any self-assessment form should be accompanied by reliability training, which allows participants to go through video assessments without scores, which improves the validity of self-assessments.

Clinical Relevance Thorough development of self-assessment allows lifelong learning and continuous professional improvement, which Results in student development and practitioner continuous education and ultimately translated to improved quality of the profession.

B-14 SPECIALTY CLINIC STAFF PERCEPTIONS OF PROTOCOLS FOR HIGH BLOOD PRESSURE AND SMOKING CESSATION: BUILDING FEASIBILITY, SELF-EFFICACY, AND CLINIC CAPACITY

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Background In 2013, specialty visits outnumbered primary care visits nationally, making specialty clinics and staff important for population health delivery. In prior work we found that despite routinely recording blood pressure (BP) and smoking status, rheumatology staff and

providers recommend follow-up in only 10% of visits with high BP or tobacco use. Adapting CDC-endorsed protocols, we performed two six-month pilots of rheumatology staff protocols to facilitate follow-up of high BP and connection to smoking cessation resources. In the first pilot, medical assistants (MAs) and nurses were trained to follow electronic reminders to re-measure high BPs and, if confirmed, to offer to schedule primary care follow-up (BP protocol). In the second pilot, staff were trained to assess patient smoking status and readiness to quit, and offer an electronic referral to the Wisconsin Quit Line (tobacco protocol). We previously reported that the BP protocol doubled timely follow-up and the tobacco protocol increased smoking referrals 20-fold. The objective of this study was to assess staff perceptions of protocol workflows and feasibility.

Methods Two six-month pilot projects took place during 2015–2016 in three rheumatology clinics within a single academic institution. After each intervention, paper questionnaires were administered anonymously to all participating MAs and nurses with a \$10 cash stipend. The questionnaires consisted of 15 items based on self-determination theory and five work system domains of the Systems Engineering Initiative for Patient Safety (SEIPS 2.0) model (people/staff, organization/culture, technology/tools, physical environment, and tasks). Five optional items assessed the participant demographics. Paired t-tests were used to analyze responses to pre- and post-protocol questions.

Results One hundred percent of questionnaires were returned within a month after each pilot (n=10+10). For both pilots, 90% of respondents reported the electronic order sets were “very” or “extremely” easy to use. After the tobacco pilot, 80% reported feeling “very” or “extremely” comfortable discussing smoking status and readiness to quit with patients. On an item asking “how confident were you in your abilities to do something about [elevated blood pressure] or [smoking cessation],” at baseline 20% and 10% respectively reported feeling “very” or “extremely” confident. Post-protocol self-efficacy increased significantly, with 90% feeling “very” or “extremely” confident after each protocol pilot (BP: p=0.0013, Tobacco: p=0.0002). Baseline self-efficacy was worse for smoking cessation care, and it showed the greatest improvements, with 40% feeling “extremely” confident post-protocol. After the first pilot, 0% reported that their clinic enjoyed trying new things to help patients “a great deal,” compared to 40% after the second protocol pilot.

Conclusions Overall, staff reported high feasibility of the new protocols. Pre-protocol self-efficacy was low for both hypertension and smoking cessation care but improved with protocols, with greatest gains in smoking cessation care. Limitations to this study include the small sample of nurses and MAs in a single health system, and the administration of questionnaires at a single point in time post-protocol, potentially biasing responses. Nevertheless, we found that feasible staff protocols can not only improve patient care, but also improve individual staff self-efficacy

and clinic readiness to implement new population health interventions in specialty clinics.

C-13 HEALTH CARE WORKER PERSPECTIVES OF THEIR MOTIVATION TO REDUCE HOSPITAL-ACQUIRED INFECTIONS

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Background Preventing the transmission of hospital-acquired infections (HAI) is essential for patient safety. HAI are adverse events that are considered preventable if evidence-based practices are followed. It has been estimated that between 44,000 to 98,000 individuals per year die as a result of preventable medical errors. In efforts to reduce HAI, hospitals have created protocols for healthcare workers to follow to streamline the implementation of best-practice guidelines into their workflow. However, adherence to such complex behavioral interventions to reduce HAI can be challenging and requires motivation and drive to consistently sustain. We undertook a qualitative study to examine differences among healthcare worker motivation for reducing HAI. We applied the Consolidated Framework for Implementation Research (CFIR) model to analyze motivation behind healthcare workers' approaches to infection prevention in order to determine facilitators and barriers to successful intervention implementation.

Methods A phenomenological qualitative study of healthcare workers was conducted to explore factors influencing motivation to consistently apply evidence-based preventive measures. Ten semi-structured interviews were performed of individuals involved in the implementation of HAI prevention efforts at various levels. Interviews were recorded and transcribed, and data were analyzed using a thematic approach based on the CFIR model.

Results The eight most influential topics within the CFIR model discussed by interviewees were: 1) Patient Needs & Resources, 2) External Policy & Incentives: Financial Motivation, 3) Available Resources, 4) Goals, Monitoring, & Feedback, 5) Culture, 6) Implementation Climate, 7) Leadership Engagement, and 8) Evidence Strength & Quality. The majority of participants recognized patient safety as their primary motivation for HAI prevention efforts. Many acknowledged the benefit that national policy implementation has provided by bringing attention to a need for greater resources for prevention, and by motivating leadership to support workers in their prevention efforts. Many interviewees discussed the impact that the culture of the teaching hospital has had on their motivation to improve HAI prevention.

Conclusions Several factors influence healthcare worker motivation to reduce HAI. Future studies in other hospital settings should examine if perspectives in academic learning centers differ from those found in non-academic learning centers and by healthcare worker role.

C-14 CLINICODEMOGRAPHIC PREDICTORS OF THE IMPACT OF INFECTIONS ON MYASTHENIA GRAVIS

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Background Myasthenia Gravis (MG) is an autoimmune disease which necessitates use of long term immunosuppressive treatment and thus makes them vulnerable to infections. The objective of this study was to assess the impact of infections on MG and its exacerbations and identify the clinicodemographic predictors which contribute to MG exacerbations needing Emergency Department (ED) visits and hospitalizations.

Methods A retrospective chart review was performed on 127 MG patients between 2011 and 2016. All acquired infections (vaccine preventable infections-VPI included were pneumonia and seasonal influenza and vaccine non-preventable infections-VNPI including opportunistic infections) were noted for each patient, compared to the immunization records, and analyzed for their significance in MG exacerbation.

Results The average age of the cohort was 61.9 years, average disease duration 8.8 years, with 95% Caucasian population. A total of 212 flare-ups requiring 106 ED visits, 141 hospitalization, and an average admission for 6 days were noted. Infections were responsible for 34% of all MG exacerbations, 44% of ED visits, 40% of hospital admissions and second longest average duration of a hospital admission (approximately 7 days at total cost of \$11,000–14,000). VPIs were the most common reason for MG exacerbation needing an ED visit and hospitalization–60% whereas only 20%VNPIs needed ED visit and admission. Common VPIs included pneumonia 16.5% and influenza 11%. Two patients had developed infection despite vaccine (both influenza), whereas rest were not immunized. The most common VNPI was an upper respiratory infection at 20%. Older patients (both at the diagnosis and current age) were at an increased risk factor for VPIs ($p < 0.05$) but not for VNPI.

Conclusion Infections are one of the most common triggers for MG exacerbations and contribute to prolonged admissions and hospital costs. Vaccine preventable infections are a common cause of MG exacerbation in older patients primarily due to lack of immunization.

Gastroenterology/Clinical Nutrition

A-22 LIPOXIN A4 IN PATIENTS WITH OBESITY-ASSOCIATED TYPES OF GASTROINTESTINAL CANCERS

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Introduction Obesity remains a very important preventable risk factor of various gastrointestinal (GI) cancers, such as gastric and/or pancreatic adenocarcinoma.

However, the molecular factors responsible for the association between excessive accumulation of adipose tissue, and development of GI cancers are very poorly understood. Here we tested an original hypothesis that abnormal interactions between bioactive lipids, such as lipoxin A4 (LxA4), may be an overlooked mechanism linking the pathogenesis of aforementioned cancers in humans with body mass and/or metabolic status. Specifically, we i) examined and compared peripheral levels of LxA4 among patients with GI cancers and healthy volunteers; ii) verified the potential associations between LxA4 concentrations and clinical staging of GI malignancies, as well as, iii) estimated potential diagnostic benefits that can be derived from measurements of LxA4 in those patients.

Methods To this study a total of 85 patients with gastric/pancreatic adenocarcinoma and 40 healthy volunteers were recruited. Systemic LxA4 levels were measured using commercially available ELISA kits.

Results In comparison to healthy volunteers cancer patients had significantly higher LxA4 concentrations ($p < 0.05$ for all). Interestingly, systemic levels of this bioactive lipid were correlating with BMI values in both healthy volunteers and cancer patients ($p < 0.05$ for all). No significant differences in LxA4 concentrations were observed between metabolically-healthy and diabetic individuals from either cancer or control groups ($p > 0.05$ for all). Furthermore, in cancer patients LxA4 levels were correlated with TNM cancer staging. Finally, ROC curves demonstrated that systemic LxA4 concentrations appear to hold diagnostic potential in confirming/excluding the presence of obesity-associated types of GI cancers (AUC of 0.53–0.78; $p < 0.05$ for all).

Discussion In patients with obesity-associated types of GI cancers an abnormal systemic biochemical balance in LxA4 occurs. This phenomenon is associated with body mass but not metabolic status of examined individuals. Our study highlights LxA4 as potential novel lipid marker of GI cancers in humans. Supported by the TANITA Healthy Weight Community Trust.

A-23 INCIDENCE AND OUTCOMES OF POST PARACENTESIS LEAK IN CIRRHOTIC PATIENTS

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Background Ascites is a common complication of liver disease often requiring diagnostic and therapeutic paracentesis. The latter is considered a safe procedure when performed by experienced hands, and might only rarely have a few complications. Post-paracentesis leak is a rare complication of paracentesis that is often overlooked. Studies assessing its incidence and outcomes in cirrhotic patients are scarce. Aim: To determine the incidence of post paracentesis leak in cirrhotic patients and to compare outcomes to cirrhotic controls without leak.

Methods A retrospective chart review of all adults subjects with cirrhosis and undergoing an abdominal paracentesis during six-month period from January through June 2015

was conducted. A univariable analysis was performed to assess differences between subjects with and without leaks. Mixed linear regression analysis was performed to assess changes in time for each of the labs of interest. Survival analysis was done to assess differences in survival rates between the groups. Follow-up time was defined as months from January 1st 2015 to time of death; subjects were censored at their last follow-up visit if still alive. A Kaplan-Meier plot was constructed and a log-rank test was used to compare the groups. A p value < 0.05 was considered statistically significant.

Results A total of 319 cirrhotic subjects were included in the analysis; 9.4% of them had leakage at some point during the study period. There were no significant differences between the groups in terms of demographics or laboratory **Results** at the start of the study period. Subjects with leakage were followed for a longer period of time (p < 0.001), yet there was no significant difference in terms of complications or survival. In addition, there was no significant difference in absolute neutrophil counts (p = 0.31), bilirubin (p = 0.59), neutrophil percent (p = 0.77), sodium (p = 0.48) or WBC (p = 15). The majority of leaks (85%) required suturing for optimal closure, whereas the remainders were controlled with pressure dressing. All patients reported social embarrassment from soiling their clothing.

Conclusion Post-paracentesis leak is not too uncommon and it does not lead to serious medical complications or negatively impacts patients' survival. However, when it happens, it primarily affects the patients' quality of life. Such a complication should be documented in the medical records and associated with an ICD code.

A-24 ISOLATED CONGENITAL HEPATIC FIBROSIS DIAGNOSED IN ADULTHOOD WITHOUT RENAL INVOLVEMENT

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Introduction Congenital hepatic fibrosis (CHF) is a rare disorder that affects the portobiliary systems resulting in ductal plate malformation. This **Results** in abnormal branching of intrahepatic portal veins resulting in eventual portal tract fibrosis and the development of portal hypertension. CHF is commonly associated with hepatorenal fibrocystic diseases. We present a unique case of a young adult patient diagnosed with CHF by liver biopsy without renal disease.

Case presentation A 36 year old male with a past medical history of splenectomy presented with one month of melena. He denied any recent blood transfusions, any new sexual partners or a family history of liver disease. Physical exam was unremarkable with no signs of stigmata of liver cirrhosis. Liver function panel and coagulation studies were normal. He underwent an esophagogastroduodenoscopy (EGD) which was notable for gastric varices (GOV1) with healed superficial erosions. No evidence of peptic ulcer

disease, AVMs, or other potential sources of bleeding were seen. Esophageal variceal band ligation was performed with successful deployment of (how many) bands without complications. Subsequently, an abdominal ultrasound and CT scan showed a nodular liver with coarsened echotexture consistent with cirrhosis. There was no evidence of liver lesions or biliary ductal dilatation. The kidneys were normal, without cysts or parenchymal abnormalities. Laboratory workup for liver cirrhosis was performed. Tests for Hepatitis A, B, C, HIV, HSV, Epstein Barr virus (EBV), Anti-mitochondrial antibody (AMA), anti-smooth muscle antibody (ASMA), immunoglobulins, celiac, alpha1 anti-trypsin, ceruloplasmin, iron studies and anti-liver-kidney microsomal antibody (ALKM) were all negative. As a result liver biopsy was performed revealing variably sized dense fibrous septa occasionally enclosing nodules and periportal fibrosis with benign bile duct proliferation in the absence of inflammation. The findings were consistent with congCHF (Figure A & B).

Discussion CHF is a rare congenital disorder with a few hundred cases reported in the literature. It is characterized by ductal plate malformation and abnormal branching of the intrahepatic portal veins resulting in periportal fibrosis progressing to cirrhosis. The disease commonly presents in neonates, however, delayed presentation is seen in children and adults. Although the exact reason is unclear, CHF is commonly associated with Autosomal Recessive Polycystic Kidney Disease (ARPKD). We present a case which illustrates a unique presentation of a rare disorder. Despite being a congenital disorder, the patient was diagnosed in adulthood which is not well understood. In addition, there was no evidence of cystic renal disease or impairment of renal function. Although rare, CHF needs to be considered in the workup of patients with cryptogenic cirrhosis even in the absence of polycystic renal disease.

A-25 IMPACT OF RACIAL DISPARITIES ON CLINICAL PRESENTATION AND SURVIVAL IN YOUNG ONSET COLORECTAL ADENOCARCINOMA

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Introduction Colorectal Adenocarcinoma (CRC) is a leading cause of cancer related mortality in the United States. Although implementation of screening guidelines have helped in fight against CRC, it still remains a major health problem in the US. Recently published data have especially noticed increasing incidence in young (<50 years) patients. We aim to highlight racial disparities in young onset (<50 years) CRC through our study.

Methods A retrospective single center study was performed where 103 patient charts with a diagnosis of young onset CRC from January 1, 2004 to December 31, 2014 were reviewed. Data collected on each patient included age, gender, ethnicity, primary site and histological stage at the time of diagnosis. Survival time over the course of 5 years was documented for patients from January 1, 2004 to December 31, 2009. Overall differences between the

racial groups were assessed by Chi-square and ANOVA testing, using a $P < 0.05$ as the threshold for significance. Kaplan-Meier estimation for groups was conducted to assess survival times over a 5-year follow-up period.

Results Study population consisted of 23.6% African Americans, 66% Caucasians, and 10.6% Hispanics. Mean age of CRC presentation was found to be 43 years for Caucasians, 43.6 years for African Americans, and 33.6 for Hispanics. A significant number of Hispanics (45.4%) presented with CRC before age 40 as compared to Caucasians and African Americans (20.5% and 20.8% respectively). Gender disparity within racial groups was also noted as majority (72%) of Hispanic patients were females as compared to African Americans (37.5% females) and Caucasians (42.6%). Majority of patients presented at advanced stage of CRC (Stage III=31%, stage IV=26.2%). As expected, distal colon including rectum was the most common site of CRC (65.9%) with the exception of Hispanics where 45.5% of patients presented with CRC in distal colon. African Americans showed worse survival probability over 5 years as compared to Caucasians ($p < 0.05$). Hispanics also showed worse survival probability as compared to Caucasians but **Results** were not statistically significant.

Conclusion There is lack of studies performed on racial disparities in young onset CRC in the US. Our study highlighted some important clinical differences of CRC presentation in different racial groups which are not well studied and can be used to formulate future multi-center studies to assess disease behavior in young patients.

A-26 MALIGNANT MELANOMA- A RARE CAUSE OF METASTATIC PANCREATIC CANCER

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10.1136/jim-2017-000448.46

Introduction Metastatic pancreatic melanomas are extremely rare. We report a patient who presented with metastatic melanoma of pancreatic tail who was successfully treated for superficial malignant melanoma about 13 years ago.

Case report A 56-year-old Caucasian female who is a practicing minister started behaving unusually during one of her services. She began walking up to the altar at inappropriate times and her family was concerned about her behavior. This change in mentation continued into the next day and the decision was made to bring her to the hospital. The patient had a history of superficial malignant melanoma to the left axilla, which was treated with axillary dissection 13 years ago. Sentinel lymph node biopsy at the time was negative and the patient did not receive any further chemotherapy or radiation. She was monitored for 5 years with serial PET scans every 6 months along with chest X-rays, routine blood work and annual skin exams without evidence of disease recurrence. On this presentation, the patient had multiple episodes of tonic-clonic seizures while in the ED for which she was given Ativan, Versed and IV Keppra. The patient denied previous CNS symptoms including headache, seizures, or vision changes.

Imaging of the head revealed a large hemorrhagic frontal temporal brain lesion with smaller scattered lesions concerning for metastatic disease. CT scan of the chest, abdomen and pelvis showed a 2.2×1.6 cm peripancreatic tail mass. An endoscopic ultrasound was performed which showed a mass in the region of the tail of the pancreas. FNA was done with pathology positive for metastatic melanoma. Patient was referred to Oncology service for further management.

Discussion A variety of primary neoplasms metastasize to the pancreas. About 2% of pancreatic tumors are metastatic tumors. Common metastatic sites include the kidney, lung and colon. Metastasis of malignant melanoma to pancreas occurs as manifestation of widespread disease burden. Several factors influence survival in patients with primary melanoma, including specific clinical and pathological factors, histological subtype, anatomical location and lymph node involvement. Prognostic factors influencing survival in patients with malignant melanoma are largely unknown, but a longer disease free interval between the successful resection of primary malignancy and eventual development of metastasis to the pancreas has been reported to be associated with improved survival. Our patient presented 13 years following the treatment of primary melanoma. The prognosis of metastatic malignant melanoma is poor. Studies suggest a mean survival of only 6–8 months in patients with systemic disease from melanoma. In several case series five-year survival rates are reported at less than 10%.

Conclusion Most pancreatic metastases occur in the first 1–3 years after treatment of the primary tumor and current guidelines recommend follow up 3–5 years thereafter. This **Case report** raises a question about how long patient should be monitored after the successful treatment of superficial malignant melanoma.

A-27 A RARE CAUSE OF ABDOMINAL PAIN

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10.1136/jim-2017-000448.47

Introduction Median arcuate ligament syndrome is a rare disorder that is clinically characterized by the triad of post-prandial abdominal pain, weight loss and often an abdominal bruit. Given non-specific symptoms, this is a rare and difficult diagnosis to obtain. We present a patient with non-specific abdominal pain in whom etiology was ultimately determined to be median arcuate ligament syndrome.

Case report A 38 year old woman with no known past medical history presented to the emergency room with diffuse, cramping, non-radiating abdominal pain episodes lasting for 30–60 minutes. Patient also had associated symptoms of nausea and bilious vomiting which temporarily relieved the pain. These episodes had no known precipitating factor and were not associated with food or exercise. She had two similar episodes in the past and was admitted to hospital four months ago. Imaging and labs at that time were normal. She denied any significant alcohol, tobacco or drug use. She also denied any significant family medical

history. Her physical examination revealed mild epigastric tenderness to palpation but no other abnormalities. CBC, LFTs, lipase, and urine analysis were all within normal limits. Esophagogastroduodenoscopy showed mild antral gastritis. However, pantoprazole failed to relieve severe pain episodes. A mesenteric ultrasound was eventually ordered which demonstrated increased celiac axis flow velocities with a peak systolic velocity of 320 cm/s. These findings were suggestive of significant stenosis greater than 70%. A computed tomography (CT) scan of abdomen with contrast showed superior compression of celiac axis with focal narrowing at origin and post-stenotic dilation. These findings confirmed diagnosis of median arcuate ligament syndrome. Patient was referred to surgery for a laparoscopic release of median arcuate ligament.

Discussion Median arcuate syndrome also known as mesenteric artery compression syndrome and Dunbar syndrome was first described by Harjola in 1963. The etiology of the disease is incompletely understood and may be related to external compression of the celiac artery and celiac plexus by an abnormally low-lying ligament. This compression leads to visceral ischemia with abdominal symptoms such as epigastric pain, nausea, vomiting, and weight loss. In general population, celiac artery compression has been found in 10–24% of patients on CT analysis. Despite the relatively high prevalence of celiac artery compression, clinically relevant celiac artery compression syndrome is very rare. The diagnosis requires imaging to confirm compression of the celiac artery by median arcuate ligament. Compression of celiac artery can be suggested on Duplex ultrasound and confirmations can be achieved with CT scan with contrast, magnetic resonance imaging (MRI) or traditional angiography.

Conclusion This case illustrates that the diagnosis of celiac artery compression syndrome is difficult due to its non-specific symptoms and should be considered in patients especially young females with abdominal pain which does not have a clear etiology.

B-15 IQGAP1-MTORC1 INTERACTION COORDINATES LIPID METABOLISM

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10.1136/jim-2017-000448.48

Introduction Dysregulation of lipid metabolism in the liver is associated with a number of diseases including obesity, insulin resistance, non-alcoholic fatty liver disease, and cancer. The mechanistic target of rapamycin (mTOR) complex 1 (mTORC1) is a kinase signaling complex that regulates fed state metabolism and has been implicated in a number of these conditions. Multiple components of mTORC1 bind to IQ motif-containing GTPase Activating Protein 1 (IQGAP1), a multifunctional scaffolding protein. However, the metabolic impact of IQGAP1 is yet to be elucidated. The objective of this study is to identify the role for the scaffolding protein IQGAP1 in regulating lipid metabolism.

Methods Adult male 129/SVJ wild-type and *Iqgap1*^{-/-} mice were either fed normal chow ad libitum, or fasted

24 hours with access to water, or fed a ketogenic diet (calories from fat –90.5%, protein –9.1%, and carbohydrates –0.4%) for 4 weeks. Liver, gonadal white adipose tissue (gWAT), and serum were collected from these animals for analysis using a variety of techniques including qPCR, western blot, histology, and biochemical serum assays.

Results Hepatic IQGAP1 expression was induced by a 24 hour fast, suggesting that IQGAP1 may participate in the fasting response. However, fasting-mediated ketogenic genes and serum ketone body levels did not differ between *Iqgap1*^{-/-} and WT mice. Since mTORC1 is active in the fed state, we next assessed the activation of mTORC1 in fed WT and *Iqgap1*^{-/-} mice. Excitingly, phosphorylation of the bona fide mTORC1 target S6K1 was dramatically reduced in *Iqgap1*^{-/-} mice, which indicates that IQGAP1 is important for mTORC1 activity. Notably, mTORC1 activation was restored by ectopic overexpression of IQGAP1 in the livers of *Iqgap1*^{-/-} mice. mTORC1 regulates fatty acid synthesis by increasing the activity of the nuclear receptor SREBP1c. In line with the decreased mTORC1 activity, hepatic gene expression of *Srebp1c* and its target *Fasn* were decreased in *Iqgap1*^{-/-} mice. Furthermore, *Iqgap1*^{-/-} mice have lower serum triglycerides and 20% smaller gWAT depots. This phenotype is exacerbated under ketogenic diet conditions, where *Iqgap1*^{-/-} mice accumulate 30% less gWAT compared to the WT animals. Interestingly, ketogenic diet resulted in higher hepatic triglyceride content but reduced levels of serum ketone bodies in *Iqgap1*^{-/-} mice, which reflect improper lipid storage along with a defective ketogenesis in the liver. It is known that elevated mTORC1 activation inhibits ketogenesis, so we examined the level of mTORC1 activity under ketogenic conditions and found it elevated in *Iqgap1*^{-/-} mice compared to WT. This result is in contrary to the reduced mTORC1 levels observed in the fed state in *Iqgap1*^{-/-} mice suggesting that the nutrient state drives the IQGAP1-mTORC1 interactions.

Conclusions Scaffolding protein IQGAP1 is required for proper regulation of lipid metabolism by mTORC1 under both fed and ketogenic nutritional states.

B-16 AORTOENTERIC FISTULA PRESENTING WITH RECURRENT SEPSIS

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Introduction Aortoenteric fistula (AEF) is a rare but life-threatening condition. It most often presents with gastrointestinal bleeding. We present a patient with recurrent sepsis in whom the etiology was ultimately determined to be a non-bleeding AEF.

Case report A 60-year-old male presented with recurrent sepsis of unclear etiology. He underwent an aortofemoral bypass with a Dacron graft 8 years earlier, for iliofemoral occlusive disease. One year prior to presentation, he was hospitalized with sepsis. Blood cultures grew *Pasturella*. No

etiology of the bacteremia was identified. He responded to a course of antibiotics. He was re-admitted to hospital for a second time 3 months prior to this admission, with sepsis. Blood cultures grew *E. coli* and *Proteus*. No source of sepsis was identified. He responded to a course of antibiotics. He was then admitted for a third time, with fever, chills, and weakness. Blood cultures grew *Lactobacillus*. CT scan of the abdomen was unrevealing. There was an unremarkable aortic graft without surrounding inflammation or abscess. Exploratory surgery was elected. A large AEF was found between the duodenum and the aortofemoral bypass graft. There was a 3 cm perforation of the duodenum sealed by the dacron graft. The duodenal perforation was repaired, the infected graft removed and an axillary bifemoral bypass was performed. The patient was ultimately discharged in stable condition.

Discussion The aortoenteric fistula is a direct communication between aorta and intestinal lumen. There are primary and secondary forms of AEF. Primary aortoenteric fistula (PAEF) arises de novo between the aorta and the bowel. Secondary aortoenteric fistula (SAEF) can occur following any aortic reconstruction. The incidence of PAEF has been reported to be less than 1% and the incidence of SAEF following aortic surgical reconstructions ranges from 0.36 to 1.6%. Bleeding is the most common initial presentation. However, other symptoms of AEF can occur including sepsis.

Conclusion An AEF should be considered in patients who present with sepsis and a history of aortic aneurysm repair.

B-17 SPONTANEOUS LIVER HEMATOMA: RARE PRESENTATION OF PREECLAMPSIA

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During pregnancy, liver function abnormalities can lead to severe impairment in maternal and neonatal functioning. Spontaneous subcapsular liver hematoma (SLH) is a life-threatening complication often linked with preeclampsia and HELLP (hemolysis, high liver enzymes, and low platelets) syndrome. SLH was reported in 1–2% of pregnancies with HELLP. The incidence of SLE is higher in white, multiparous, and advanced maternal aged patients. This case describes a 35-year-old woman who developed SLH a few hours before an emergency cesarean section due to preeclampsia, for which conservative management was used. A 35-year-old female presented to the emergency department at 37 weeks of gestation complaining of severe epigastric pain for 2 hours. She had blood pressure of 170/110 mm Hg and sustained fetal bradycardia with fetal heart rate in 70 s. Patient underwent emergent lower segment transverse cesarean section and delivered successfully. Intraoperatively, bright red blood was found in right para-colic gutter with persistent bleeding in right upper quadrant. Thus, immediate surgical intervention was performed. Laparotomy showed ruptured subcapsular hematoma. Pharmacological anticoagulation was achieved with

fibrin sealant and pressure with laps to stop the bleeding, with 2 units of PRBC transfused. Laboratory results showed WBC 16.6 k/cmm, Hgb 8.3 gm/dl, MCV 96 fl), normal platelet counts, mild transaminitis (ALT 89U/l, AST 108U/l), and normal GGT and alkaline phosphatase. LDH was elevated at 350 IU/L but haptoglobin, coagulation profile, fibrinogen, and creatinine levels were normal. Random urine protein:creatinine ratio was elevated 2.81. Patient was monitored closely in ICU, and treated with magnesium sulfate for seizure prophylaxis for possible atypical preeclampsia. Her health progressed thereafter, and during follow-up 6 weeks later, she remained stable. SLH is the buildup of blood between the Glisson capsule and liver parenchyma. The pathogenesis remains unclear. Symptoms include epigastric, right upper quadrant or shoulder pain, abdominal distension, nausea and vomiting. Severe preeclampsia may result in high transaminases, subcapsular hemorrhage, or hepatic rupture, which can lead to disseminated intravascular coagulation, acute liver, and kidney failure. Abdominal ultrasound, computerized tomography (CT), and magnetic resonance imaging (MRI) can be used as diagnostic tools. HELLP syndrome laboratory criteria includes microangiopathic hemolytic anemia, thrombocytopenia (<100 k/cmm), total bilirubin ≥ 1.2 mg/dL, and serum AST >2 times upper limit. Our patient did not meet HELLP diagnostic criteria. Instead, she had elevated blood pressure and protein:creatinine ratio ≥ 0.3), suggesting preeclampsia with ruptured liver capsule with hematoma formation. Management in hemodynamically stable patients is mostly conservative and includes intensive fluid replacement as well as blood and fresh-frozen plasma transfusions. If rupture occurs and the patient is unstable hemodynamically, surgery (percutaneous transcatheter hepatic artery embolization) can be necessary. Bleeding surfaces are packed with collagen fleece or fibrin sealant and perihepatic space is drained. If still hemorrhage occurs acute liver failure occurs, liver transplantation should be considered. In our case, since hemodynamic status was not compromised, noninvasive conservative management was successfully administered with blood products, steroids to treat preeclampsia, and daily follow-up with imaging technique. In conclusion, SLH with severe preeclampsia is a rare clinical. Conservative management should be the first choice of treatment. Early diagnosis could decrease morbidity and mortality burden for both mother and fetus.

C-15 FATTY ACID PROFILE AND TRIGLYCERIDE MOLECULAR SPECIES OF NUTRACEUTICAL RICH BLENDED AND INTERESTERIFIED OIL OF MORINGA OLEIFERA SEED OIL (PKM1 VARIETY) WITH CORN OIL

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Abstract Dietary polyunsaturated fatty acid (PUFA) play a vital role in maintaining serum lipids at desirable levels. Omega-6 PUFA such as linoleic acid(LA) lowers serum total and LDL cholesterol. But, excess intake of LA increases vulnerability of LDL lipids to peroxidation which initiates

cascading events leads to foam cell formation and atherosclerotic plaque formation. Therefore, intake of antioxidants along with PUFA rich diet is recommended to overcome the oxidative stress. Modern diets typically have ratios of omega-6 to omega-9 more than 10 to 1, some as high as 20 to 1, partly due to corn oil consumption is higher in western countries which has high amount of omega-6. The optimal ratio must be 4 to 1 or lower. In the present study, *Moringa Olefera* seed oil (MO) of PKM1 variety and corn oil (CO) were chosen for blending and interesterification to augment nutraceuticals to obtain an ideal ratio of omega-9 and omega-6. MO is a good source of oleic acid (omega-9 FA, MUFA) and antioxidants mainly phenolics and flavonoids whereas CO contains higher amount of linoleic acid. To incorporate omega-9 FA with CO to obtain a balanced amount of omega-9/omega-6 ratios, a blends of MO+CO were prepared in different ratios. The ideal blend was selected based on fatty acid composition. The blend was subjected to enzymatic interesterification to improve functional properties. Among the blends, 40:60 near to 1. Interesterified oil showed a significant change in physical properties of oils as compared to blended oils. Moreover, the triacylglycerol (TAG) molecular species of interesterified oil transformed the composition of major TAG molecular species eventhough overall fatty acid composition and nutraceuticals of blended and interesterified oil remains same. In conclusion, MO and CO combination (40:60) is appropriate to obtain an omega-9/omega-6 ratio (1:1) along with enrichment of nutraceuticals in blends. This reposition of fatty acids along with nutraceuticals may enhance functional properties and beneficial for lowering cholesterol and oxidative stress.

C-16 RECTAL MUCOSAL SCHWANN-CELL HAMARTOMA: A CASE REPORT

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Mucosal Schwann cell hamartoma is a newly recognized entity to describe lesions which share some features but are distinct from schwannomas and neurofibromas. This mesenchymal lesion, consisting of a proliferation of Schwann cells in the lamina propria and a strong positivity for the S-100 protein, should be differentiated from other similar lesions because it exists solely in the intestines as a polypoid lesion. Here, we report on a case of Schwann cell hamartoma diagnosed on pathology of rectal polyp removed during colonoscopy. Our patient is a 60 y/o male who presented for an outpatient colonoscopy to evaluate weight loss (20 pounds over one year) and intermittent hematochezia. Colonoscopy revealed sigmoid diverticulosis and a small 5 mm rectal polyp. The polyp was sessile and removed with a cold biopsy forceps that was then sent for pathological analysis. In the pathological reports, the rectal polyp showed S-100 positivity and had benign bland spindle cell proliferation in the lamina propria. These findings were consistent with a diagnosis of Mucosal Schwann cell hamartoma. A follow up colonoscopy was recommended in 3 years. Mucosal

Schwann cell hamartoma is considered a benign lesion and no reports of malignant transformation have been described. However, further follow up data is needed before making final recommendations. Key-words: Schwann cell, neuroma, polyp, hamartoma, neurofibroma.

Genetic & Molecular Medicine

A-28 PARTICULATE MATTER PROMOTES EPITHELIAL-TO-MESENCHYMAL TRANSITION IN HUMAN LUNG EPITHELIAL CELLS VIA ROS PATHWAY

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BACKGROUND: Epidemiologic studies have linked exposure to airborne pollutant particulate matter (PM) with increased cases of chronic cardiopulmonary diseases, including asthma and idiopathic pulmonary fibrosis (IPF). Several investigations have suggested that epithelial-to-mesenchymal transition (EMT) may contribute to the complex pathobiology of pulmonary fibrosis. The present study is designed to characterize the mechanisms of PM-mediated EMT in human lung epithelial cells. **METHODS:** Using fine PM samples (aerodynamic diameter 0.1–0.3 μm) collected from Ft. McHenry Tunnel (Baltimore, MD). We assessed PM-mediated changes in fibronectin (FN), ROS generation in human bronchial epithelial cells (HBEC). Western blotting was conducted to determine FN protein levels in HBEC lysates. Real-time PCR was performed to detect EMT biomarker genes expression level. **RESULTS:** PM induced significant dose (0–100 μg/ml) and time (0–72 h)-dependent increases in FN protein levels in HBEC lysates. HBEC exposure to PM resulted in significant ROS generation (~3 fold increase) and HBEC pretreatment with the antioxidant, N-acetyl-cysteine (NAC, 5 mM) served to abolish FN production in protein (~60% reduction). HBEC pretreatment with a NF-κB inhibitor, BAY11-7082 (5 μM) served to abolish FN production in protein (~50% reduction). The biomarker of EMT (SNAI1, SNAI2 and Acta2) in PM-treated HBEC were significantly increased in comparison to WT cells. **CONCLUSION:** These results demonstrate that PM increases the level of fibronectin protein via ROS-dependent pathways. In addition, PM exposure induces EMT in human lung epithelium cells, supporting a novel mechanism for PM-induced pulmonary fibrosis.

A-29 OCULAR VASCULAR OCCLUSIONS: A DIAGNOSTIC WINDOW TO FAMILIAL AND ACQUIRED THROMBOPHILIA

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Purpose We assessed the etiologic contribution of thrombophilia in patients presenting with ocular vascular occlusions (OVO).

Methods Measures of thrombophilia and fibrinolysis were made in 301 patients referred for evaluation by retinologists including patients presenting with central retinal artery occlusions (CRAO), central retinal vein occlusions (CRVO), and non-arteritic anterior ischemic neuropathy (NAION). These patients were compared to 110 normal controls.

Results Within the 301 patients with OVO, 66 presented with CRAO (41 females and 24 males), 215 with CRVO (132F and 83M), and 20 with NAION (15F and 5M). Of the 66 patients with CRAO, homocysteine levels were significantly greater (dated cut point ≥ 10.4 – 13.5 $\mu\text{mol/L}$) than in controls (14/65 [22%] vs 5/107 [5%], $p=0.0009$). Of the 215 patients with CRVO, homocysteine levels were higher than controls (44/207 [21%] vs 5/107 [5%], $p<0.0001$) as well as anticardiolipin antibody (ACLA) IgM levels (dated cut point ≥ 10 – 13 MPL, 20/204 [10%] vs 2/109 [2%], $p=0.009$). Of the 20 patients with NAION, heterozygosity for the G20210A prothrombin gene (PTG) mutation was greater in patients with NAION than healthy controls (4/19 [21%] vs 3/110 [3%], $p=0.009$). Taken together, 59 (20%) of all patients with OVO had high homocysteine levels (vs 5/107 [5%], $p<0.0001$) and 26 (9%) of all patients with OVO had elevated ACLA IgM levels (vs 2/109 [2%], $p=0.14$). Of all patients presenting with OVO, 53% (139/262) had hypertension vs 65% of U.S. adults age >60 , 18% (47/261) had diabetes mellitus vs 33% of U.S. adults age >65 , and 59% (158/267) had LDL cholesterol >100 mg/dl vs 30% of U.S. adults age >65 . Twenty percent (52/257) had a significant smoking history vs 9% of U.S. adults age >65 .

Conclusions The role of ubiquitous, non-specific risk factors in OVO is well known, however the contribution of thrombophilia to OVO remains underappreciated. Within our patients, those with OVO were more likely to present with hyperlipidemia and smoking histories and less likely to present with diabetes and hypertension when compared to the normal population. Familial and acquired thrombophilias were much more likely in cases with OVO than controls ($p<0.05$). Patients presenting with OVO provide ophthalmologists the opportunity to identify familial and acquired thrombophilia and facilitate in early treatment and prevention of subsequent systemic thrombosis. Patients presenting with ocular ischemic events should be evaluated for acquired or familial thrombophilia particularly when presenting with additional risk factors such as exogenous estrogen use, personal thrombotic events, and family history of venous thromboembolism.

A-30 VALIDATION OF MYLK1 AS A CANCER-ASSOCIATED GENE UTILIZING RARE SNP IMPUTATION

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Introduction Pseudogenes are originally derived from paralogues of functional genes and are defunct due to either the lack of regulatory elements or the presence of frameshift mutations. Recent evidence suggests that pseudogenes are regulators of gene expression. There are many pseudogenes present in the genome, and their roles in

disease are largely unknown. MYLK1 is a pseudogene of MYLK, which encodes myosin light chain kinase (MLCK). We aim to elucidate the cellular and molecular physiology of the functional pseudogene, MYLK1, using in vitro cell assays, genotyping, and single nucleotide polymorphism (SNP) imputation.

Methods Proliferation and migrations assays were performed with transfected cells. In order to determine if SNP genotype affects promoter activity, each SNP was transfected via luciferase construct into several different cell types. Promoter activity was measured using a standard luciferase assay using several NSCLC cell lines (A549, H441, H23, H358) and other cell lines (MDA-MB-231, SW60, Beas2b, LLC) in order to comprehensively assess the role of the SNPs in determining promoter activity. SNP Imputation with 750 formalin fixed paraffin embedded (FFPE) cancer samples (QC filtered down to 548) was performed after per-imputation quality control. Samples were filtered using call rate, Hardy-Weinberg Equilibrium, minor allele frequency, and analyzed for principal components. 409 cases passed post-imputation QC and were phased (SHAPEIT2) and rare SNPs imputed (IMPUTE2). 376 controls from a healthy population were used to compare two promoter SNPs.

Results MYLK1 transfection into cancer cell lines H441 and A549 and showed an increase in proliferation and migration. Promoter activity, measured via luciferase assay, showed an increase in MYLK1 expression in cancer cell lines Beas2b and H522. Specifically, rs12497343 and rs12490683 SNP mutations in the promoter region showed an increase in MYLK1 levels when compared to transfection of the normal promoter region of MYLK1. Genotyping **Results** of the MYLK1 gene confirmed four potential promoter SNPs that were statistically different in African American and European populations. After SNP imputation of a validation population, two promoter SNPs (rs12497343 and rs12490683) were found to be represented in control versus case samples (rs12490683 $p=0.013$, rs12497343 $p=0.042$).

Conclusion Cells that express MYLK1 show increased proliferation and migration in cancer cell lines. Populations with the two promoter SNPs (rs12497343 and rs12490683) are differentially expressed in European American and African American populations.

C-17 SYNTHETIC RECEPTORS WITH THIOUREA FUNCTIONAL GROUP INDUCE ANTI ANGIOGENIC MILIEU IN CYTOTROPHOBLAST CELLS

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Synthetic receptors (SR) were used to explore the receptor/ligand binding affinity using cytotrophoblast (CTB) cells.

The human extravillous CTB cells (Sw.71) used in this study were derived from first trimester chorionic villus tissue. Culture media of CTB cells treated with a ≥ 1 nM SR level revealed sFlt-1 (Soluble fms-like tyrosine kinase-1) and sEnd (a soluble form of endoglin) secretions that were significantly increased while VEGF (vascular endothelial growth factor) and PlGF (placental growth factor) were decreased in the culture media. The AT₂ receptor (Angiotensin II receptor type 2) expression was significantly upregulated in ≥ 1 nM SR-treated CTB cells as compared to basal; however, the AT₁ (Angiotensin II receptor, type 1) and VEGFR-1 (vascular endothelial growth factor receptor 1) receptors expression was downregulated. The anti-proliferative and anti-angiogenic effects of this compound on CTB cells are similar to the effects of cardiotoxic steroids (CTS). The receptor/ligand affinity of SR on CTB cells provides us a critical clue to the design of a potent inhibitor to prevent CTS-induced impairment of CTB cells.

Hematology and Oncology

A-31 ARSENIC DRIVES TRANSFORMATION BY ACTIVATING P62-KEAP1-NRF2 PATHWAY THROUGH AUTOPHAGY FLUX BLOCKADE IN PROSTATE STEM-PROGENITOR CELLS

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Introduction Inorganic arsenic (iAs) is a ubiquitously distributed environmental toxicant which increases cancer risk, including prostate cancer. However, the underlying biological mechanisms for iAs-induced prostate carcinogenesis are poorly understood. Our previous study suggests that arsenic dysregulates human prostate stem-progenitor cell homeostasis, perturbs autophagy and drives transformation through accumulation of SQSTM1/p62. The present study sought to determine downstream pathways of p62 accumulation in prostate stem-progenitor cells.

Methods Primary human prostate epithelial cells (PrEC) from disease-free donors and non-transformed human prostate epithelial cell line RWPE1 were used. Stem-progenitor cells were isolated by 3D prostatesphere (PS) culture. iAs-dysregulated genes were revealed by Illumina HumanHT12 Gene Expression microarray. Stably knockdown of target gene was established by shRNA-lentivirus infection. Transformation was determined by soft agar colony formation assay. For in vivo study, prostate stem-progenitor cells mixed with UGM were renal-grafted in nude mouse, mice were exposed to 5 ppm iAs in drinking water for 6 months.

Results Upon 2-week 1 μ M iAs exposure, 1352 genes were dysregulated in prostate stem-progenitor cells (Fold change >1.5 , $P < 0.05$). As downstream of p62, Keap1-Nrf2 pathway was one of the enriched pathways revealed by WikiPathways analysis. Microarray data was validated by qPCR, Keap1-Nrf2 pathway marker genes (HMOX1, NQO1, GCLM) were induced by iAs in PS, western blotting further confirmed HMOX1 protein induction. In addition, increased HMOX1 and Nrf2 staining in

iAs-treated renal-graft and mouse prostate confirmed Keap1-Nrf2 pathway activation in vivo. Although the mRNA and protein level of Nrf2 remain unchanged, nuclear translocation of Nrf2 was observed upon iAs exposure in PS, indicating iAs activates Keap1-Nrf2 pathway in post-translational level. Knockdown of p62 attenuated iAs-induced HMOX1 protein expression in PS, which confirmed that Keap1-Nrf2 is the downstream of p62. Interestingly, inhibition of autophagy initiation by knockdown ATG7 or Beclin1 also reduced iAs-mediated HMOX1 induction in PS, suggesting autophagy is required to activate p62-keap1-Nrf2 pathway by iAs. Importantly, knockdown of Nrf2 attenuated iAs-induced soft agar colony formation in RWPE1 cells, indicating Keap1-Nrf2 pathway is involved in iAs-induced prostate epithelial cell transformation.

A-32 A UNIQUE CASE OF HODGKIN'S LYMPHOMA OF THE NASOPHARYNX

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Introduction Hodgkin's lymphoma (HL) arises from germinal center or post-germinal center B cells. It accounts for 0.7% of all new malignancies in the United States with an incidence of approximately 8,000 per year and a bimodal age distribution peaking in the second and sixth decades of life. HL is most often localized in a single axial group of lymph nodes. Involvement of Waldeyer's ring has sporadically been observed and reported in the literature in the form of case reports. This rare entity often presents with non-specific upper respiratory symptoms, commonly mistaken for otitis media, allergies or sinusitis not responsive to first line therapy. This case serves to be the third case of HL identified in this rare anatomical location in the past decade.

Clinical Presentation: A 57 year old Caucasian male with no medical history presented to his primary care provider (PCP) complaining of left ear pain and fullness. He was treated with antibiotics without response and upon his return there was a mass in the sub-mental region. Fine needle aspiration of the mass showed atypical cells. CT scan showed a nasopharyngeal mass with extensive bilateral upper cervical adenopathy, suggestive of nasopharyngeal carcinoma with metastatic adenopathy. Initial laboratory work consisted of CBC, BMP, ANA, HIV, hepatitis panel which were all unremarkable except for mild leukocytosis WBC of 13.2 with a neutrophil predominance and a mildly elevated ESR of 26 mm/hr. The patient was referred to ENT and underwent biopsy of the nasopharyngeal mass in conjunction with lymph node biopsy. Pathology results showed a fibrosclerotic background with small lymphocytes, and large Reid Steinberg cells positive for CD 15 and CD30 and negative for CD20, CD45(LCA), consistent with the Nodular Sclerosing variant of HL. Flow cytometry testing, EBV stain, bone marrow biopsy, and FISH were unremarkable. The patient was staged IIEA and treated with 4 cycles of Adriamycin, Bleomycin, Vinblastine, Dacarbazine (ABVD) with subsequent resolution of symptoms. PET scan 2 weeks after chemotherapy showed full

response to therapy. The patient is scheduled to receive adjuvant radiation therapy.

Discussion Review of the literature revealed less than 90 reported cases making this an extremely rare entity. The tumor characteristically remains localized in the nasopharynx +/- lymph node involvement. It has not been known to involve the bone marrow or any other organs, which is a phenomenon that remains unexplained on a molecular level. Understanding the nature of this tumor on a molecular level in terms of local spread would aid in eliminating unnecessary diagnostic testing in the future. Primary care physicians should give consideration to nasopharyngeal HD in cases of upper respiratory symptoms with adenopathy resistant to antimicrobial therapy and give early referral for a multi-disciplinary approach.

A-33 A METHYLQUERCETIN INHIBITS THE MIGRATION AND INVASION OF OVARIAN CANCER CELL

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Objective Quercetin is a representative flavonoid that presents widely in variety of foods and medicinal plants. So far quercetin has been reported to inhibit migration and invasion of cancer via decreasing the matrix metalloproteinase (MMP)-2. 3,4',7-O-trimethylquercetin (34'7TMQ) was synthesized from rutin as a starting material in order to evaluate the anti-migration and anti-invasion activity of ovarian cancer cells.

Study Design We evaluated the effect of 34'7TMQ on three ovarian cancer cells SK-OV-3, CRL-1978, and CRL-11731 function in vitro. Each Cell lines were treated with different concentrations of 34'7TMQ (0.0, 3.125, 6.25 and 12.5 μ M). For each cell line cell proliferation, migration and invasion were measured by using a CellTiter Assay (Promega), Cytoselect Assay (Cell Biolabs) and by using a FluoroBlock Assay (BD) respectively. Proliferating Cell Nuclear Antigen (PCNA) was also evaluated in cell lysates of 34'7TMQ-treated these 3 ovarian cancer cells by western blot analysis. Expressions of urokinase plasminogen activator (uPA) and plasminogen activator inhibitor 1 (PAI-1) and matrix metalloproteinase-2 (MMP-2) were also evaluated in 34'7TMQ-treated ovarian cancer cells by western blot analysis. Statistical comparisons were performed using analysis of variance with Duncan's post hoc test.

Results 34'7TMQ significantly inhibited migration and invasion of three ovarian cancer cells. 34'7TMQ had no effect on proliferation and PCNA expression in ovarian cancer cells. Moreover, 34'7TMQ significantly inhibited the expressions of uPA and MMP-2 for all ovarian cancer cells.

Conclusion These data indicate that 34'7TMQ inhibited migration and invasion of ovarian cancer cell without inhibiting the proliferation. 34'7TMQ may inhibit the metastasis activity of ovarian cancer cell by decreasing uPA and MMP-2 expression. 34'7TMQ might be further investigated as a novel anti-ovarian cancer agent.

A-34 THE HIGH INCIDENCE OF ACUTE KIDNEY INJURY AND THE PROTECTIVE ROLE OF HMOX1 IN SICKLE CELL ANEMIA

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Acute kidney injury (AKI) is associated with tubulointerstitial fibrosis and nephron loss and may lead to an increased risk for subsequently developing chronic kidney disease (CKD). In adults with sickle cell anemia (SCA), high rates of CKD have been consistently observed, although the incidence and risk factors for AKI are unknown. In this study, we evaluated the incidence of AKI in a cohort of 161 adult SCA patients with genotyping data available from the University of Illinois at Chicago. Acute kidney injury was defined as per the KDIGO guidelines as a rise in serum creatinine by ≥ 0.3 mg/dL within 48 hours or ≥ 1.5 times baseline within the prior seven days. Baseline clinical and laboratory variables were determined from the date of DNA sample collection. Short (≤ 25 , S) and long (>25 , L) *HMOX1* GT-tandem repeats, α -thalassemia, *BCL11A* rs1427407, and the *APOL1* G1/G2 risk variant status were determined by PCR. Comparisons based on AKI history were performed using Kruskal-Wallis or Chi-square analysis, and median values are provided. Variables with a $P \leq 0.1$ in univariate analysis were entered into the initial regression model and a stepwise approach was applied to select the final regression model adjusting for age, gender and hydroxyurea use. Between January 2001 and December 2016, 210 AKI events were observed in 83 (52%) SCA patients. SCA patients with AKI were older (34 vs. 27 years, $P=0.003$) and had a lower baseline hemoglobin concentration (8.5 vs. 8.9 g/dL, $P=0.04$) versus those without AKI. Similar rates of hydroxyurea use were observed between SCA patients with (60%) versus without AKI (51%). AKI was most commonly observed in the setting of increased hemolysis during an acute chest syndrome (52/210) or vaso-occlusive crisis (35/210) followed by pre-renal azotemia (33/210). Consistent with increased hemolysis being a risk factor for AKI, 64% (95 of 149 AKI events with urinalysis data available) were preceded by hemoglobinuria. When comparing the inheritance of genetic factors associated with a lower degree of hemolysis, we observed trends for lower co-inheritance of α -thalassemia (30% vs. 42%, respectively; $P=0.1$) and the *BCL11A* rs1427407 T variant (40% vs. 47%, respectively; $P=0.3$) in SCA patients with versus without AKI. Coinheritance of the *APOL1* G1/G2 risk variants, a strong predictor of CKD in African Americans, was similar between those with AKI (11%) versus without AKI (10%). *HMOX1* is the rate limiting enzyme that metabolizes the toxic heme moiety released from red blood cell hemolysis.

We observed higher rates of AKI in SCA patients with longer *HMOX1* promoter GT-tandem repeats (S/S: 33%, S/L: 41%, L/L: 58%) ($P=0.05$) and with the *HMOX1* rs743811 variant (33% vs. 19%) ($P=0.05$). On logistic regression analysis, AKI risk was associated with increasing age (10-year OR 1.8, 95% CI: 1.2–2.5; $P=0.002$), longer GT-repeats (additive model OR 2.5, 95% CI: 1.2–5.1, $P=0.01$) and a lower baseline hemoglobin concentration (1 g/dL OR 0.8, 95% CI: 0.6–1.0; $P=0.06$). The association with the longer *HMOX1* GT-repeats (additive model OR 2.4, 95% CI: 1.2–5.0; $P=0.02$) and lower hemoglobin concentration (1 g/dL OR 0.8, 95% CI: 0.6–1.0; $P=0.09$) persisted after adjusting for baseline eGFR. In conclusion, AKI is commonly observed in adults with sickle cell anemia, occurs most frequently in the setting of increased hemolysis, and is associated with increasing age, a lower baseline hemoglobin concentration, and longer GT-tandem repeats in the promoter region of *HMOX1*. Future studies understanding the mechanisms and consequences of AKI on the subsequent development of CKD in SCA are warranted.

A-35 INCIDENCE AND SURVIVAL TRENDS IN MANTLE CELL LYMPHOMA

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Mantle cell lymphoma (MCL) is a distinct subtype of B-cell non-Hodgkin lymphoma (NHL) characterized by the t(11;14)(q13;32) translocation resulting in cyclin D1 overexpression. Over the past decade, a better understanding of the molecular pathogenesis led to major advances in MCL, most notably the emergence of several new therapeutic agents. The last Surveillance, Epidemiology and End Results (SEER) update on MCL was published in 2008. This analysis used data from Nov 2006 SEER data submission and precedes the broader use of rituximab, availability of novel agents, and more widespread use of hematopoietic cell transplantation (HCT). We hypothesized that survival for patients diagnosed with MCL in the U.S. has since improved and intended to measure outcome improvements and identify possible disparities. We used the population-based SEER-18 registry to calculate the incidence and relative survival rates (RSR) of MCL in the US for two time periods consistent with notable changes in MCL treatment, 2000–2006 (time period-1: prior to evidence for rituximab and novel agents) and 2007–2013 (time period-2). We calculated age-adjusted incidence rates and corresponding 95% confidence intervals using the rate function and RSR using the survival function in SEER*Stat 8.3.2. The use of RSR, as opposed to overall survival (OS), minimizes the effect of competing causes of death and better indicates the effect of the disease on survival. Contrary to disease-specific survival, RSR is not influenced by cause of death attribution. There were a total of 8755 MCL patients diagnosed between 2000 and 2013, of which 3799 were diagnosed during time period-1 and 4956 diagnosed during

time period-2. The median age at diagnosis in both the time periods was 67 years. MCL incidence (MCL cases per 100,000 persons) increased from 0.711 in 2000–2006 to 0.800 in 2007–2013 ($P<0.001$). An increase in the incidence rate was significant among older patients (≥ 65 years) (3.662 to 4.321, $P<0.001$), both males (1.128 to 1.267, $P<0.001$) and females (0.386 to 0.427, $P=0.008$); Non-Hispanic Whites (NHW) (0.814 to 0.924, $P<0.001$) and Hispanics (0.557 to 0.708, $P=0.002$), but not among <65 years (0.284 to 0.290, $P=0.54$) and Non-Hispanic Blacks (NHB) (0.309 to 0.360, $P=0.16$). The RSR at 5 years (RSR-5), compared between 2000–2006 and 2007–2013 improved for the overall population (50.7% to 54.5%, $P=0.01$). In particular, significant improvement was noted among patients diagnosed with stage IV disease (48.0% to 55.1%, $P<0.001$), age 50–64 (61.3% to 67.4%, $P=0.004$), and age 65–74 (49.4% to 56.6%, $P=0.01$). There was no improvement in RSR-5 among patients with stage I–III disease (54.3% to 53.8%, $p=0.85$), <50 years (75.6% to 75.4%, $P=0.90$) or age ≥ 75 (35.7% to 36.2%, $P=0.90$). Improvement in RSR at 5 years was more evident among Hispanics (43.0% to 52.7%, $P=0.04$) than among NHW (51.4% to 53.3%, $P=0.24$) and NHB (51.4% to 58.1%, $p=0.90$). Improvements in OS occurred at similar magnitude of improvements in RSR. Five-year OS reached 74.2%, 64.1%, 50.4% and 24.5% for patients <50 , 50–64, 65–74 and 75+ years respectively at the time of diagnosis. Our study has several important observations. Firstly, there has been a significant increase in the incidence of MCL over the last 7 years, mostly due to increased incidence among older patients. Secondly, there was a modest, yet significant increase in RSR-5 for the entire population over the last 7 years, most notably among patients <65 years and those with stage IV disease. The finding of increased incidence of MCL in the time period-2 may be attributed to greater awareness among the pathologists and clinicians, in that, cases that would have been missed in the time period-1 are now more recognizable with possibly more widespread testing for the presence of t(11;14). The incidence of MCL in older patients has been increasing over the past two decades and may be related to the biology of the disease, genotoxic exposures and “cohort effect”. The significant gain in RSR-5 for MCL patients in the time period-2 is likely due to the introduction of rituximab, intensification of induction regimens, novel agents and widespread use of HCT. In conclusion, although our findings confirm a continuous improvement in the outcomes of MCL patients over the past decade, they also highlight the challenge of improving long-term outcomes, particularly among older patients.

A-36 MULTIFOCAL OSTEONECROSIS SECONDARY TO FAMILIAL THROMBOPHILIA REQUIRING ANTICOAGULATION DURING PREGNANCY

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Background Familial thrombophilia is etiologic for primary multifocal osteonecrosis (ON). In patients with

Factor V Leiden heterozygosity (FVL), anticoagulation before joint collapse (Ficat stages I-II) often slows or stops progress of ON, avoiding total joint replacement. In a patient with multifocal primary ON and FVL heterozygosity, our specific aim was to assess success of anticoagulation in slowing-stopping progression of osteonecrosis, and to detail therapeutic approaches to optimize pregnancy outcome.

Case description The 32 year old female proband developed multifocal ON at age 26, documented as primary. She was found to have FVL heterozygosity, C677T MTHFR homozygosity with associated hyperhomocysteinemia, and hypofibrinolytic 4G4G homozygosity for the PAI-1 gene. ON was present in her right femoral head (Ficat stage I-II), both knees (already collapsed, Ficat Stage III-IV) and shoulders, leading to bilateral total knee replacement (4, 6/2011). Lovenox (40 mg BID, started 9/2010) was given for 3 months, and then Pradaxa was initiated (150 mg BID, started 12/2010). Within 10 months of starting Pradaxa, hip-shoulder pain improved markedly. After 11 months on Pradaxa, MRI revealed no changes in hip or shoulders. After 6 years of treatment with Pradaxa, hip and shoulder ON has not progressed. The most recent imaging (10/2014) showed improvement in ON of the right femoral head without collapse or fracture (remaining Ficat stage I-II). Currently, she is free of joint pain with good functional mobility. She presented on 1/2016 for follow-up with a desire to pursue a pregnancy, having been on Jolivet (0.35 mg daily) for birth control. Lovenox 40 mg BID was restarted, as Pradaxa is contraindicated in pregnancy. As of 11/2016, she conceived, remaining on Lovenox with a fetus at 5 weeks gestation without complication.

Discussion When primary multifocal ON develops in the absence of common causes of secondary ON (high dose, long term corticosteroids, alcoholism, dislocation, sickle cell disease, etc), thrombophilia-hypofibrinolysis should be evaluated, since such cases often have a treatable hypercoagulable etiology. Provided that the ON is primary, idiopathic, and early (no joint collapse, Ficat stage I or II), anticoagulation in the presence of thrombophilia-hypofibrinolysis may slow or stop the progress of ON. Anticoagulation, as in this case (6 years to date) will often prevent joint collapse in joints with early (Ficat stage I-II, pre-collapse disease), which, in the untreated state, inevitably leads to total joint replacement within 2 years from the initial diagnosis of ON. Long term anticoagulation with Lovenox and Pradaxa preserved the patient's hip and shoulders from progressive ON for 6 years. Lovenox during pregnancy protects against maternal and fetal thrombosis as well as placental insufficiency and early spontaneous abortion due to thrombosis of the spiral arteries of the placenta, while continuing to arrest ON.

B-18 IDENTIFICATION OF HUMAN PROSTATE STEM CELLS AT SINGLE CELL RESOLUTION

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Background Isolating adult stem cells is still a major challenge in the field. Prostate stem cells population enriched by the methods used in the past decade including prostatesphere (PS) assay is still a heterogeneous mix with progenitor cells.

Methods We herein developed a novel PS-based label-retention assay to identify prostate stem cells at a single cell level and further separate them from their daughter progenitors. Prostate epithelial cells were pre-labeled with BrdU and/or CFSE, Far red followed by wash-out in PS culture. In this 3-D system, only stem cells can survive by symmetric self-renewal and asymmetric cell division giving rise to daughter stem and progenitor cells to form PS. Self-renew and regenerative abilities were accessed using in vitro PS formation and in vivo renal graft assays. RNA-seq was used for gene profiling analysis while ICC was used to examine protein expression. Gene knockdown was done by siRNA while metabolic activity was evaluated by Mito-stress assay.

Results In 3-D PS culture, while daughter stem cells are relatively quiescent to retain detectable BrdU-labeled parental DNA and CFSE/Far red, daughter progenitor cells lose the labels by rapid proliferation. Labeling-retaining PS cells can be identified at single cell level by a fluorescent confocal microscopy and a 3-D imaging system. Label-retaining PS cells were further separated from the non-retaining PS cells by FACS. Label-retaining PS cells show increased PS forming ability in vitro and regenerative ability in vivo. RNA-seq and gene ontology analyses demonstrated stemness gene signatures unique in label-retaining PS cells with down-regulated metabolic related processes. KRT13 and PRAC1 were further identified as potential prostate stem cell biomarkers. Moreover, label-retaining PS cells exhibit decreased levels of KRT14 and E-cadherin, increased Wnt10b protein and augmented autophagy activity. Finally, our novel stem cell assays are capable of identifying label-retaining cancer stem-like cells.

Conclusions We have identified label-retaining PS cells at a single cell resolution and further verified these cells as prostate stem cells. These create a useful tool that permits the full characterization of prostate stem cells and cancer stem-like cells, which provide opportunities for translational studies to screen potential therapies targeting prostate cancer stem-like cells.

B-19 LIN52 STABILITY AND FORMATION OF CELL CYCLE GENE REGULATORS, THE DREAM AND MMB COMPLEXES

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Cell cycle events are normally precisely timed and tightly coordinated. Cell cycle deregulation is, in turn, a hallmark of cancer. The DREAM (DP, RB-like, E2F, and, MuvB) and MMB (Myb-MuvB) complexes are important for maintaining appropriate cell cycle gene expression. DREAM plays a

role in repressing 800 cell cycle genes during G1 or G0 (quiescence), and the MMB complex contributes to increased G2/M gene expression, required for cell division. LIN52 is part of the MuvB core of proteins, shared in both of these complexes, and is necessary for their assembly and function. Data from The Cancer Genome Atlas reveal that deletions in the LIN52 gene are associated with decreased survival in some cancers. The mechanism and cellular consequences of LIN52 alterations, however, are unknown. Here, we investigated the mechanisms controlling the degradation of LIN52 and how it may influence the formation of DREAM and MMB. DYRK1A (dual-specificity tyrosine-regulated kinase)-mediated phosphorylation of LIN52 at the serine-28 residue (S28) is critical for LIN52 binding to p130 and, in turn, DREAM formation. We noted that LIN52 protein levels are increased when it cannot be phosphorylated due to a loss or inhibition of DYRK1A, or when S28 was replaced with alanine (S28A). Ectopic expression of either LIN52-V5 or LIN52-S28A proteins resulted in a dramatic downregulation of native LIN52, suggesting that LIN52 levels are tightly regulated in the cell. Our results support proteasome-mediated degradation of LIN52 following its phosphorylation by DYRK1A. Specifically, cells treated with cycloheximide showed a progressive decrease in LIN52 levels that was reversed by co-treating those cells with the proteasomal inhibitor, MG-132. We also found evidence of LIN52 ubiquitination using mass-spectrometry and Western blotting. Furthermore, harmine inhibition of DYRK1A, loss of DYRK1A expression, or S28A mutation all resulted in increased stability of LIN52. Using RT-qPCR, we observed that LIN52 mRNA levels slightly increased upon loss of DYRK1A activity and decreased when recombinant LIN52 was overexpressed, suggesting that transcriptional regulation could play a role in control of LIN52 levels. However, the differences in protein levels between LIN52-V5 and LIN52-S28A mutant, despite equivalent mRNA expression, could be only explained by protein-level regulation. Altogether, these results suggest DYRK1A-mediated phosphorylation of LIN52 may lead to LIN52 degradation by the proteasome. These observations place LIN52 in a position to influence the formation of the DREAM and MMB complexes and, in turn, impact cell cycle regulation. The potential role of LIN52 stability in influencing transitions between DREAM and MMB will be discussed.

B-20 **DECODING THE POTENTIAL DELETERIOUS HEMOLYTIC EVENTS IN ABO INCOMPATIBLE PLASMA TRANSFUSION IN PATIENTS WITH MINOR POPULATIONS OF PNH CELLS USING AN EX VIVO MODEL**

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Introduction Transfusion of anti-A/anti-B in ABO mismatched plasma or plasma containing components can cause overt hemolysis. We propose that such hemolytic events could be related to the immune factors of patient's effector arm rather than the antibodies in the blood

product itself. One plausible scenario is the presence of an unknown paroxysmal nocturnal hemoglobinuria (PNH) clone in a transfusion recipient. PNH red blood cells (RBCs) are characterized by the absence of complement-regulating cell surface molecules, decay-accelerating factor (DAF) and membrane inhibitor of reactive lysis (MIRL). In the present study, we developed an ex vivo model of a PNH clone to decipher the underlying pathophysiological effect of hemolysis in transfusion recipients. **Methodology:** Since, transfusion of Group O plasma and its components is a routine practice at hospitals in the absence of patient compatible blood product hence, in the current study we simulated the clinical setting by using Group O plasma as a source of mismatched antibodies. As an example, Group A1 RBCs were used to create 3 functional null mutants: 1) DAF-negative, 2) MIRL-negative and 3) both DAF/MIRL-negative. The null mutants were combined with wild-type RBCs in a ratio of 1:5 (v/v) and incubated with Group O plasma at 37°C for 30 minutes. The RBCs were sub-sampled for the detection of bound anti-A using anti-IgG. The remaining samples were washed and incubated in fresh Group AB serum at 37°C for 60 minutes for complement (C3 b/d) activation. Post-incubation, RBC hemolysis was determined by evaluating plasma at OD 412 nm for free hemoglobin. Later, the cells were washed 4 times and complement activation was detected using anti-C3 b/d.

Results Incubation of wild-type RBCs with Group O plasma resulted in IgG binding but not the deposition of C3b/d. C3b/d could be detected on RBCs with DAF-deficient mutants. In contrast, hemolysis was observed with the 20% MIRL and 20% DAF/MIRL mutants. Interestingly, there was a failure to detect complement coated RBCs in the DAF/MIRL deficient mutant.

Conclusions The results indicate that a potential explanation for overt hemolysis in transfusion recipients of ABO incompatible plasma is the presence of a PNH clone. The data reveals the possibility for complete hemolysis of the DAF/MIRL red cell mutants in a way that a post-transfusion direct antiglobulin test (DAT) could result in a false negative finding for complement activation. The outcomes of our study highlight the significance of overt hemolysis (although a rare event) in the absence of a positive DAT with complement following ABO incompatible plasma transfusions indeed warrants the need for investigation of a PNH clone in transfusion recipients.

B-21 **ONCOTRIPSY - SELECTIVELY TARGETING CANCER CELLS VIA RESONANT HARMONIC EXCITATION**

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Introduction Ultrasound has a promising application in cancer therapeutics as non-invasive method to ablate surgically inaccessible tumors. However current implementations such as high intensity focused ultrasound (HIFU) are non-specific and can harm healthy tissue within their focal zone. The theory of "ultrasound oncotripsy" suggests that specifically tuned ultrasound signals that exploit the

resonant frequencies of cancer cells may cause cancer-specific cell lysis while having minimal effect on healthy tissue.

Background Computational studies performed at Caltech suggest that cells undergo resonant oscillation in response to low intensity ultrasound excitation at specific critical frequencies. These studies further predict that the cytoskeletal and micro-environmental differences between cancerous and healthy tissues would cause these two systems to have different critical frequencies. These studies suggest that by exposing a tumor to ultrasound at the critical frequencies of cancerous cells, we may specifically disrupt cancer cells without posing non-specific or thermal damage to healthy cells. **Methodology** In this abstract, we show preliminary in vitro studies that reveal that different lineages of suspension cells respond in a manner consistent with the ultrasound oncotripsy theory. K562 and SUDHL-4 leukemia cell lines were exposed to pulsed ultrasound excitation using a 300 kHz transducer at 10% duty cycle and an acoustic pressure of less than 0.8 MPa. Each cell sample, 1 e6 cells/mL, was exposed to 1 minute of ultrasound at a different frequency ranging from 250 to 350 kHz, while keeping other acoustic parameters constant. The effect on cellular permeability was measured through ethidium homodimer-1 fluorescence.

Results Both the K562 and SUDHL-4 cell lines experienced an increase in cell membrane permeability in a largely frequency dependent manner. The most significant peaks in permeability occurred at different critical frequencies for each cell type (SUDHL-4 shows peak at 275 kHz, K562 shows peak at 310 kHz). The presence of these unique critical frequencies at which the ultrasound waves induced the most significant effect on the different cell types is as predicted by the theory of ultrasound oncotripsy.

Conclusion These studies demonstrate that by altering the frequency of low-intensity ultrasound excitation, cell-lineage specific targeting of suspension cells can be achieved. This preliminary evidence that cells may be targeted by ultrasound based upon their mechanical properties supports the theory of ultrasound oncotripsy. These precepts may be used for the development of more cancer cell-specific ultrasound therapies.

B-22 CHEMOTHERAPY EFFECTS ON MOTIVATED BEHAVIORS IN MALE AND FEMALE RATS

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Objective To evaluate paclitaxel effects on rates of positively reinforced operant responding in male and female rats as a measure of behavioral depression.

Background Paclitaxel is a cancer chemotherapy drug with adverse effects that include chemotherapy-induced peripheral neuropathy (CIPN), neuropathic pain, and depression of behavior and mood. These adverse effects can limit the clinical use of paclitaxel and reduce patient well-being for decades. Preclinical research on expression and treatment of paclitaxel-induced neuropathic pain has relied almost

exclusively on hypersensitive reflex-withdrawal responses to mechanical or thermal stimuli as the primary measure of "pain." It is unknown if paclitaxel can also produce signs of pain-related behavioral depression in animals.

Methods To test the hypothesis that regimens of paclitaxel treatment sufficient to produce neuropathy and mechanical allodynia would also depress rates of positively reinforced operant responding in assays of intracranial self-stimulation (ICSS) and food-maintained responding. Male and female Sprague Dawley rats (total n=66) were trained in operant assays and treated with paclitaxel (4 injections on alternating days of vehicle, 0.63, 2.0 or 6.0 mg/kg in separate groups of rats). Body weight and rates of operant responding were evaluated daily before, during, and for three weeks after paclitaxel treatment. Mechanical allodynia was assessed weekly using von Frey filaments. Neuropathy was assessed with histological measures of intraepidermal nerve fiber (IENF) density in hind paw skin at the end of the experiment.

Results and Significance Paclitaxel produced weak but significant decreases in rates of both ICSS and food-maintained responding. In analysis of individual data, the magnitude of depression in operant responding did not correlate with either IENF loss or decreases in mechanical sensitivity threshold. These results suggest that neuropathy and mechanical allodynia do not cause behavioral depression and may have different mechanisms than behavioral depression.

B-23 ENDOPLASMIC RETICULUM STRESS ASSOCIATED RESPONSE IN INFLAMMATORY BREAST CANCER

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The endoplasmic reticulum (ER), a major organelle, is responsible for multiple cellular functions. ER participates in calcium signaling, protein folding and maturation and the maintenance of cellular homeostasis. ER stress can be activated by various pathological and physiological conditions which induce unfolded protein response (UPR). The tumor microenvironment in which cancer cells exists consists of network of soluble cytokines, chemokines, growth, and angiogenic factors. Cancer cells adapt to the tumor microenvironment induced ER stress. The role of ER stress in inflammatory breast cancer biology needs extensive study to develop a better understanding of potential new therapeutic treatments and precise prognosis. In the present study, we detected high expression of ER stress markers including C/EBP homologous protein; CHOP, IRE1 α , ATF4, XBP-1, Grp78, and GADD3 in human primary inflammatory breast cancer cells (SUM149PT and SUM190PT). Compared to the control, human mammary epithelial cells (HMEC), breast cancer cells expressed remarkably high levels of ER stress proteins PERK, IRE1 α , PDI. Similarly, we also examined ER stress response using human inflammatory breast cancer tissue sections. Interestingly, inflammatory breast cancer cells were chemosensitive to salubrinal treatment. Salubrinal is a synthetic

cell permeable chemical agent known to elevate the levels of phosphorylated eukaryotic translation initiation factor 2 α (eIF2 α), which is a marker of ER stress. Studies are in progress to determine if salubrinal can exhibit therapeutic value against inflammatory breast cancer by arresting cell cycle and inducing apoptosis. These findings suggest that controlling ER stress with salubrinal may provide a promising strategy to target the growth of inflammatory and aggressive forms of breast cancer.

B-24 EFFECT OF STATINS IN INFLAMMATORY BREAST CANCER

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Inflammatory breast cancer is aggressive and requires better understanding for the development of new treatments and more accurate prognosis. Interestingly, we recently reported that human breast cancer tissue samples displayed high expression of fatty acid synthase, a multifunctional enzyme involved in lipid biosynthesis and active lipogenic pathways (Goswami S and N Sharma-walia, *Oncotarget*. 2016;13;7(37):58953–74). Statins help curb the production of endogenous cholesterol by inhibiting HMG-CoA reductase. HMG-CoA reductase is a major point of intervention for pharmaceutical drugs as this is the first and rate-limiting step in the conversion of HMG-CoA to mevalonate and finally cholesterol. Since statins work through either directly targeting lipids or targeting the cell signal transducers, here we tested the effect of statins such as Simvastatin, Lovastatin, and Fluvastatin on inflammatory breast cancer cells. We used primary human mammary epithelial cell (HMEC) as non-IBC control cells. SUM149PT and SUM190PT (human IBC cell lines) and MDA-IBC3 (primary human breast cancer cells isolated from pleural effusion fluid obtained from a patient with IBC at MD Anderson Cancer Center) were used as IBC cell lines. We observed beneficial anti-tumorigenic effects of statins on inflammatory breast cancer cells and these were associated with the regulation of various lipid metabolism pathways in these cells. These findings implicate that clinically approved statins may provide a safer and more effective strategy to target the lipogenic metabolic pathways in inflammatory breast cancer.

B-25 AZITHROMYCIN-INDUCED THROMBOCYTOPENIA: A RARE CASE REPORT

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Drug-induced thrombocytopenia (DITP) is well-documented but often unrecognized by clinicians. The condition can be asymptomatic, but can also lead to life-threatening bleeding. Azithromycin is a macrolide antibiotic usually prescribed for

acute bronchitis. This drug has few adverse effects, and is specified for respiratory, urogenital, dermal and other bacterial infections. Although DITP cases are well-known, thrombocytopenia caused by azithromycin is very rare. In fact, to our knowledge, there are no previous cases reported on this. An 81-year-old female with a history of type II diabetes mellitus presented to emergency department for hematuria, epistaxis and ecchymosis for 3 days. Ten days ago, she was diagnosed with acute bronchitis and was given azithromycin for 5 days. Physical examination displayed generalized ecchymosis ranging from 5 x 5 mm to few cm in diameter. There was no lymphadenopathy. She also had dark black clots in nostrils and oral cavity, but no signs of active bleeding. Labs showed platelet count of 5 k/cmm. The diagnosis of azithromycin-induced thrombocytopenia was made. Patient received 2 units of platelets, 1 mg/kg intravenous-immunoglobulin (IVIG), and IV dexamethasone for 5 days. The next day, platelets count increased to 60 k/cmm, and to 116 k/cmm on day 3. RBC, platelets, PT/APTT, fibrinogen, antiplatelet antibodies, autoimmune disease workup, hepatitis viral panel, HIV test, non-treponemal antibodies, and tick-borne disease panel were all negative, and no splenomegaly was seen in ultrasound abdomen. A follow-up of complete blood count was completed 2 days after discharge with platelet count of 270 k/cmm. During follow-up 1 month later, there was no further episode of thrombocytopenia. Azithromycin-induced severe thrombocytopenia is a rare adverse effect, with an estimated 10 per million affected by DITP annually. Thrombocytopenia becomes clinically evident when patients are exposed to the sensitizing medication for at least one week. Typical symptoms in DITP range from asymptomatic thrombocytopenia to life-threatening hemorrhage. The onset is often rapid, and platelet count is usually below 20 k/cmm. The etiology of DITP could be divided into low platelet production and high platelet destruction. Most medications hasten platelet destruction through immune-mediated reaction. At least 100 types of medications were suggested as possible causes of drug-dependent, immune thrombocytopenia, including: cinchona alkaloids, non-steroidal anti-inflammatory agents, various antibiotics, anticonvulsants and sedatives, and platelet inhibitors. The diagnosis of DITP is made by excluding other causes. Since our patient's therapy with azithromycin preceded thrombocytopenia, quick recovery of platelet count after the discontinuing azithromycin, azithromycin being the sole drug used before onset of thrombocytopenia, and other causes were ruled out, level of evidence 2 (criteria 1–3) was fulfilled to confirm a causative relationship in DITP. Initial treatment for DITP is to discontinue the medication, causing symptoms to improve within 2 days and platelet count to become normal within a week. In patients with life-threatening bleeding, second-line treatment, such as IVIG and/or steroids and plasmapheresis, can be administered. Platelet transfusion is used with severe thrombocytopenia and high risk of spontaneous hemorrhage, or with myelo-suppressive medications. Our patient's platelets count began increasing on day 2, and became normal in 3 days by after discontinuing antibiotics and receiving IVIG and steroids. The patient was advised to avoid azithromycin in the future for antimicrobial treatment. In conclusion, azithromycin-induced thrombocytopenia is extremely rare, and usually discontinuing the drug usually resolves the case.

B-26 EWING SARCOMA/PNET IN THE UTERUS: A RARE SIGHTING

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Primitive neuroectodermal tumors (PNET) are highly malignant and rare neoplasms, making up 1% of all sarcomas. PNET is part of the Ewing sarcoma (ES) family of tumors, which usually begins in the skeletal system. ES/PNET has a t(11:22)(q24;q12) translocation with ES gene fused onto chromosome 22 and FLI1/EWS gene. Unlike PNET, ES tumors lack neuroectodermal differentiation. PNET/ES commonly occurs on the chest wall, extremities, and paravertebral region, and less frequently in the pelvis, hip region, and retroperitoneum. PNET usually occurs in young males, predominantly Whites and Hispanics. Extrasosseous ES/PNETs of the female tract are rare, with few cases reported from the vagina, uterine corpus, and ovaries. To date, less than 50 cases were previously described as ES/PNET in the uterine corpus; however, only seven cases were molecularly analyzed to confirm that diagnosis. We present the case of a 35-year-old female with ES/PNET arising in the uterus. A 35-year-old G2P2 Caucasian female presented to the ED complaining of right pelvic pain and intermittent vaginal bleeding for 6 months. Transvaginal US showed 3.2×2.6 cm right anterior fundal fibroid and right ovarian cysts. The patient underwent open myomectomy with right ovarian cystectomy. Pathology report displayed positive for PNET with extensive necrosis. Immunostains showed positive for CD99 gene and negative for desmin, synaptophysin, chromogranin, and CD10. Fluorescence in situ hybridization (FISH) analysis confirmed EWSR1 gene (22 q12) and diagnosed ES/PNET. Computed tomography (CT) of abdomen/pelvis with contrast did not show metastases. Positron emission tomography (PET)/CT showed activity within the uterus and adnexa. Total abdominal hysterectomy with bilateral salpingo-oophorectomy and lymphadenectomy. Tumor margins were negative, and categorized as stage T1bN0. One month post-surgery, patient underwent PET/CT. Since ES patients usually present with micrometastatic disease with relapse rate >90% without adjuvant chemotherapy, dose-intensified regimen including vincristine, doxorubicin, cyclophosphamide with alternating ifosfamide and etoposide (VDC/IE) was given. Patient was tolerating chemotherapy in 1-month follow-up. The most common symptoms for PNET/ES are abnormal vaginal bleeding and a uterine mass. Over 75% of uterine ES-PNET cases occur in postmenopausal age. Many uterine PNET cases are diagnosed at advanced stages with aggressive nature. Diagnosis of ES is based on positive immunohistochemical reactions for vimentin, CD99, and FLI1, and negative reaction for desmin, actin, ML, and CD10. CD99 is a highly specific marker for PNET. Histologically, tumors are described by monotonous primitive blue round neoplastic cells and occasionally true/Homer-Wright pseudo-rosettes are found.

Polymerase chain reaction (PCR) or FISH are confirmatory diagnostic techniques. Hysteroscopy and CT may have a role in preoperative staging of advanced cases. Treatment for PNETs includes multimodal therapy with surgery, adjuvant chemotherapy, and radiation. Multimodal therapy improves disease free survival. In PNET, surgery is considered the first step, with typical treatment of total hysterectomy with bilateral salpingo-oophorectomy with/without chemotherapy and/or radiotherapy. Intensive chemotherapy regimens include alkylating agents (cyclophosphamide or ifosfamide), vincristine, actinomycin-D, and doxorubicin. Combination therapy improves 5-year overall survival by 13% compared to surgery alone. Fertility sparing surgery is mandatory in young women to restore uterus function. In conclusion, case reports on uterine PNET are very rare in literature. Mortality remains high despite use of combination therapy. Early diagnosis is essential for patients to respond well to multi-modality treatment.

B-27 IMPLICATIONS OF GLI PROTEINS IN INFLAMMATORY BREAST CANCER

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Hedgehog (Hh) signaling is a necessary, evolutionarily conserved developmental process for human embryogenesis and organogenesis. First identified in *Drosophila melanogaster*, Hh signaling is a contribution for explaining the complex topic of cell segment number patterning; further research identified its important morphogenic properties for cell proliferation, polarity and differentiation. Oncogenic mechanisms, however, can alter these fates in adult tissues and cause aberrant upregulation of Hh signaling pathway. This can include cell proliferative investments such as angiogenesis, epithelial to mesenchymal transition (EMT), and invasive migration patterns typical of metastatic tissues. In recent years the Hh signaling pathway with downstream GLI protein activity has suggested important contributions to tumor initiation/progression to more advanced tumor stages and inappropriate Hh signaling plays a role in more than 30% of human cancers. Further evidence for GLI contributions to metastatic potential includes knockdown studies of GLI2 that supports its role in migration and invasion in cell lines for osteosarcoma, prostate cancer, and hepatocarcinoma. In this study, we detected changes in marker levels that lead to the phenotype of EMT typical of tissue metastases (E-cadherin, β -Catenin and vimentin) in human inflammatory breast cancer cells SUM149PT and SUM190PT. Compared to the control, human mammary epithelial cells (HMEC), IBC cell lines exhibit markedly higher levels of GLI1 and GLI2 expression; knockdown studies of both proteins suggests a strong association between GLI proteins and markers of EMT. These findings implicate that managing GLI proteins with targeted therapies can dramatically alter the early stages of metastasis in Inflammatory Breast Cancer.

B-28 THE ROLE OF AQUAPORINS (AQPS) IN INFLAMMATORY BREAST CANCERS.D. Dajani. *Rosalind Franklin University, United States of America*

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The Role of Aquaporins (AQPs) in Inflammatory Breast Cancer Salah Dajani, Asha Kumari, Miroslava Repak, Sidney Iriana, Arjun Ranade, Sudeshna Goswami and Neelam Sharma-Walia As a highly conserved ubiquitous protein structure, Aquaporins play a role in the development and progression of cancer. By trafficking water and other small molecules, aquaporins play a vital role in maintaining the cellular environment. Due to their critical role in cell stability, previous research has targeted and shown that aquaporins are indicated in cancer progression. When aquaporins alter the cellular environment, there may be numerous downstream effects. Changes in the intracellular levels of certain molecules may lead to these molecules serving as second messengers, having numerous downstream alterations that promote cancer progression. In numerous cancer types, aquaporin expression has had a correlation to tumor stage and prognosis. Aquaporins are expressed in numerous tissues and a thorough examination of aquaporins will show that each aquaporin type plays a meaningful role in specific cancer types. Furthermore, aquaporins assist in angiogenic processes, which is critical for the progression of cancer. This indicates that aquaporin proteins may be a viable therapeutic target or biomarker of prognosis. In this study, we detected changes in levels of various aquaporins in inflammatory breast cancer cells SUM149PT and SUM190PT. Compared to the control, human mammary epithelial cells (HMEC), IBC cell lines exhibit markedly higher levels of aquaporin expression. Knockdown of aquaporin 3 resulted in downregulation of signaling cascade proteins such as FAK, Src, ERK, and AKT. All these signaling pathways are involved in tumor progression.

C-18 CHRONIC LYMPHOCYTIC LEUKEMIA WITH CHYLOTHORAXM. Azharuddin, D. Prudence, P. Shukla, P. Chandler. *Internal Medicine, Monmouth Medical Center, NJ, United States of America*

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Chylothorax is lymphatic fluid filled with fat and its digestive products are immersed by intestinal epithelium (chyle) into the pleural space. The main mechanism of chylothorax is chyle leaking into the pleural space due to thoracic duct disruption from mediastinal adenopathy. Lymphoma is the leading cause of chylothorax, followed by lung cancer. Chylothorax is diagnosed when chylomicrons are found in pleural fluid, or the triglyceride levels in the pleural fluid are >110 mg/dL. Chronic lymphocytic leukemia (CLL) is an indolent B-cell non-Hodgkin's lymphoma in the bone marrow, blood, or lymph nodes. It is a chronic lymphoproliferative disorder predominantly in the elderly. Chylothorax commonly occurs in non-Hodgkin's lymphoma, but rarely in CLL. Less than ten cases of CLL-induced chylothorax have been previously reported.

An 85 year old female with a history of hypertension, hyperlipidemia, and chronic lymphocytic leukemia (treated by chemotherapy cytoxan, vincristine, obinutuzumab, and prednisone) came with shortness of breath on both exertion and rest with orthopnea and bilateral pedal edema for two weeks. On examination, vitals were normal and she was afebrile. Her chest exam revealed dullness to percussion on bilateral chest with decreased breathing sound. Chest X-ray showed bilateral large pleural effusion. Trials of furosemide were unsuccessful. Echocardiogram confirmed absence of systolic or diastolic dysfunction. Computed tomography (CT) chest displayed large bilateral pleural effusion, with significant lymphadenopathy in the chest and upper abdomen suggestive of lymphoma. CT-guided thoracentesis showed chylous appearing pleural fluid with alkalotic pH of 7.73, lactate-dehydrogenase 128 IU/L, protein 4.3 g/dL, albumin 2.9 g/dL, triglyceride 345 mg/dL, and no malignant cells. Pleural fluid analysis lead to diagnosis of chylothorax. The patient's shortness of breath markedly improved and thoracostomy tube was removed before she was discharged to home. The etiology of chylothorax is divided into four groups: tumor, trauma, idiopathic and miscellaneous. Dyspnea and chest discomfort are the principal complaint. CLL commonly manifests as lymphadenopathy, splenomegaly, hepatomegaly, skin lesions and membranoproliferative glomerulonephritis, sometimes with chylous and hemorrhagic ascites, portal hypertension, and rarely with chylothorax. CLL-induced chylothorax can be treated initially with pleural drainage and total parenteral nutrition. Treatment options include mediastinal irradiation followed by talc pleurodesis of the pleural space, or surgery through thoracic duct ligation with/without pleurodesis. With mediastinal adenopathy, either chemotherapy or radiotherapy can be done. Thoracic duct ligation is performed in refractory cases, either in the thorax or abdomen, or to create a pleuroperitoneal shunt. CLL-induced chylothorax causes significant increase in morbidity and mortality, since pleural effusion is difficult to maintain despite treatment measures. Repetitive thoracenteses can be safe with bridging until definitive surgical ligation of the thoracic duct. Clearly, each case of chylothorax must be evaluated on its own to implement a reasonable and effective treatment regimen.

C-19 DIFFERENCES IN THE MUTATIONAL LANDSCAPE IN AFRICAN AMERICANS AND CAUCASIANS WITH TRIPLE NEGATIVE BREAST CANCERF.O. Ademuyiwa,¹ Y. Tao,² J. Luo,³ K. Weillbaecher,³ C. Ma³. ¹*Oncology, Washington University School of Medicine, St Louis/United States of America;* ²*Washington University School of Medicine, MO/United States of America;* ³*Washington University School of Medicine/United States of America*

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Background Triple negative breast cancer (TNBC) is one of the most aggressive subtypes of breast cancer and occurs at higher frequency in African Americans compared with Caucasians. It is unclear if the biology and clinical outcome of TNBC is different in African Americans versus Caucasians. In this study, we sought to evaluate racial differences in the molecular pathology and outcome in patients

with TNBC. Methods-Using publicly available data from The Cancer Genome Atlas, we identified all breast cancer patients with information on race. We analyzed racial differences in clinical characteristics, tumor somatic mutations, and gene expression patterns from whole exome and microarray data using ANOVA for continuous variables and chi square or Fisher's exact test for categorical variables. Two sample t tests were used to identify differentially expressed genes.

Results 1104 breast cancer patients were identified, of which 178 had TNBC. TNBC was more frequent in African Americans than Caucasians (33.3% vs 14.9%; $p < 0.001$). Although, more African Americans than Caucasians overall were classified as having aggressive basal-like breast cancers from PAM50 gene expression analysis (34.8% vs 16.1%; $p = 0.001$), no differences in the TNBC cohort were observed. Median tumor somatic mutation counts were higher in African Americans versus Caucasians (39.5 vs 34; p value 0.022), but no racial differences in the mutation counts in TNBC were observed. Somatic mutation analysis revealed racial differences in specific high prevalence genes in all patients- [TP53: 46% in African Americans vs 27% in Caucasians; p value < 0.001 , PIK3CA: 23% in African Americans vs 34% in Caucasians; p value 0.021, and MLL3: 12% in African Americans vs 6% in Caucasians; p value 0.034]. TNBC patients did not have any specific high prevalence genes associated with racial differences. There were no racial differences in gene expression patterns in selected genes involved in breast cancer biology. Although African Americans, overall, had a shorter time to progression and worse disease free survival than Caucasians, racial differences in outcomes were not observed in the TNBC cohort.

Conclusion The mutational landscape of TNBC is similar between African Americans and Caucasians. The higher frequency of TNBC in African Americans is therefore not associated with a different genomic profile of common established tumor regulatory pathway genes. Other modifiable factors may exist that contribute to the racial disparity in TNBC incidence.

C-20 IATROGENIC EXTREME HYPERFERRITINEMIA

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Background Profound elevations in serum ferritin with levels greater than 50000 mcg/l are seldom encountered. In a retrospective study of 113 adult patients with ferritin > 50000 mcg/l, the most common causes were renal failure, hepatocellular injury, hematologic malignancy, hemophagocytic lymphohistiocytosis, iron overload, rheumatologic and inflammatory conditions. It is imperative to consider these conditions when managing a patient with extremely high ferritin levels. Intravenous (IV) iron is used to support erythropoiesis in patients on hemodialysis. Conversely, excessive iron administration is associated with the risk of iron overload. KDIGO guidelines of 2012 recommend against iron administration in patients with serum ferritin > 500 mcg/l. Here we

present a rare case of extreme iatrogenic hyperferritinemia in a patient receiving IV iron at different outside institutions after being lost to regular follow up.

Case report A 53 year old female with a past history of end stage renal disease secondary to hypertensive nephrosclerosis presented to us with volume overload. She had missed her last two consecutive dialysis sessions. Of note, patient had been receiving her dialysis treatments on an emergent basis at different emergency rooms in the city for the past 3 months. Her rationale was dissatisfaction with her regular dialysis facility. Initial blood work showed hemoglobin of 9.0 g/dl, iron of 346 mcg/dl, TIBC of 153 mcg/dl, transferrin saturation > 99% and ferritin of 94336 ng/ml. White cell count and platelet count was normal. Hematology/Oncology and infectious disease consultation was obtained. CT Chest/Abdomen/Pelvis was acquired which did not demonstrate any lymphadenopathy or visceromegaly. Bone marrow biopsy did not reveal any abnormality. Flow cytometry was also negative for immunophenotypic abnormalities. Additionally C282Y and H63D mutation analysis was negative. Work up for bacterial, viral and fungal infections was additionally negative. Liver function tests, lipid panel, CD25 level, coagulation studies, antinuclear antibody and erythrocyte sedimentation rate were normal. We obtained records from other hospitals which confirmed that she had been receiving erythropoietin and intravenous iron with each dialysis treatment in different emergency rooms. She had not received a blood transfusion over this time period. On her last visit to her nephrologist 3 months prior, her iron studies had shown a low serum ferritin. We intervened by discontinuing iron supplementation and establishing care at a set dialysis unit. Her ferritin had decreased to 1008 on 3 month follow up.

Discussion Extreme hyperferritinemia triggers work up for rare diagnoses. However, more common diagnoses may be dismissed on account of being mundane. In a study involving review of 65000 ferritin levels drawn, chronic transfusion was associated with levels of 10000 to 54000. In light of these numbers, it is easy to reject the more obvious etiology. To date, ferritin as high as 94000 from IV iron has not been reported in literature. Our case highlights the need to exercise caution with intravenous iron administration.

C-21 COMPARISON OF CINobufatalin INDUCED APOPTOTIC SIGNALING IN THREE DIFFERENT OVARIAN CANCER CELL LINES

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Introduction Ovarian cancer is relatively rare and accounts for about 1.3% of all new cancer cases. Risk factors for

ovarian cancer include age, genetics, family history, and gynecological/obstetric history. Besides studying the origin and pathogenesis of ovarian carcinoma, there has been significant progress in the field of translational research in order to identify substances, which may exhibit medicinal attributes against this type of cancer. Cinobufatalin (CINO), a cardiotonic steroid has shown the ability to inhibit the proliferation, migration, and, invasion of three different types of ovarian cancer cells. CINO is extracted from the skin secretions of the traditional Chinese medicine giant toads (Chan su). CINO has been used as a cardiotonic, diuretic and a hemostatic agent. In this study, we assessed the ability of CINO to induce apoptotic signaling on three different ovarian cancer cell lines; SK-OV-3, CRL-1978 and CRL-11731 to confirm whether the effect of CINO is cell specific or a common effect.

Study Design We evaluated and compared the differential inhibitory effect of CINO on SK-OV-3, CRL-1978, and CRL-11731 cancer cell lines in vitro. SK-OV-3, CRL-1978, and CRL-11731 cells were seeded on coverslips in a 6-well plate and allowed to adhere overnight. The cells were then stimulated with 0, 0.5, and 5 μM CINO for 48 hours. Afterwards the cells were incubated with biotinylated Annexin-V (Roche Applied Science) and then Cy3-labeled streptavidin (GE Healthcare), the coverslips were mounted on microscope slides with the nuclei marker 4', 6' diamidino-2-phenylindole (DAPI, Invitrogen). Mitochondrial membrane potential was measured by fluorescence-activated cell sorting (FACS) analysis. SK-OV-3, CRL-1978, and CRL-11731 cells were treated in serum free media with DMSO, 0.1, 0.5, 1, 5, and 10 μM CINO for 12 h and 24 h before measuring their mitochondrial membrane potential.

Results The Annexin V staining showed the expression of Pro-Apoptotic signaling in the three types of cancer cells. We stained the three cell lines (SK-OV-3, CRL-1978, and CRL-11731) using Annexin V, Rhodamine, and DAPI to study and observe how CINO induces apoptotic signaling in these three cell lines. We had three treatments: DMSO or control, 0.5 μM CINO, and 5 μM CINO. The treatment was done for 48 hours. According to the results of the staining, at lower concentrations of CINO (<0.5 μM), there are more DAPI stains compared to Annexin V stains. DAPI stains the nucleus of viable cells. At higher concentrations of CINO (>0.5 μM), the appearance of Annexin V staining increasing while the DAPI decreases. This demonstrates that CINO is inducing apoptotic signals in the SK-OV-3, CRL-1978, and, CRL-11731 ovarian cancer cell lines.

Conclusions CINO can induce apoptotic signaling through the mitochondria in two different pathways. The apoptotic signal can be induced through the intrinsic pathway or the extrinsic pathway. The results of Mitochondrial membrane potential for the SK-OV-3 cell line shows that treatment with higher concentration of CINO lowers the Mitochondrial Membrane Potential (MMP). In the CRL-1978 and CRL-11731 cell lines, higher concentrations of CINO either increases the MMP or there is no change in the MMP. Therefore, we conclude that CINO differentially inhibits mitochondrial membrane potential in ovarian cancer cell.

C-22 POST TRANSPLANT DRUG ASSOCIATED THROMBOTIC MICROANGIOPATHY

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Thrombotic microangiopathy (TMA) is a multifactorial disease where generalized endothelial dysfunction leads to microangiopathic hemolytic anemia, intravascular platelet activation, and formation of platelet-rich thrombi within the microcirculation. TMAs, though uncommon, are of considerable clinical importance because of their abrupt onset and high mortality when left untreated. The two major classes of drugs associated with drug-induced transplant-associated TMA (DTA-TMA) be it allogeneic hematopoietic cell transplantation (HCT) or solid organ transplantation (SOT) include calcineurin inhibitors (CNI) and mammalian target of rapamycin inhibitors (mTORi). Given the rarity of the disease, there are no evidenced-based treatment guidelines for management of DTA-TMA. Though the experts agree that the offending medication should be discontinued, the role of other treatment modalities in the management of DTA-TMA is unclear. Due to this ambiguity surrounding the optimal treatment for DTA-TMA, we conducted this study to evaluate the impact of different treatment strategies in patients with DTA-TMA and focusing on response rates, relapse rates and overall survival (OS). We retrospectively reviewed patients treated at our center between Jan 1, 2008 to Dec 31, 2015. A total of 74 patients with TMA after HCT (n=14) and SOT (n=60) were identified from the transplant registry database. However, only 14 (HCT=9; SOT=6) remained after excluding TA-TMA not related to drugs. Tacrolimus (CNI) was identified as the cause of DTA-TMA in 11 cases while Sirolimus (mTORi) was associated with three cases. The median duration of medication use prior to the diagnosis of DTA-TMA was 116 days (range, 23–1260 days). The offending drug was held within 7 days of DTA-TMA diagnosis. 57% received plasmapheresis (PLEX) with a median of 4 sessions (range, 3–12). Among the patients who received PLEX, rituximab was administered in 37% of patients and eculizumab in 63%. Among the patient who did not get PLEX, none of them got rituximab or eculizumab. When evaluated by the transplant type, majority (80%) of DTA-TMA after SOT received PLEX while only 44% of DTA-TMA received PLEX after HCT. Of note, the offending drug was not restarted in any case. A total of 64% demonstrated response with overall response rates (ORR) for those who received PLEX post HCT and SOT being 25% was 100% respectively. The ORR among the patients who got rituximab and eculizumab were 67% and 60% respectively. Based on the transplant type, all patients with DTA-TMA after SOT demonstrated response while only 44% had a response in DTA-TMA after HCT. The median time to response was 78 days (range, 43–503 days). The median OS for patients who received PLEX versus those who did not receive PLEX in DTA-TMA after SOT

was 430 days (range, 54–691 days) vs 368 days, respectively, while after HCT was 58 days (range, 3–700 days) vs 381 days (range, 156–537 days), respectively. There were 2 relapses noted in our study population and both were in the HCT group. 8 patients died (5 who did not achieve response and 3 who had a response) with DTA-TMA being the cause of death in all of them. Our study has several important observations. Firstly, we noted that, while there was no benefit of PLEX in patients with DTA-TMA post HCT, it did improve outcomes in DTA-TMA related to SOT. Secondly, the ORR was fairly high in patients who received eculizumab. Thirdly, the relapse risk in our study population was low. Finally, the cause of death in all the patients who died in our patient population was related to DTA-TMA. In our study, there was no added benefit of PLEX in patients with DTA-TMA post HCT. In fact the median OS was lower in patients who received PLEX compared to those who did not get PLEX. This may be due to the lack of autoantibodies against ADAMTS13 and potential adverse effects associated with PLEX. However, in patients with DTA-TMA related to SOT (especially renal transplant), the response rates were high in our study and are comparable to the published literature. This is the first study in English literature that has tried to answer the question whether cessation of drug and supportive care is sufficient for the management of DTA-TMA over other interventions. We feel that discontinuation of the offending agent may be sufficient for treatment of DTA-TMA post HCT. More importantly there seems to be a role for eculizumab in the treatment of refractory DTA-TMA, but warrants validation in a randomized trial setting.

C-23 EXPLORING AN ANTI-INFLAMMATORY DRUG, LIPOXIN, TO TREAT KSHV INFECTION

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Lipoxins are host anti-inflammatory molecules that play a vital role in restoring tissue homeostasis. The efficacy of lipoxins and their analog epilipoxins in treating inflammation and related diseases has been well documented. Kaposi's Sarcoma (KS) and Primary Effusion Lymphoma (PEL) are two well-known inflammation related diseases caused by Kaposi's Sarcoma-Associated Herpesvirus (KSHV). Controlling inflammation is one of the strategies adopted to treat KS and PEL, a primary motivation for exploring and evaluating the therapeutic potential of using lipoxins. Recently published work showed that KSHV infected cells downregulated lipoxin secretion via its miRNA cluster. Treating KSHV infected endothelial cells with lipoxin downregulated key inflammatory molecules such as NFκB, ERK and AKT. This study documents the influence of lipoxin treatment on KSHV lifecycle, and its mechanism. Several host transcription factors including EGR-1, SP-1, AP-1, and PPARs, have known to influence KSHV life cycle. Lipoxin alters the level of these host transcription factors to modulate KSHV life cycle. Treating PEL

cells with lipoxin has shown to decrease cell proliferation and enhance cell death. This study provides a new insight into the treatment of KS and PEL using nature's own anti-inflammatory molecule, lipoxin.

C-24 A CASE OF SWEETS SYNDROME ASSOCIATED WITH AZACITIDINE CHEMOTHERAPY, NO REOCCURRENCE WITH RECHALLENGE

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A 64 year old elderly male with no significant previous medical history was diagnosed with Myelodysplastic neoplasm after he was incidentally found to have very elevated platelets (in millions) and anemia. Bone marrow Biopsy reflected that he had MDS/MPN but chromosomal analysis and cytogenetics were normal for him. He was initially started on hydrea for the thrombosis and was later started on Azacitidine chemotherapy. Shortly after Azacitidine therapy, he started having febrile episodes, neutropenia, AKI and also developed right upper extremity and right flank skin lesions. On exam patient had 12×8 cm ulceration with surrounding erythema present on the R back/flank and in addition erythematous plaque with central necrosis and bullae formation were present on the left forearm. Subsequent skin biopsy showed intense neutrophilic infiltration of the epidermis and dermis. The morphologic findings were essentially those of a neutrophil-rich acute inflammatory process with the main differential being a neutrophilic dermatosis, Sweet's Syndrome. Patient was started on prednisone oral therapy and responded dramatically with the lesions completely resolved at one month follow up. Patient completed second cycle of Azacitidine immediately after resolution of sweet's syndrome and subsequently finished the third cycle without any reoccurrence. Azacitidine therapy for MDS treatment is rare to cause sweet's syndrome and there are only few cases reported since its FDA approval in may 2004. We present a case of Sweet's syndrome following chemotherapy with azacitidine and resolution with prednisone therapy and no reoccurrence when rechallenged with azacitidine therapy again. This case shows that it is safe to resume further cycles of azacitidine without need to switch to a different chemotherapy due to concerns of reoccurrence of sweet's syndrome.

C-25 CUTANEOUS PLASMACYTOMA MIMICKING PAPULAR URTICARIA

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A 69-year-old male with a remote history of Hodgkin's lymphoma (in remission) presented with a 2-month history of three discrete pink-red smooth plaques on the back and

shoulder. Skin biopsy revealed a CD79+/IgG+ lymphoplasmacytic dermal infiltrate with kappa-restriction, consistent with plasma cell dyscrasia. Laboratory studies showed marked ESR elevation and a kappa/lambda light chain ratio of 3.8 (well below 100, the myeloma-defining ratio). SPEP, UPEP, bone survey and bone marrow biopsy were unremarkable. Together, these findings support primary cutaneous plasmacytoma. Twelve cycles of electron beam radiation treatment were completed with good clinical response. Cutaneous plasmacytoma results from clonal proliferation of plasma cells in the skin and may be primary (without underlying multiple myeloma) or secondary (direct extension or spread of multiple myeloma). Primary cutaneous plasmacytomas are rare (2–4% of extramedullary disease) and <30% later develop multiple myeloma. Secondary cutaneous plasmacytomas suggest extensive tumor burden and poor prognosis. Lesions are non-tender red or violaceous smooth nodules, with clonal plasma cell infiltrates in the reticular dermis±subcutis on histology. Biopsy and immunohistochemistry are diagnostically important. Electron beam radiation has successfully treated primary disease. For secondary disease, management is aimed at treating underlying multiple myeloma and includes chemotherapy and autologous stem cell transplant.

C-26 TIMING OF 101 VENOUS THROMBOEMBOLISM EVENTS AFTER STARTING TESTOSTERONE IN 84 PATIENTS

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10.1136/jim-2017-000448.82

Specific aim We examined the timing of 101 venous thromboembolism events (VTE) after starting testosterone therapy (TT) in 84 patients sequentially referred to our center because of previously unexplained VTE. **Materials:** We conducted studies of familial and acquired thrombophilia and hypofibrinolysis in 84 patients (76 men, 8 women) compared to 110 patient controls (53 men, 57 women) having VTE without TT. Cases on TT differed from VTE controls (no TT) for factor V Leiden heterozygosity (22 of 82 [27%] vs 14/110 [13%], $p=0.016$) and for lupus anticoagulant (11 of 76 [14%] vs 4/91 [4%], $p=0.03$). The timing of VTE events was graphed, and a quadratic spline curve was fitted to illustrate the VTE density along the time since starting TT.

Results There were 101 VTE events in our cohort of 84 patients. As displayed in the quadratic spline curve, the greatest density of thrombotic events occurred around 3 months after starting TT with a rapid decline in density of events by 10 months. We observed that 60% of the thrombotic events occurred <1 month to 8 months after starting TT.

Conclusions Increased frequency of VTE events within first 6 months of initiation of TT with subsequent decline in VTE thereafter in patients with underlying familial or acquired thrombophilia may be explained by the depletion of susceptibles effect whereby the at-risk thrombophilic

patients were selected out of the distribution due to the interaction of TT with thrombophilia.

C-27 IN VITRO ANTI-METASTATIC ACTIVITY OF CINobufOTALIN IN SK-OV-3, CRL-1978 AND CRL-11731 OVARIAN CANCER CELL LINES

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Objective Cinobufotalin (CINO), a cardiotoxic steroid (CTS) or bufadienolide is extracted from the skin secretions of the traditional Chinese medicine giant toads (Chan su). CINO has been used as a cardiotoxic, diuretic and a hemostatic agent. Previously we have shown that CINO inhibits the cytotrophoblast cell function. Recently other study has shown that CINO inhibits A549, a lung cancer cell function. In this study, we assessed the effect of CINO on three different ovarian cancer cell lines; SK-OV-3, CRL-1978 and CRL-11731 to confirm whether the effect of CINO is cell specific.

Study Design We evaluated the effect of CINO on three ovarian cancer cells SK-OV-3, CRL-1978, and CRL-11731 function in vitro. Each Cell lines were treated with different concentrations of CINO (0.1, 1, 5 and 10 μ M). For each cell line cell proliferation, migration and invasion were measured by using a CellTiter Assay (Promega), Cytoselect Assay (Cell Biolabs) and by using a FluoroBlock Assay (BD) respectively. Proliferating Cell Nuclear Antigen (PCNA) was also evaluated in cell lysates of CINO treated these 3 ovarian cancer cells by western blot analysis. Cell Cycle arrest and Cell viability were determined by fluorescence-activated cell sorting (FACS) analysis. We also performed Annexin V staining on CINO treated these 3 ovarian cancer cell lines by immunofluorescence to evaluate the pro-apoptotic protein expression. In addition mitochondrial membrane potential has also been measured for all these 3 ovarian cell lines after CINO treatment using MMP kit, by FACS analysis.

Results Concentration of CINO at 0.5 μ M inhibit SK-OV-3, CRL-1978, and CRL-11731 ovarian cancer cells proliferation, migration and invasion without cell death and loss of cell viability but cell viability differs for each cell line. Each cell lines differ in response to CINO doses for PCNA expression as well as Annexin V pro-apoptotic protein expression. CINO decreases mitochondrial membrane potential for SK-OV-3 but not for CRL-1978 and CRL-11731.

Conclusion CINO is cell specific, as each cancer cell line responds differently. These data demonstrate that the mode of action of CINO is different on these 3 types of ovarian cancer cells.

C-28 SULFAMETHOXAZOLE-TRIMETHOPRIM INDUCED THROMBOCYTOPENIA AND PULSE STEROIDS

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Background Reported incidence of 10 cases per million population per year, categorizes drug-induced immune thrombocytopenia (DITP) as a rare clinical occurrence. Diagnosis of DIPT may be challenging to identify given its similar presentation to other pathologies, however resolution of symptoms will occur with prompt clinical identification and treatment.

Case report A 20-year-old female with prior medical history of acne vulgaris presented to the emergency department (ED) with a fever and diffuse rash. She was found to be febrile to 102.7 Fahrenheit and other vital signs were unremarkable. Physical exam was only significant for a diffuse, patchy, macular erythematous rash involving the face, trunk and upper and lower extremities sparing the palms and soles. Laboratory studies revealed severe thrombocytopenia with platelets of 4 K/mcL, neutropenia with white blood cell count of 1.8 K/mcL and bands of 14%. PT was elevated to 14.1 seconds, D-dimer of 1740 ng/ml, fibrinogen of 285 mg/dL, fibrin split products of 5 mcg/mL, reticulocyte of 0.84% and an LDH of 337 U/L. All other laboratory work up was negative. Peripheral blood smear was unremarkable and did not reveal schistocytes, bite cells or platelet clumping. Upon further history, it was revealed that the patient was started on sulfamethoxazole-trimethoprim three weeks prior to her presentation, for treatment of acne vulgaris. Over two days, she was transfused a total of 10 units of platelets and pulsed with methylprednisolone sodium succinate 1 gram for two subsequent doses. Later, she was transitioned to prednisone 60 milligrams and eventually weaned off. White blood cell count and platelets normalized, and patient was discharged home safely.

Conclusion DITP can be caused by a diverse category of drugs and it is clinically significant for its diagnosis to initiate appropriate therapy. DIPT is an accelerated platelet destruction from drug-dependent antiplatelet antibodies binding to platelet antigens via Fab regions. A hybrid paratope is generated increasing the antibody's binding affinity to platelet surface antigens.

C-29 MULTIPLE MYELOMA INDUCED HYPERAMMONEMIC ENCEPHALOPATHY

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Multiple myeloma (MM) typically presents with hypercalcemia, renal insufficiency, anemia, and bone lesions. Hyperammonemia manifesting as altered mental status is a

rare complication in a MM patient. We report an interesting case of hyperammonemic encephalopathy (HE) in a 73-year-old male with advanced relapsing kappa-light chain MM. After our patient was diagnosed with kappa-light chain MM, he underwent chemotherapy. Due to inadequate response, he was started on second and third line chemotherapy. Following third line chemotherapy, MM progressed and showed plasma cell leukemia. Having already failed three drug treatments, the patient was started on a fourth chemotherapy treatment with daratumumab and dexamethasone. After his first dose treatment of daratumumab, the patient became progressively lethargic. Laboratory findings showed leukocytosis with a high percentage of plasma cells and severe thrombocytopenia. Benadryl was held, but rapid neurologic deterioration ensued and the patient became unresponsive to verbal stimuli. CT head and MRI brain were unremarkable. Liver function tests and abdominal CT scan showed no evidence of hepatic dysfunction. Ammonia levels were sent and he was confirmed to have an encephalopathic picture with elevated ammonia of 120 mg/dL. The patient was started on lactulose, rifaximin, and empiric antibiotics, but his elevated ammonia levels persisted. Considering his severe cytopenia and failure to respond to prior chemotherapy, the patient was deemed a poor candidate for further aggressive treatment and died within 5 days from disease progression. Although the likelihood of developing HE in a MM patient is rare, the complication has high mortality. Little is known about the characteristics of the complication, but our case supports the reported association of the appearance of peripheral blood myeloma cells to the development of HE. Most importantly, our case illustrates that patients with MM who present with altered mental status should be promptly evaluated for primary HE as a potential cause.

C-30 NUCLEON'S ROLE IN INFLAMMATORY BREAST CANCER

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Inflammatory breast cancer is a rare type of breast cancer that is characterized by redness and swelling of the skin around the breast, similar to that of inflammation. Diagnosing inflammatory breast cancer can be difficult, and further research is needed to clearly understand this disease. Nucleolin is found to be involved in cell proliferation and cell death in many cancers including breast cancer. Previous study of mass spectrometry data from our lab showed nucleolin is a binding partner of osteoprotegerin (OPG) in inflammatory breast cancer cell lines. We used primary human mammary epithelial cell (HMEC) as non-IBC control cells. SUM149PT and SUM190PT (human IBC cell lines) and MDA-IBC3 (primary human breast cancer cells isolated from pleural effusion fluid obtained from a patient with IBC at MD Anderson Cancer Center) were used as IBC cell lines. Nucleolin expression was

found to be higher in IBC cell lines SUM149PT, SUM190PT, and MDA IBC-3 as compared to control HMEC cells. By examining the role of nucleolin on the apoptotic pathway, we will get a molecular understanding of its function in cell death in inflammatory breast cancer. Understanding the functionality of nucleolin in the signaling pathways of inflammation in breast cancer scenario will provide new avenues of promising therapeutic targets.

C-31 REMOTE WEB DIAGNOSIS OF FAMILIAL AND ACQUIRED THROMBOPHILIA IN 127 SELF-REFERRED PATIENTS WITH OSTEONECROSIS

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Background In primary osteonecrosis (ON), before joint collapse, anticoagulant treatment of thrombophilia can slow and often stop the progress of ON, relieving pain, and preventing the need for total joint replacement.

Specific Aim In 127 patients with osteonecrosis (ON), self-referred via the world-wide-web, we assessed familial and acquired thrombophilia as an important etiology.

Methods After self-referral, medical and orthopedic history was systematically gathered by emailed and faxed forms. Using laboratory request forms sent to each patient, measures of thrombophilia and hypofibrinolysis were obtained, with comparison to 110 healthy normal controls from our center. Given remote laboratory testing, not all measures of thrombophilia could be obtained in all cases.

Results ON was primary in 92 cases, and secondary in 35 (alcohol, steroids, etc). There were 82 women and 45 men; median age 40 years. Of the 127 patients, 103 had the ON location documented, 52 had only hip ON, 15 had only knee ON, 7 had hip+knee, 13 had multifocal ON (≥ 3 joints), and 16 had other joints. The 72 patients with hip ON had 133 hips involved and the 34 with knee ON had 59 knees involved. Of hips with radiographic staging, 63% were pre-collapse as were 90% of knees. The 127 cases were more likely than controls to have heterozygosity for the Factor V Leiden (FVL) mutation, 10/78 (13%) vs 2/109 (3%), $p=0.004$; high ($>150\%$) Factor VIII, 25/70 (36%) vs 7/103 (7%), $p<0.0001$; high homocysteine, 14/71 (20%) vs 5/107 (5%), $p=0.002$; low antigenic antithrombin III, 14/66 (21%) vs 2/96 (2%), $p<0.0001$; high anticardiolipin antibody IgM, 12/76 (16%) vs 2/109 (2%), $p=0.0009$; and high Lp(a), 21/62 (34%) vs 21/107 (20%), $p=0.044$. Similar ON case-control differences in procoagulants were seen in 92 cases with primary ON. The mutant eNOS T786 allele, associated with reduced nitric oxide production and ON, was present in 39% of cases vs 20% of controls, $p=0.013$.

Conclusions Familial and acquired thrombophilia, and the eNOS T786 mutation, potentially treatable with anticoagulation and 9 g/day of L-arginine in primary ON before joint collapse, were common in young patients with ON

self-referred via the web. Particularly in areas without readily available orthopedic and hematologic consultative expertise, remote consultation via the Web has promise in efficient, geographically expanded diagnosis and medical treatment of ON.

C-32 PITUITARY ADENOMA, OR IS IT SOMETHING MORE SERIOUS? A CASE OF WIDELY METASTATIC NEUROENDOCRINE TUMOR, INITIALLY THOUGHT TO BE A PITUITARY ADENOMA

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We report a case of metastasis to pituitary gland of a diffusely metastasized neuroendocrine tumor of unclear primary source that initially mimicked a pituitary adenoma. A 41-year-old otherwise healthy male with PMH significant only for schizoaffective disorder presented to the hospital with headaches, galactorrhea and peripheral vision loss for a period of one month. On further workup he was found to have 2.5 cm sellar and suprasellar mass on MRI with extension into left orbital cavity. Trans-sphenoidal resection showed that tumor was immunopositive for GH, prolactin and ACTH. His post surgical hospital course was complicated by pan-hypopituitarism. In the subsequent 2 months, patient was admitted twice for acute adrenal crisis episodes which were managed appropriately but he kept declining clinically so further workup was pursued which revealed diffused intra abdominal metastatic disease involving the pericardium, liver, intraperitoneal and retroperitoneal spaces. Interestingly the biopsy showed cytomorphology similar to patient's previous adenoma and favored spread from patient's pituitary tumor, thus patient was presumed to have metastatic pituitary cancer at that time. Pet scan performed few weeks later further clouded the picture of the primary source of cancer with additional diffused nodus of hypermetabolism in right middle lobe of lung, lymph nodes, vertebral bones, chest wall, gonads and adrenals. Radical orchiectomy was performed for testicular mass that once again revealed neuroendocrine cells identical to the previous lesions. At this juncture, in lieu of patient's rapid clinical decline he decided to forgo any further workup for accurate diagnosis of the primary lesion, chemotherapy that was briefly started was discontinued and home hospice was pursued. The patient expired within few months of initial presentation. Metastasis to pituitary tumors is an unusual clinical presentation and even more rare in cases of neuroendocrine tumors. If it presents before the diagnosis of primary tumor it can mimic a pituitary adenoma further delaying workup for the identification of the primary source thus it should be a differential in case of invasive lesions of sellar region even without any previously diagnosed malignancy in the patient.

Infectious Disease

A-37 NOT SO BENIGN HEMATURIA: A CASE OF STRONGYLOIDES HYPERINFECTION IN A RENAL TRANSPLANT

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Introduction *Strongyloides stercoralis* an intestinal nematode that is unique in its ability to complete its entire life cycle in the human host. In immunocompromised hosts, progression of the chronic intestinal infection can lead to a potentially fatal hyperinfection syndrome. We describe an interesting case of an immunocompromised Vietnamese man with hyperinfection two decades after initial exposure to the parasite.

Case report A 71-year-old Vietnamese man was diagnosed with chronic kidney two years after immigrating to the United States. He had been a prisoner of war for 14 years in the jungles of Vietnam 5 years before arriving to the US. He underwent a successful cadaveric renal transplant 19 years after immigration from a US-born donor. One year after the transplant, he presented to his nephrologist for the evaluation of gross hematuria with cough productive of yellow sputum, shortness of breath, intermittent chills, weight loss, and fatigue of several weeks duration. The physical exam was notable for the presence of rales on both lung bases, left more than right. The abdomen was soft with no hepatosplenomegaly or masses. No rash was noted. A urine analysis showed hematuria, pyuria and proteinuria. The urine culture failed to isolate an organism. Peripheral eosinophilia of 1200/ μ L (normal range 0–500/ μ L) was noted on the complete blood count (CBC) and further evaluation of the records showed that he had had intermittent mild peripheral blood eosinophilia (for at least 7 years before transplantation. No screening for *S. stercoralis* had been done and screening for HTLV-1 was negative. A *Strongyloides stercoralis* IgG was therefore obtained which yielded a positive result of 1.96 IU (<1 IU is negative considered negative). *Strongyloides* larvae were easily identified on a wet mount of a stool specimen. A computed tomography (CT) of the chest showed mild peribronchial thickening with a mosaic pattern within the bilateral lobes suggestive of infectious etiology. The patient was treated with a three-week course of ivermectin at a dose of 200 μ g/kg/day with resolution of his symptoms before the end of therapy. Larvae were no longer visualized in 3 consecutive stool specimens using an agar culture method at the end of treatment and 2 weeks after completion of therapy. The peripheral eosinophilia resolved 4 weeks after therapy, and the IgG reverted to negative after 3 months of completion of treatment.

Discussion Hyperinfection usually develops in immunocompromised states when reduced immune surveillance leads to an unrestricted proliferation of worms through accelerated autoinfection. Although transmission of *Strongyloides* can occur from an infected renal allograft, most are the result of the uncontrolled proliferation of the nematode in an immunocompromised recipient with potential exposure before transplantation. In our case, the

patient had eosinophilia for several years before transplantation making acquisition of the infection in the jungles of Vietnam likely. Ivermectin is the first line therapy, as it is more effective than thiabendazole or albendazole, and has fewer side effects, minimum treatment of 2 weeks is required. Hyperinfection requires a longer course of treatment and current guidance dictates for ivermectin to be given until microscopic clearance of larvae from infected sites is documented.

B-29 MAVERIC: MODELING APPROACHES TO REDUCE THE INCIDENCE OF CLOSTRIDIUM DIFFICILE

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Background *C. difficile* is the foremost infectious cause of healthcare-associated diarrhea. It increases the average hospital length of stay by 6 days and is annually responsible for 500,000 infections, 29,000 deaths, and 5 billion dollars in direct healthcare costs. In recent years, hospitals nationwide have sought to curtail *C. difficile* transmission by implementing bundled interventions that simultaneously combine two or more *C. difficile* reduction strategies. However, results of these initiatives are highly variable and the optimal composition of intervention bundles is still unknown. The complexity of *C. difficile* transmission in healthcare settings does not lend itself to study by conventional study designs such as randomized controlled trials. To circumvent this, we aimed to develop an innovative agent-based mathematical *C. difficile* transmission model that incorporates intervention fidelity and patient-centered interventions. A mathematical simulation model is ideal for delineating the clinical effectiveness of individual infection control strategies and investigating the intricacies of *C. difficile* transmission dynamics.

Methods Agent based modeling is an extension of traditional mathematical simulation, in which individuals in the model have unique attributes and interact with each other. The model parameter estimates are based on primary data collection conducted at the University of Wisconsin hospital and supplemented with results from relevant studies in the literature. Model construction was conducted using Netlogo software.

Results We have developed an agent based simulation that models interactions between individual patients, visitors, healthcare workers, and the hospital environment, as each pertains to *C. difficile* transmission. We incorporated ten infection control interventions in the model, including novel patient centered interventions such as patient and visitor hand hygiene initiatives and surveillance for asymptomatic colonization. Intervention fidelity measures were also incorporated into the model as parameters for each intervention. These included personnel compliance to an intervention and the effectiveness of a conducted intervention at decreasing microbial burden.

Discussion This is the first *C. difficile* transmission model to incorporate patient centered interventions and intervention fidelity. In the future, this tool will be leveraged to provide much needed direction to healthcare workers regarding which *C. difficile* interventions to prioritize to optimally control transmission. Although our model focuses on *C. difficile*, many of the included interventions are horizontal approaches to infection control that have wide-ranging effects on the reduction of hospital acquired infections.

B-30 SYSTEMIC LUPUS ERYTHEMATOSUS CEREBRITIS VERSUS WEST NILE ENCEPHALITIS: A DIAGNOSTIC DILEMMA IN CRITICAL CARE SETTING

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Introduction Neurological manifestations of systemic lupus erythematosus (SLE) are observed in about 25–40% of patients with the illness. They pose a diagnostic challenge as there are no specific serologies or imaging that confirm the diagnosis. The mainstay of treatment is empiric immunosuppressants as well as symptomatic management. In addition, the presence of an infectious etiology that can produce similar symptoms adds to the complexity of such a clinical scenario, as occurred in this case.

Case description We present the case of a 64 year old female with medical history of coronary artery disease, hypertension, diabetes mellitus and SLE on chronic steroid therapy, admitted to the intensive care unit with altered mental status. Four weeks prior to presentation the patient was noted to have fevers, rhinorrhea and non-productive cough after being outdoors over Labor Day weekend. Upon arrival, the patient was obtunded, unresponsive to vocal/tactile stimuli and had acute flaccid paralysis. She subsequently developed respiratory failure requiring mechanical intubation. Metabolic, immunological and infectious workup showed anemia, positive antinuclear antibody at a 1:1280 titer, anti-dsDNA (93 unit/ml) and anti-Smith (>8) and decreased C3 and C4 complement levels. The patient had no skin, joint or oral lesions. MRI of the brain was negative for any vascular findings. Given her high autoantibody titers, she was treated with high dose steroids, but without clinical improvement. A diagnostic lumbar puncture was then performed which detected West Nile Virus IgM (8.47IV) in the cerebrospinal fluid, with elevated protein, glucose, lactate levels and a nucleated cell count of 41 cells/mcL. Additionally, electromyography two weeks later showed extensive diffuse axonal polyneuropathy. Symptomatic treatment was continued throughout the remainder of her admission. However, the patient was unable to be weaned off the ventilator and underwent tracheostomy. Her neurological status only mildly improved until discharge to a long term acute rehabilitation center.

Discussion The CDC reports 1,548 cases of West Nile Virus (WNV) in the United States in 2016, which is transmitted by infected mosquitoes. While the majority of cases remain asymptomatic, neurological complications including meningitis, myelitis and encephalitis are seen in less than

1% of cases. Diabetes mellitus, hypertension, advanced age and male sex are independent risk factors for developing neuroinvasive disease. It is readily diagnosed with detection of WNV-specific IgM in the CSF. In contrast, the non-specific symptoms of lupus cerebritis along with the lack of a diagnostic gold standard confounds its diagnosis. We suggest from our experience that clinicians should have high suspicion for other possible causes of neuroinvasive disease in such cases, especially if patients are not showing improvement on steroid therapy.

B-31 WHAT'S IN A DAY? IMPACT OF PROSPECTIVELY STEWARDING NON-INFECTIOUS CAUSES AND PROLONGED DURATIONS OF THERAPY

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Background It is estimated that 50% of hospitalized patients are prescribed an antibiotic, and perhaps up to 30% of those could be improved or are unnecessary. Opportunities lie with avoiding antibiotic exposure in patients with non-bacterial conditions (NBC) and limiting prolonged durations of therapy (“Therapy Complete” or TC). Through prospective audit and feedback (PAF), Antimicrobial Stewardship Program (ASP) may alert providers to these opportunities, however, it has yet to be quantified the impact on institutional antibiotic use. We retrospectively reviewed our institution’s ASP interventions to quantify the number of antibiotic days of therapy avoided (DOTA) in patients deemed to be either NBC or TC. **Methods** The ASP database was used to identify patients, deemed to be either NBC or TC who received written recommendations to stop antibiotics. Data on antibiotic name, route, DOT, planned duration of therapy per the primary team, and indication was collected. If duration of therapy was described, this was used as the basis for days avoided; if a planned duration was not described by the primary, an assumed duration range based on national infectious diseases guidelines was used.

Results From January 2015 through December 2016, 543 patients deemed to be NBC or TC received a written recommendation to stop 953 antibiotics; 67% (305/457) of NBC and 74% (366/496) of TC interventions were accepted and antibiotics were stopped, from which 671 DOTA if we prevented one more day of exposure after the intervention. Asymptomatic bacteriuria was the most common NBC (43.6%); respiratory infections were the most common TC (45.6%). Only 19.5% (131/671) of cases had documented planned duration of therapy, so we applied these documented durations and national guideline recommended durations when needed. Overall, we estimate 671–2958 DOTA, of which 411–1846 potentially could have been via intravenous route. The largest impacts were on 3rd and 4th generation cephalosporin use (194 if one DOTA, range 194–577 DOTA) and quinolones (173 if one DOTA, range 173–975 DOTA).

Conclusions ASP PAF to stop antibiotics in NBC and TC scenarios is well-received and can avoid unnecessary

antibiotic use. Few providers document planned duration but many accept ASP recommendations.

B-32 INFECTIOUS COLITIS PRESENTING AS AN INCIDENTAL FINDING

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A 58-year-old Hispanic male with a past medical history of heart transplant, diastolic heart failure, and chronic kidney disease was admitted with right lower leg pain, swelling and erythema. He was initially treated for cellulitis and was discharged home on Cefadroxil after he had clinically improved. He returned three weeks later with worsening right lower extremity pain, swelling, subjective fevers and chills. He denied any history of sick contacts or recent travel. Review of his systems was negative except for constipation over the past seven months. On examination he was afebrile, tachycardic and hemodynamically stable. He had 2+ pitting edema in his right leg below the knee, associated with erythema and tenderness to palpation. His abdomen was soft, non-distended with minimal tenderness over the right lower quadrant. The remainder of his exam was within normal limits. His labs on admission revealed WBCs of 11.4 thousand/mcL, serum sodium of 126 mmol/L, BNP 1058 pg/mL, albumin 1.7 gm/dL. Lower extremity dopplers were negative for deep vein thrombosis. Blood cultures grew *E. Coli* and Zosyn was started. Over the next few days he started developing gradual abdominal distension and his right lower leg swelling and erythema faded and now appeared on his left lower leg. Repeat dopplers were negative. A skin biopsy of his leg was considered but was not pursued due to concern of abnormal healing. Due to *E. Coli* bacteremia and concurrent abdominal distension, a CT abdomen without contrast was done that showed ileus. Subsequently a colonoscopy was performed that revealed a right sided colitis with discrete ulcerations. He was started on mesalamine due to suspicion for inflammatory bowel disease. Colonic tissue histopathology was negative for CMV done by PCR, but showed inflammatory exudate with scattered foci of acute cryptitis. Stool enteric cultures were sent which were positive for *Campylobacter* species. He completed a three day course of Azithromycin with clinical improvement of his erythema and distension. This case illustrates the potential for atypical presentations in immunosuppressed individuals. This patient's focal infectious colitis presented with minimal abdominal symptomatology. In addition, although his lower extremity erythema may have been a separate process such as streptococcal cellulitis or stasis dermatitis, we could also consider an extra-intestinal presentation of *C. Jejuni*. Recognition of this syndrome is critical for institution of appropriate medical therapy. A rare but lethal complication of missed treatment includes bowel perforation. Skin rash remains a rare culprit of the disease but can mimic cellulitis, erythema nodosum, urticaria and vasculitis among others.

B-33 VERTEBRAL OSTEOMYELITIS BY STREPTOCOCCUS CONSTELLATUS

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Vertebral osteomyelitis (VO) is a bacterial infection of the vertebral body, and 2–4% of all pyogenic osteomyelitis cases are from the intervertebral disc. VO occurs in about 1/250,000 annually, and recently has increased its incidence. Previous literature revealed the rare discovery of streptococci constellatus (SC) as a causative agent of VO. SC pathogens were found to irregularly infect the cervical and lumbar spines as well as the iliac and femur bones. While streptococci infections are well-known, streptococcal vertebral osteomyelitis (SVO) is rare, with less than ten cases reported. Given the lack of literature, we report a case of VO caused by SC, to evaluate its characteristics and emphasize the importance of early diagnosis and proper treatment. A 74 year old female with history of urinary incontinence due to uterovaginal prolapse status post of bilateral salpingo-oophorectomy presented to the emergency department for progressive lower back pain for 3 weeks and vaginal bleeding for 4–5 days. She had dark brown vaginal discharge which increased and turned bright red without clots, with right lower quadrant pain. On examination, patient was afebrile, with tachycardia, tenderness on right-sided parathoracic, and paralumbar palpation. Blood was noted in vaginal vault. Magnetic resonance imaging of pelvis showed osteomyelitis at L5-S1 disc, with fistula between uterine fundus and L5-S1 disc. Blood cultures were positive for *Streptococcus constellatus* (SC) and sensitive to penicillin and ceftriaxone. Thus, intravenous ertapenem was initiated, as she was allergic to penicillin. Patient underwent laparoscopic repair of fistula, anterior lumbar discectomy, irrigation and debridement, bone graft of L5-S1. Patient was able to ambulate with assistance, and was discharged with a peripherally inserted central catheter line to complete a 6-week course of ertapenem. On follow-up visit, the patient's condition remained stable. *Streptococci milleri* (SM) organisms are commensals of the oral cavity and gastrointestinal tract. SM, including *S constellatus*, *S anginosus* and *S intermedius*, are causes of pyogenic, invasive infections. Previous reports found SC in head/neck abscesses, liver abscess, thoracic empyema, spinal epidural abscess and endocarditis. Patients with medical conditions including cirrhosis, diabetes mellitus, and malignancies are susceptible to SC infections. Although unusual, a few findings on infective endocarditis by SC organisms were previously reported. Early diagnosis is critical as it may prevent bone damage and neurological involvement. However, early diagnosis is difficult as symptoms occur about 4 weeks before consultation. The most common symptoms of VO are back or neck pain, and others include pain in the arms, shoulders, chest, or abdomen, fever, leukocytosis, and elevated erythrocyte sedimentation rate. MRI is the ideal technique to diagnose VO. To manage VO, antibiotics such as the fluoroquinolones, rifampin, clindamycin are preferred orally and early as they have

high bioavailability and diffusion. Clindamycin has the best bone-to-serum ratio. The most preferred antibiotic is penicillin. In most series, antibiotic therapy is given intravenously then orally for 4–6 weeks to 2–3 months or more. Our patient received 6 weeks of IV ertapenem. Antibiotic therapy alone, with bed rest and immobilization with orthosis, resolves most PVO cases. Some cases require surgical intervention to manage complications or if medical therapy failed. Surgery evacuates the infective debris and corrects the spinal deformity. In conclusion, the present case reports about rare bone infection due to SC and illustrates the susceptibility of this organism to produce bacteremia and abscesses with osteomyelitis.

C-33 SCREENING FOR HIV AFTER DIAGNOSING MILIARY TUBERCULOSIS

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Learning Objective Investigate HIV and HIV associated disease status in patients presenting with miliary TB case A 55-year-old Caucasian male with a past medical history of hepatitis C, abdominal aortic aneurysm, and sensorineural deafness presented to his primary care physician for 3 months of weight loss, productive cough, and night sweats and follow up of a perianal abscess. He was born and raised in the US and was homeless 15 years ago, but denied IV drug use, international travel, history of HIV, or infectious contacts. An abdominal CT to evaluate the perianal abscess revealed multiple necrotic celiac and para-aortic lymph nodes. A PPD test was positive and follow up chest X-ray demonstrated moderate reticular interstitial prominence. Chest CT showed peribronchial airspace opacities and scattered pulmonary nodules with mediastinal, hilar, supraclavicular and abdominal lymphadenopathy. A subsequent left supraclavicular lymph node biopsy revealed necrotizing granulomas with acid fast bacilli (AFB). Immediately afterwards, he was admitted to the hospital. Physical exam revealed palpable left supraclavicular lymph nodes. Labs revealed hyponatremia. 2 of 3 sputum cultures for AFB were positive and PCR revealed *M. tuberculosis*. Treatment for miliary TB was initiated with rifampin, isoniazid, pyrazinamide, and ethambutol. Despite negative history of HIV, HIV screening and confirmatory tests were positive, which triggered an exploration for HIV-associated infections. Additional labs revealed a CD4 count of 54 and elevated toxoplasma IgG. Pneumocystis pneumonia prophylaxis with azithromycin was initiated. Public health officials were alerted and patient was discharged in stable condition with an appropriate follow up plan to continue directly observed treatment for TB and to begin antiretroviral therapy. Impact: More often, HIV status is already known prior to diagnosis of miliary TB. This case highlights the importance of evaluating HIV status early in a patient initially admitted for miliary TB. This also emphasizes the role of internal medicine physicians in identifying and responding to undiagnosed HIV.

Discussion Individuals with HIV are 20–30 times more likely to develop TB. Miliary TB makes up as few as 3.7% of all TB cases in the US but affects 10% of HIV infected persons. Thus, an investigation to identify underlying HIV infection in patients with miliary TB is warranted given the increased morbidity and mortality (25–30%) associated with an HIV-miliary TB coinfection. Given the association between HIV and miliary TB and patient's history of homelessness and hepatitis C, we had a reasonably high index of suspicion for HIV. Alarming, the patient had not been screened for HIV before. HIV test results prompted an investigation of HIV associated infections and influenced TB therapy as rifampicin was replaced with rifabutin as the latter has fewer drug-drug interactions. ART therapy was initiated after anti-TB therapy as early ART therapy has been shown to improve outcomes.

C-34 JOURNEY FROM A CONTAMINANT TO A PATHOGEN: LELLIOTTIA AMNIGENA, A CASE REPORT

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Introduction *Lelliottia amnigena*, previously known as *Enterobacter amnigenus* is a gram-negative aerobic bacillus of the family Enterobacteriaceae. Once thought to be a contaminant and with doubtful pathogenicity, this organism has been reported in several case reports causing endophthalmitis (per se and after cataract surgery), post transfusion sepsis and post traumatic infection of the lower limb. These case reports prompted researchers to conduct retrospective and cross sectional studies on the incidence of *L. amnigena* and its antimicrobial susceptibility. The results have shown a wide range of antibiotic susceptibility including numerous beta lactams. Here, we describe a unique case of cavernous sinus thrombosis with culture results growing *Lelliottia amnigena* as the responsible microorganism.

Case description Our patient is a 61 y/o female with a history of recurrent right sided sinus infections for two years following a traumatic nasal fracture. She presented with nasal congestion, foul smelling sinus drainage, increasingly severe headaches, right eye pain and bulging of the eyeball associated with fevers and vomiting. On exam, she had bilateral proptosis, ophthalmalgia, chemosis, an enlarged superior ophthalmic vein, elevated intraocular/episcleral venous pressure and tenderness of the right frontal and maxillary sinuses. Laboratory findings included leukocytosis with a left shift and increased ESR. Head computed tomography (CT) showed complete right maxillary sinus opacification, mild opacification of right ethmoid sinuses and near complete opacification of sphenoid sinus. She was diagnosed with cavernous sinus thrombosis and underwent a right maxillary antrotomy, total ethmoidectomy, and sphenoidotomy. Operative sinus culture and blood cultures both yielded *L. amnigena* sensitive to piperacillin/tazobactam, 3rd generation cephalosporins, quinolones, aminoglycosides, tetracycline and carbapenems. She was discharged with a 6 week course of intravenous vancomycin and ultimately made a full recovery.

Discussion Though historically considered largely a contaminant, our case report, in addition to several others, emphasizes the importance that this organism be considered a pathogen in the appropriate clinical setting. To our knowledge, this is the first case report describing *Lelliottia amnigena* as the cause of cavernous sinus thrombosis. Key-words: *Lelliottia*, contaminant, cavernous sinus, antibiotic.

C-35 HERPES SIMPLEX VIRUS (HSV) ENCEPHALITIS AND RHABDOMYOLYSIS WITH BLAND CSF STUDIES

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Background Rhabdomyolysis is characterized by muscle necrosis and release of cell constituents into the bloodstream. This condition is often found in elderly patients after a fall with an extended period on the ground prior to being found. The elderly population has a higher prevalence of dementia and a greater susceptibility to delirium from many diseases including rhabdomyolysis. In the setting of a patient with rhabdomyolysis and altered mentation, it is vital to establish an accurate baseline of mental status at home as well as on presentation to the hospital.

Case report A 78-year-old female with no prior medical history presented to the emergency department (ED) after being found down at home by the fire department. Patient lived alone and was likely on the floor for approximately 48 hours prior to presentation. Reportedly was fully functional and living alone; however, her mental status at time of presentation was minimally verbal. Initially, had stable vital signs and was afebrile. Physical exam was unremarkable, but significant for altered mentation, without focal neurologic deficits and all cranial nerves were intact. Laboratory studies were only noteworthy for an elevated creatinine kinase (CK) of 2577 U/L. All other laboratory studies were found to be within normal range. Computed tomography (CT) scan of the head without contrast revealed mild periventricular white matter small vessel disease. A Chest X-Ray showed severe scoliosis. 24 hours after presentation she was found to have further decline in mental status and an episode of fever to 102.4 Fahrenheit. Infectious workup was promptly initiated with a lumbar puncture, despite the difficulties of severe scoliosis. A repeat chest X-Ray revealed left mild pleural effusion (after normal saline infusion for rhabdomyolysis). Cerebrospinal fluid (CSF) studies revealed: glucose 63 mg/dL, protein 44 mg/dL, white blood cell count of 2, red blood cell count of 4, gram stain and culture negative, and HSV polymerase chain reaction (PCR) positive. Patient was started on cefepime, vancomycin, ampicillin, and acyclovir immediately after obtaining CSF. Acyclovir was continued for a total of 14 days with improvement in her mental status and physical activity, however had a new declined, baseline mental status. Patient was stable for discharge to sub-acute rehabilitation facility for further improvement.

Discussion Rhabdomyolysis and sepsis are a fatal mixture, if not treated promptly. Our patient initially presented without any signs of underlying infection yet deteriorated

dramatically during the second day of admission. It is crucial to establish an accurate understanding of a patient's mental status both at presentation and prior to admission when the patient was in their usual state of health. This information proved vital to the timely recognition of a collapsing complex patient who ultimately improved from her acute illness. Studies have indicated that HSV encephalitis has a poor prognosis and a significant percentage of patients remain obtunded. Length of delay in initiation of acyclovir after 24 hours is correlated with an increased mortality rate. There is an inverse relationship between survival and time of initiating treatment.

C-36 INFECTIVE ENDOCARDITIS AND HEART FAILURE

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Background Although medical management is advancing every day in different fields, the rate of IE admission is still increasing annually and about 11,000 to 15,000 new cases are diagnosed every year in the US. This carried us to investigate those people as there are many factors that have an impact on the prognosis of infective endocarditis patients. In this study, we looked up to find a relationship between IE and previous history of congestive heart failure (CHF) and to how extent this relation may affect prognosis of IE. Method: Retrospective chart analysis for the patients who diagnosed with Infective endocarditis based on Duke's criteria with a history of CHF between 2000–2010.

Results Mortality rate in IE is higher in patient with a history of CHF 16 of 51 patients (31.4%) comparing to non- CHF patients 31 of 194 patients (16%) (Odds ratio: 2 P<0.01). No significant different between IE with a history of CHF Vs non-CHF patients in term of 30-day readmission (23.5% vs 22.7%). Diastolic CHF more than systolic (64.7% vs 35.3%, p<0.05). No significant different between systolic and diastolic in term of mortality and readmission. Most common infection is *Staph. aureus*, Group D enterococcus and *Strep. viridina*, respectively.

Conclusion Pre-existing heart failure is a risk factor for IE, especially diastolic heart failure which is because the most common cause of diastolic HF is valvar disease.

Nephrology

A-39 CARDIOTONIC STEROIDS MEDIATE INFLAMMATION IN RENAL EPITHELIUM VIA THE NA/K-ATPASE ALPHA-1-SRC KINASE SIGNALING PATHWAY

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Introduction Cardiotonic steroids (CTS) are Na/K-ATPase alpha-1 isoform (NKA α -1) ligands that are increased in volume expanded states associated with cardiovascular and renal diseases. We have shown that binding of CTS to NKA

α -1 activates Src kinase and directs a number of important cellular functions including protein trafficking, gene expression, cell growth, and ROS production. While initiation and resolution of inflammation is an important component of cellular injury and repair in renal disease, it is unknown whether CTS activation of the NKA α -1-Src signaling axis regulates the inflammatory response in these settings.

Hypothesis We tested the hypothesis that CTS can promote pro-inflammatory effects in renal epithelial cells and this process is mediated by the NKA α -1-Src signaling mechanism.

Methods/Results First, in order to test whether NKA α -1/Src complex mediates CTS induced inflammatory response, we used proximal tubular epithelial cell lines including human HK2 cells as well as two other stable cell lines derived from LLC-PK1 porcine proximal renal tubules which had either normal levels of NKA α -1 (P11 control) or 90% NKA α -1 knock-down (PY17 knock-down). We found that while the CTS Telocinobufagin (TCB) activated Src at 15 minutes in P11 control cells, the effect was abolished in PY17 α -1 knock-down cells or by pretreatment of P11 cells with a specific peptide inhibitor of the NKA α -1-Src kinase pathway, pNaKtide (1 μ M, 30 minute pretreatment). TCB also enhanced collagen expression in P11 control cells and this was attenuated by pretreatment with the Src inhibitor PP2. Furthermore, TCB activated pro-inflammatory cyto/chemokines including MIF, IL-12P70, CCL1/309 and CXCL10/IP-10 in P11 control cells and these effects were attenuated in the PY17 α -1 knock-down line. Finally, TCB activation of pro-inflammatory cyto/chemokines including IL-2, TPO, MIG, C-CSF and IL-13 was significantly attenuated by pNaKtide (1 μ M, 30 minute pretreatment) in human HK2 renal epithelial cells.

Conclusion These findings suggest that CTS can stimulate inflammatory cytokine /chemokine production in renal epithelium and that this is mediated via the NKA α -1 Src kinase signaling pathway.

B-34 **EXTRACELLULAR VESICLES RELEASED FROM MESENCHYMAL STEM/STROMAL CELLS PROTECT THE RENAL MICROVASCULATURE IN PIGS WITH METABOLIC SYNDROME AND RENOVASCULAR DISEASE**

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Background Metabolic syndrome (MetS) is a cluster of cardiovascular disease-related risk factors that is frequently associated with chronic kidney disease (CKD), and increases its progression towards end-stage renal disease. Superimposition of the MetS on renovascular disease (RVD) amplifies intrarenal microvascular loss, and is linked to poorer outcomes after revascularization, underscoring the need for targeted interventions capable of preserving the post-stenotic kidney in subjects with MetS. We have previously shown in swine RVD that intrarenal delivery of

mesenchymal stem/stromal cells (MSCs) preserves the renal microvasculature and improves renal function beyond the stenotic lesion. However, with the increasing clinical translation testing the safety and efficacy of MSCs in patients, it is imperative to elucidate the mechanisms underlying their beneficial effects. Extracellular vesicles (EVs) released from adipose tissue-derived MSCs may mediate their paracrine effect, but their efficacy to protect the renal microcirculation in RVD complicated by MetS remains unclear. Using a novel swine model, we tested the hypothesis that EVs would attenuate microvascular loss and improve renal function in MetS+RVD.

Methods Four groups of pigs (n=7 each) were studied after 16 weeks of diet-induced MetS (high-cholesterol/high fructose diet) and unilateral RVD (MetS+RVD), MetS +RVD treated 4 weeks earlier with a single intra-renal delivery of pre-labeled EVs harvested from autologous MSCs, and Lean and MetS Sham controls. Stenotic-kidney renal blood flow (RBF) and glomerular filtration rate (GFR) were measured in-vivo (multi-detector CT), whereas EV characteristics (next-generation mRNA sequencing), renal microvascular architecture (3D micro-CT), and injury pathways ex-vivo.

Results Transmission electron microscopy reveals that MSCs release large amounts of EVs that exhibit the classic “cup-shape” morphology on negative staining, and expressed common microvesicle, exosome, and MSC markers. mRNA sequencing of EVs and their parent MSCs revealed that EVs were enriched with pro-angiogenic genes, including vascular endothelial growth factor (VEGF)-A, VEGF-C, and Von Willebrand Factor (vWF)-A Domain Containing-1 (VWA)-1. In addition, protein expression of VEGF and vWF was higher in EVs compared to MSCs. Four weeks after intra-renal delivery, EVs were detected ex-vivo in the stenotic-kidney internalized by tubular and endothelial cells. Treatment with EVs restored renal expression of the pro-angiogenic factors VEGF, Notch-1, and Notch ligand delta-like-4 (DLL4), and improved cortical microvascular density and peritubular capillary density. Tubulointerstitial fibrosis increased and RBF and GFR decreased in MetS+RVD vs. MetS, but were restored in MetS+RVD+EV.

Conclusions This study demonstrates that MSC-derived EVs preserve the structure and function of the post-stenotic kidney in coexisting experimental MetS and RVD. A single intra-renal delivery of autologous EVs restored intra-renal expression of angiogenic factors, reduced microvascular remodeling and loss in the stenotic RVD kidney, and in turn stenotic-kidney tissue injury. Importantly, the protective effects of EVs might be attributed partly to their cargo of pro-angiogenic genes and proteins, and their capacity to improve microvascular disease, an important determinant of renal function beyond a stenotic lesion. Therefore, our observations may shed light into the mechanisms underlying the renal reparative properties of MSCs, and suggest a novel cell-free regenerative strategy to treat MetS+RVD. Acknowledgments: This study was partly supported by the NIH (DK73608, DK104273, HL123160, and DK102325, DK106427), and the Mayo Clinic Mary Kathryn and Michael B. Panitch Career Development Award.

B-35 MITOCHONDRIAL METABOLIC DYSREGULATION AND STRUCTURAL ABNORMALITIES IN A RAT MODEL OF POLYCYSTIC KIDNEY DISEASE

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Background Polycystic Kidney Disease (PKD) is a group of monogenic disorders that result in renal cyst development, being Autosomal-dominant polycystic kidney disease (ADPKD) and Autosomal-recessive polycystic kidney disease (ARPKD) the most common forms. ADPKD is the fourth leading cause of renal failure in adults worldwide and affects approximately 1:500 to 1:1000 live births. ADPKD is a multisystem disease characterized by the progressive development of bilateral renal cysts, and can additionally present with a wide variety of extrarenal manifestations that include hepatocystic disease, intracranial aneurysms and cardiac defects among others. Despite great advances in the understanding of the genetic and molecular pathogenesis of PKD, the mechanism of cyst formation and disease progression remain elusive. Recent evidence suggests that a metabolic reprogramming may underlie the dysregulation of several signaling pathways known to be affected in PKD. Therefore, identifying changes in cellular metabolic pathways represents a major opportunity for therapeutic interventions. The purpose of this study was to investigate the metabolic pathways associated with cystogenesis in the PKD kidney, using ¹H-NMR spectroscopy to characterize the urinary, plasma, and tissue metabolome of PCK (a well-established model of PKD) compared to Sprague-Dawley (SD) wild-type rats.

Methods We included male and female PCK and SD rats that were treated with dDAVP (synthetic vasopressin hormone) (PCK-D, n=16 or SD-D, n=12) to aggravate the cystic phenotype and achieve animals with different degrees of disease severity for a given age, or saline solution (PCK-S, n=16 or SD-S, n=12) as controls. Total kidney volume (TKV), gold standard to assess disease severity, was measured sequentially *in vivo* at day p10, p21 and p35 by MRI, and was adjusted by animals' body weight (TKV/BW). A onetime 24 hrs urine collection was obtained at day p30, and plasma and kidney tissue were collected at the time of euthanasia (p37) following our optimized protocol. Urinary, plasma, and tissue metabolites were measured by proton nuclear magnetic resonance, ¹H-NMR. Kidney metabolites identified from renal tissues were correlated with TKV. Mitochondrial structure was assessed by electron microscopy in proximal tubules (PT), medullary thick ascending limb (mTAL), distal tubules (DT), and collecting ducts (CD).

Results Consistent with previously published data, administration of dDAVP significantly aggravated the disease in PCK rats as evidenced by TKV/BW at p10, p21 and p35 ($p < 0.001$). However, administration of dDAVP did not increase significantly TKV/BW or generate a cystic phenotype in SD rats ($p = 0.65, 0.09$ and 0.92). Analysis of PCK and SD metabolomes by Partial least squares-discriminant analysis (PLS-DA) score plots showed a significant

separation between the groups. Integration of tissue, urine and plasma analysis revealed 5 metabolites (α -ketoglutarate, fumarate, malate, citrate, and hippurate) consistently differentially expressed, among which 4 participate in the mitochondrial tricarboxylic acid (TCA) cycle. Moreover, tissue TCA cycle metabolites α -ketoglutarate, fumarate, malate and citrate correlated directly with TKV/BW ($R^2 = 0.8297, 0.6429, 0.5473$ and 0.8276 respectively). Electron microscopy in PT, mTAL, DT, and CD from PCK and SD rats showed that mitochondrial area and matrix density were preserved in PT, mTAL, and DT of PCK rats. Interestingly, a disruption of cristae membranes, swelling, and decreased matrix density were observed in their CD cystic cells.

Conclusions Comprehensive multilevel metabolomics analysis showed significant dysregulations of several mitochondrial TCA cycle metabolites in PCK rats, which further aggravated with the more severe phenotype. Notably, these changes were associated with mitochondrial structural abnormalities in the CD. These observations suggest that mitochondrial damage and metabolic dysregulations may be implicated in cystogenesis and position mitochondria metabolic pathways as a potential target for therapies.

B-36 TARGETED DISRUPTION OF CD40 SIGNIFICANTLY REDUCES RENAL FIBROSIS FOLLOWING RENAL TRANSPLANTATION IN EXPERIMENTAL RENAL ISCHEMIA

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Introduction We have shown that the CD40 receptor (an essential mediator of immunity and inflammation) predicts changes in renal function in patients with renal ischemia, and that CD40's soluble ligand (sCD40L) is significantly elevated in this setting. In order to further elucidate the role of CD40 in the development of renal ischemia, we created a novel Cd40 mutant (in which Cd40 function is abolished) on the **Background:** of the genetically hypertensive Dahl S rat (S rat), which is prone to the development of renal disease. Following induction of renal ischemia by the Goldblatt two-kidney, one clip (2K1C) method, we have previously demonstrated a significant reduction in renal fibrosis in the clipped ischemic kidneys derived from the Cd40 mutants as well as a significant improvement in renal function compared to S rat controls.

Hypothesis We used reciprocal kidney transplants performed between Cd40 mutants and S rats followed by 2K1C ischemia to test the hypothesis that renal expression of Cd40 significantly contributes to the development of ischemic renal fibrosis. Additionally, we sought to determine if activation of Cd40 on renal fibroblasts could serve as a potential mechanism of renal fibrosis.

Methods Male Cd40 mutants and age-matched S rats were subjected to reciprocal kidney transplants followed by 2K1C ischemia to determine the contribution of renal Cd40 in the development of ischemic renal fibrosis. The 2K1C surgery was performed on the transplanted kidneys. Western blot analysis and trichrome staining were

performed on kidney tissue derived from Cd40 mutants and S rats four weeks following 2K1C surgery. Primary rat renal fibroblasts were grown to confluence, serum starved for 24 hrs, and treated with two concentrations of sCD40L (100 ng/ml and 200 ng/ml) to stimulate CD40 receptor signaling. Cell lysates and supernatant medium were collected 24 hrs after treatment. Western blot analysis and real-time PCR assays were performed in rat renal fibroblasts for markers of inflammation and fibrosis.

Results Following reciprocal renal transplants, kidneys from Cd40 mutants transplanted into S rats and subjected to 2K1C ischemia demonstrated a significant decrease in renal fibrosis (as assed by trichrome staining) compared to clipped ischemic kidneys from S rats transplanted into Cd40 mutants four weeks following 2K1C ($p < 0.01$). In addition, primary rat renal fibroblasts stimulated with sCD40L demonstrated a significant increase in Cd40 expression, the pro-inflammatory mediator monocyte chemoattractant protein-1 (MCP-1), as well as a significant increase in procollagen-1 ($p < 0.01$).

Conclusions Reciprocal renal transplantation confirms that Cd40 expressed within the kidney contributes to renal fibrosis in ischemic renal disease, and this process is potentially mediated by activation of Cd40 in renal fibroblasts. Our results indicate that Cd40 provides a potential therapeutic target for the treatment of ischemic renal disease.

B-37 SUCCESSFUL MANAGEMENT IN TREATMENT-REFRACTORY CISPLATIN-INDUCED HYPOMAGNESEMIA

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Cisplatin is one the most commonly used chemotherapy agents in treating solid tumors, and about 30–60% of patients have long-term nephrotoxicity. Patients can present with hypokalemia, hypomagnesemia, hypocalcaemia, and metabolic alkalosis. Hypomagnesium is often associated with fatigue, muscle weakness, and ventricular arrhythmia, and patients often require long-term magnesium replacement. To date, no case of severe treatment-refractory hypomagnesemia was reported. A 67-year-old woman with a history of hypertension, diabetes, hypothyroidism was recently diagnosed with cervical adenocarcinoma, for which she received cisplatin and radiation. The patient presented with one week of weakness, nausea, vomiting, and watery diarrhoea. The patient was hospitalized with suspected electrolyte abnormality secondary to vomiting and diarrhoea. Physical examination displayed positive Chvostek sign. EKG showed sinus rhythm with prolonged QTc (522 ms). Initial laboratory work displayed multiple electrolyte abnormalities including hypokalemia (2.5 mEq/dL), hypocalcemia (6.2 mg/dL), hypophosphatemia (1.9 mg/dL), and hypomagnesemia (0.6 mg/dL). Diagnosis was renal loss due to cisplatin-induced nephrotoxicity, which was consistent with patient's medical history and

presentation. To treat the electrolyte imbalance, calcium gluconate, magnesium sulfate, and potassium chloride were given intravenously (IV). Potassium level and phosphorus quickly returned to normal range in three days, but hypomagnesemia persisted despite supplementing magnesium oral with IV. Eventually, 50 mg triamterene with oral 4 g magnesium sulfate was administered, and magnesium level was stabilized to normal range. The patient was discharged with 50 mg triamterene and 400 mg of magnesium oxide oral tablets. The magnesium level upon discharge was 1.9 mg/dL. During follow-up 1 week later, the patient was completely asymptomatic and his magnesium level was 2.0 mEq/L. Cisplatin has been associated with persistent hypomagnesemia in cancer patients. Cisplatin causes a renal tubular defect in magnesium reabsorption in the ascending limb of the loop of Henle and distal tubule. Cisplatin may also play a role in magnesium cellular metabolism. Previous cases were reported describing cisplatin-induced hypomagnesemia. Magnesium oxide supplementation after cisplatin therapy may be effective in preventing hypomagnesemia. One study on the effect of magnesium oxide (MgO) supplementation in patients treated with cisplatin found that there are significant differences in serum Mg levels for patients receiving MgO supplementation according to cisplatin dose (500 mg MgO per 50 mg/m² cisplatin) versus patients who did not receive any supplementation. However, there is no effective management for hypomagnesemia refractory to MgO supplementation. Triamterene, a potassium sparing diuretic, blocks epithelial sodium channels in the late distal convoluted tubule and collecting duct. It reduces functioning of sodium-potassium pump, leading to potassium retention and decreased calcium, magnesium, and hydrogen excretion. Thus, triamterene may be beneficial in hypomagnesemia. Amiloride, a drug in the same class as triamterene, was shown to be useful in hypomagnesemia patients. To date, no literature uses triamterene for cisplatin-induced hypomagnesemia. In this case, the patient's hypomagnesemia was difficult to correct using only magnesium supplementation due to cisplatin-induced nephrotoxicity and subsequent magnesium wasting. However magnesium replacement with triamterene rapidly corrected the rest of the electrolyte imbalance and helped to stabilize the magnesium level.

C-37 LOWER ABDOMINAL PAIN IN AN UNCONTROLLED DIABETIC PATIENT: EMPHYSEMATOUS CYSTITIS

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Introduction Emphysematous cystitis is a rare, yet potentially fatal infection of the urinary bladder characterized by accumulation of air within the wall and lumen of the urinary bladder. The most common organisms implicated include, *Escherichia coli* and *Klebsiella pneumoniae*. It often occurs in elderly patients with poorly controlled diabetes and has a female predominance (female-to-male ratio, 2:1). **Case presentation** A 70-year-old female patient presented to the emergency department complaining of acute onset

of abdominal pain, nausea and vomiting. She had poorly controlled insulin requiring diabetes, a history of end stage renal disease (ESRD), hypertension and stroke. On presentation, she had an elevated blood pressure (191/100), and was noted to be tachycardic (103 bpm) and having a temperature of 37.9 C. Her physical exam was significant only for hypogastric tenderness. Her laboratory tests revealed leukocytosis (WBC 10.6 103/uL), whereas her urinalysis showed significant pyuria (WBCs >100/hpf). Abdominal CT revealed the presence of gas within the wall and the lumen of the urinary bladder, that is consistent with the diagnosis of emphysematous cystitis. She was treated with intravenous antibiotics for 10 days and had complete clinical resolution.

Discussion This case illustrates a rare complicated lower urinary tract infection associated with gas formation by microorganisms, and presenting with a very common yet non-specific complaint of “abdominal pain.” The mechanism of gas formation in emphysematous UTIs is poorly understood. Elevated tissue glucose levels in diabetic patient is thought to provide more favorable environment for gas forming microorganisms. Recognizing this condition is critical to the institution of timely and appropriate antimicrobial therapy and prevention of progression to emphysematous pyelitis and/ or pyelonephritis which may have significant mortality rates of 20% and 60%, respectively. Such patients may require surgical relief of obstruction, in addition to intravenous antimicrobial therapy.

Pathophysiology

A-40 TEMPORAL EXPRESSION AND REGULATION OF ER-ALPHA AND ER-BETA IN HUMAN PROSTATE STEM-PROGENITOR CELLS

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Background Estradiol-17 β (E₂) and estrogen receptors (ERs) are implicated in prostate development and carcinogenesis. Previously, we demonstrated that E₂ regulated human prostate stem-progenitor cell amplification by directly targeting ERs. However, the receptor status of ER α and ER β in prostate stem versus progenitor subpopulations is not well delineated. The present study sought to elucidate the temporal expression and regulation of ERs in prostate stem-progenitor cells using novel stem cell assays.

Methods Prostate epithelial cells from disease-free donors and cancer specimens were cultured in 3-D to form prostatespheres (PS) with mixed stem and progenitor cells. Prostate stem cells were separated from progenitors using a PS-based BrdU-retaining assay and FACS. ER mRNA was evaluated by qPCR while protein was examined by ICC and Western blot. ER knockdown was performed by siRNA while ER over-expression utilized lentiviral vectors.

Results In day 7 PS from normal donors, ER α and ER β were detected at both mRNA and protein levels. Gene isoform analysis revealed full length ER α as the dominant

ER α variant, while ER β -2 and ER β -5 were the major ER β variants in prostate stem-progenitor cells. Neither ER β knockdown nor ER β over-expression altered ER α expression. In contrast, ER α knockdown doubled ER β expression whereas ER α over-expression blocked ER β expression, implying that ER α suppressed ER β in prostate stem-progenitor cells. Successful separation of prostate stem cells from progenitors further validated that both cell types expressed ER α and ER β . Interestingly, prostate stem cells expressed lower ER α levels which subsequently increased in daughter progenitors, but higher ER β levels which decreased in progenitors. These observations imply that low ER α levels in prostate stem cells permit robust ER β expression, whereas rising ER α expression in daughter progenitor cells suppresses ER β expression. Finally, both ER α and ER β were highly expressed in prostate cancer stem-like cells as compare to their benign counterparts.

Conclusions Our study demonstrates a temporal shift in ER expression pattern in prostate stem-to-progenitor cell commitment; and further identifies a suppressive role of ER α on ER β expression. The delicate balance between ER α and ER β may contribute to stem cell niche homeostasis regulating prostate stem cell self-renewal and progenitor lineage differentiation. This appears to be dysregulated in prostate cancer stem cells which may contribute to disease progression.

A-41 NA/K-ATPASE SIGNALING STIMULATES CD40 EXPRESSION IN RENAL PROXIMAL TUBULAR EPITHELIAL CELLS

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Background The Na/K-ATPase, a P-type ATPase, is essential in the regulation of ion homeostasis. Recent studies from our group and others have demonstrated that in addition to its canonical role as an ion-transporter, the Na/K-ATPase can form a functional signaling complex with Src, a non-receptor tyrosine kinase, and thus, has an important signaling utility as well. We have established that infusion of cardiotoxic steroids (CTS), ligands of the Na/K-ATPase, cause renal fibrosis both in vitro and in vivo. In addition, we have demonstrated that in vivo infusion of CTS causes an increase in CD40 receptor expression in the kidney cortex, which suggests that Na/K-ATPase signaling may regulate CD40 expression. Although CD40 is classically thought of as a mediator of humoral immune reactions, findings from our group and others suggest that CD40 is also involved in the pathogenesis of renal fibrosis. The mechanism by which CTS regulate CD40 expression has not been elucidated. We sought to test the hypothesis that CTS, via signaling through the Na/K-ATPase, can activate Src and regulate CD40 expression.

Methods In order to test our hypothesis that Na/K-ATPase signaling can affect the expression of CD40, we treated LLC-PK1 cells, a pig proximal tubule cell line, with telocinobufagin (10 nM for 24 hrs), a CTS that is known to be elevated in chronic kidney disease, and assayed for changes

in CD40 expression by Western blot and Real-time PCR (qPCR). In order to determine whether CTS induced changes in CD40 expression were mediated via Src, we pretreated LLC-PK1 cells with 1 μ M pNaKtide, a Na/K-ATPase/Src inhibitor developed by our group, for 30 minutes prior to addition of TCB. Finally, to ensure that any effects of CTS on CD40 expression were mediated through the Na/K-ATPase, we repeated the TCB treatments in PY-17 cells, which are a Na/K-ATPase knockdown cell line, derived from LLC-PK1 cells.

Results Twenty-four hour treatment with 10 nM TCB caused an increase in CD40 expression at the protein level ($p < 0.05$). Interestingly, no changes in CD40 mRNA expression were seen, suggesting that the mechanism by which TCB induces increases in CD40 occurs at the post-transcriptional level. Pre-treatment with our novel Na/K-ATPase antagonist, pNaKtide, attenuated TCB mediated increases in CD40 expression ($p < 0.05$), implicating Src as a key signaling molecule in this process. Finally, the effects of TCB on CD40 expression were abolished in the PY-17 cell line, which suggests that the effects of TCB are mediated specifically through the Na/K-ATPase. Importantly, 10 nM TCB is not a high enough concentration of TCB to cause inhibition of the Na/K-ATPase ion-transport function. Therefore, our results demonstrate that TCB regulates CD40 via the signaling function of the Na/K-ATPase.

Conclusions Our results suggest that CTS signaling through the Na/K-ATPase-Src signaling axis may be a novel regulatory mechanism of CD40 expression.

B-39 EXCRETION OF URINARY MARINOBUFAGENIN AND ANGIOGENIC FACTORS IN PREGNANCIES WITH INCREASED RISK FOR PREECLAMPSIA

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Background Previous work has shown an increase in urinary excretion of marinobufagenin (MBG) in patients with preeclampsia (preE) symptoms versus those without symptoms. Patients were considered at an increased risk for preE if they met U.S. Preventative Service Task Force (USPSTF) criteria for low-dose aspirin prophylaxis to include: prior history of preE, multifetal gestation, chronic hypertension, Type 1 or 2 diabetes, and renal or autoimmune disease. MBG is a novel urinary marker for preE; however, it is unknown how MBG levels fluctuate during gestation.

Hypothesis Shifts in MBG and angiogenic factors during early pregnancy identify cytotrophoblast's dysfunction, contributing to reduced vascular development with impaired perfusion and preE.

Methods In this study, we planned to prospectively enroll three groups of patients; 50 patients in each group total of 150 patients. These groups are as follows: (1) Pregnant women at risk of preE because of pre-gestational diabetes; (2) Pregnant women at risk for development of preE without pre-gestational diabetes; and (3) Pregnant women at low risk for development of preE, to assess whether clinical manifestations are associated with detectable changes in factors predicted from in vitro studies. We have already enrolled total 110 patients (10 patients of group 1, 50 patients from each of group 2 and 3) for serial collection of urine and serum during each trimester and at delivery. Patients were recruited into two cohorts: normal pregnancy and high risk for preE. Risks were calculated for each pregnancy using the sum of relative risk values. Urine samples from 110 subjects (110 in first trimester, 67 in second trimester, 67 third trimester, and 67 at delivery) were assayed using ELISA for MBG, sENG, VEGF, PIGF, sFlt-1 expressed as pg/mg creatinine and the calculated uFP (log of $10 \times$ sFLT-1/PIGF ratio). We utilized the MBG immunoassay developed by Panorama Research, Inc.; Sunnyvale, CA. Wells were coated with 100 μ L/well of 2 μ g/mL anti-MBG antibody (either 4G4 mouse anti-MBG or 201-202 human anti-MBG) in sodium carbonate, at a pH of 9.5. After washing twice with Tris-buffered saline containing 0.1% Triton X-100 (TBST; 250 μ L/well for all washes), wells were blocked for 1 h at room temperature. Samples were prepared by adding 50 μ L of MBG dilution (0.1 pg-10 ng/50 μ L) or unknown sample in Fish Gelatin Blocking Buffer (FGB: 1X Amresco Fish Gelatin Block, 1X TBST) to 50 μ L of 1 μ g/mL MBG-BSA in FGB. Samples containing MBG and MBG-BSA were then added to the wells (100 μ L/well) and incubated for 1 h at room temperature, followed by washing (2X) with TBST. HRP-anti-BSA antibody (100 μ L of 1:1000 of Jackson Labs anti-BSA-HRP in FGB) was added and incubated for 1 h at room temperature, after which the wells were washed 6X with TBST. TMB (100 μ L/well, K&P Labs) was added and incubated for 10-60 min. Reactions were stopped with 100 μ L 0.6N H₂SO₄ and read at 450 nm. Data was fit to a power function ($y=kx^p$), and the concentration of MBG in the samples were calculated using the equation $\text{pg/well} = (\text{OD}_{450}/k)^{1/p}$. The angiogenic factors were analyzed by commercially available kits.

Results Of 100 subjects, 50 had no risk for preE and 50 had relative risks on the average of 6.6 with a range of 1.4 to 16.6. There were no associations between relative risk and any of the 6 angiogenic measures during the first trimester ($p > 0.36$) and during the second trimester ($p > 0.22$) using linear regression. The no risk and high risk cohorts did not differ in any of 6 angiogenic measures during the first trimester ($p > 0.23$ using Mann-Whitney U test). However, during the second trimester, the high risk cohort had greater PIGF levels than the no risk cohort ($p < 0.05$ using Mann-Whitney U test). Comparing the serial values of 6 angiogenic measures in 67 subjects during the first, second, third trimesters and at deliveries, only MBG and PIGF varied significantly ($p < 0.05$) with MBG.

Conclusions MBG increases with progression of pregnancy and the levels of MBG are the highest during delivery. We conclude that MBG levels increase during normal pregnancy, however, the differential levels of MBG in

normal and preE pregnancies are now underway. We have already found from our previous study that urinary MBG levels are higher in PreE pregnancy compared to normal pregnancy at delivery. Relationships to development of preE symptoms and MBG levels are pending with the addition of patients and additional sample.

Pediatrics

A-42 LIPID CHANGES 8 YEARS POST GASTRIC BYPASS IN ADOLESCENTS WITH SEVERE OBESITY

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Background Severe obesity in adolescents is increasing and few effective treatments exist. Weight loss surgery is one option, but the extent to which surgery influences cardiovascular risk factors such as lipids in youth is not clear.

Purpose To study the impact of weight loss surgery in adolescents with severe obesity on lipid parameters in the Follow-up of Adolescent Bariatric Surgery-5+ (FABS-5+) study >5 years postoperatively. We predicted weight loss surgery would be associated with a greater improvement in lipids compared to no surgery.

Methods Adolescents and young adults who either underwent laparoscopic Roux-en Y gastric bypass (RYGB; "Surgical") or who were seeking weight loss treatment ("Non-Surgical") in 2001–2007 were recruited for the FABS-5+ follow-up study between 2011–2013. Baseline (pre-treatment) BMI, fasting lipids and TG/HDL-C ratio (representing small dense LDL particles) were abstracted from charts. Follow-up data were obtained at a research visit. Changes in BMI and lipids were evaluated using paired t-tests and Wilcoxon signed rank tests.

Results At baseline, surgical participants (n=58; 80% of all RYGB cases performed in 2001–2007) were a mean \pm SD age of 17 ± 2 years and 25 ± 2 at follow-up. 86% were Caucasian and 64% were female. After RYGB, BMI was 32% lower than baseline ($p<0.01$). All lipids (except total cholesterol) significantly improved with the largest changes in HDL-C and TG/HDL-C ratio (a decrease of 35% and 57%, respectively). In contrast, in the non-surgical comparison group (n=30, 47% Caucasian, 73% female, age 15 ± 2 at baseline and 22 ± 2 years at follow-up), BMI increased by 6% and lipid parameters showed no improvement over baseline.

Conclusions This is the longest term and most complete follow-up of adolescents following RYGB. Weight loss was durably maintained and significant improvements in lipid profile were observed after RYGB. Whether these lipid improvements translate into reductions in atherosclerosis

and cardiovascular events overtime remains to be determined.

A-43 ARE THERE GENDER AND RACIAL/ETHNIC DIFFERENCES IN PROBLEM BEHAVIOR IN CHILDREN 9 YEARS OF AGE?

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Child problem behavior negatively impacts children's adult quality of life. Although behavior may vary by gender and race/ethnicity, examinations of these differences with regard to specific types of behavior problems are limited. Our purpose is to describe differences in internalizing and externalizing problem behavior by gender and race/ethnicity in children 9 years of age. We use data from the Fragile Families and Child Well-Being Study. The Child Behavior Checklist was used to assess behavior, where higher scores indicate greater behavioral problems. We use analysis of variance (ANOVA) methods to compare behavior across gender and race/ethnicity. Unadjusted ordinary least squared regression models are used to model problem behavior on gender and race/ethnicity. Adjusted models control for maternal, family, and household variables. Behavior scores are standardized to a mean of 0 and standard deviation of 1. ANOVA methods indicated that internalizing behaviors were not significantly different across gender. However, male children had an average externalizing behavior score (range 0–68) of 4.55, compared to a score of 3.66 among females ($p<0.0001$). Internalizing ($p=0.0002$) and externalizing ($p=0.0001$) scores significantly differed across race/ethnicity. In adjusted regression analyses, female externalizing behavior scores were 0.21 standard deviations lower than male scores ($p<0.0001$). Black race was associated with lower internalizing scores by 0.20 standard deviations ($p<0.0001$) and lower externalizing scores by 0.11 standard deviations ($p=0.028$) compared to white race. Hispanic ethnicity was associated with internalizing behaviors scores 0.27 standard deviations lower than white race ($p<0.0001$). Although differences were relatively small in magnitude, our results highlight the need for targeted approaches for children who may receive greater benefit from interventions. Our study results provide insight into the targeted approaches that Wisconsin public health professionals may implement in order to improve pediatric mental and behavioral health. Additional research is needed to understand manifestations of these differences in adulthood.

B-40 CLINICAL AND BIOCHEMICAL OUTCOMES IN NORMAL AND PREECLAMPTIC PREGNANCIES - A PROSPECTIVE STUDY

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Background Preeclampsia (PreE) is de novo development of hypertension and proteinuria after 20 weeks of gestation with multiple pathophysiological triggers affecting 3–8% of pregnancies. PreE has a significant link to alterations of fetoplacental stress that pass to the offspring causing detrimental effects. We aimed at comparing the clinical outcomes and biomarkers from the maternal and cord blood between the patients with and without PreE.

Methods We recruited 20 normal pregnant (NP) and 20 PreE consenting patients in an IRB approved prospective study at Scott & White Memorial Hospital, Temple, Texas. We evaluated maternal age, body mass index (BMI), blood pressures, proteinuria, and gestational age at delivery. We measured serum levels of four angiogenic factors in maternal–fetal paired samples by using ELISA test. The markers are; soluble endoglin (sENG), soluble fms-like tyrosine kinase-1 (sFLT-1), vascular endothelial growth factor (VEGF) and placental growth factor (PlGF). Placental thickness and volumes were measured. We also evaluated neonates for intrauterine growth restriction (IUGR), gestational age at birth, anthropometric measurements including Ponderal Index (PI), length of hospitalization and other neonatal complications. Comparisons were performed using Student's t test, Mann-Whitney U test and Duncan's post-hoc test.

Results Maternal: The systolic blood pressure (SBP) and diastolic blood pressure (DBP) were higher in preE (SBP 162±11; DBP 97±10) compared to normal pregnancies (SBP 121±10; DBP 75±9; p<0.05). PreE mothers had higher urinary protein excretion (457 mg/24 h±140) compared to NP (160 mg/24 h±44; p<0.05 for each case). We did not find any difference in maternal BMI. Gestational age at delivery was different, 39.2 weeks vs 35.1 weeks, p<0.001. Biomarkers: For all angiogenic factors, maternal and fetal cord serum levels differ between subjects with and without PreE (p<0.001). Also for all four factors, maternal levels differ from fetuses (<0.01). Fetal measures were compared to associated maternal levels for each of the four angiogenic factors using linear regression. In general sENG and sFLT-1 had cord values that were related to the maternal value, but VEGF and PlGF were not related to maternal values. Placenta: The placental thickness in early PreE subjects was 25 mm compared to 32 mm in late PreE (p<0.05) and placental volume in early PreE 296 cm³ compared to 393 cm³ (p<0.05) but there was no difference in placental volumes between NP & PreE

pregnancies. Neonatal: Gestational age at delivery in early PreE is 35.4 weeks vs 36.8 weeks in late PreE (p<0.05). About 56% of the infants who are born to early PreE are small for gestational age (SGA) and 30% of the infants who are born to late PreE are SGA. The PI was 3.05 in NP babies vs 2.63 in PreE babies (p<0.05). Average hospital stay for PreE babies were longer (20 days±5) compared to NP (2 days±1; p<0.05). There were no complications observed among the NP babies however multiple adverse outcomes (both maternal and neonatal) were observed in PreE pregnancies.

Conclusion PreE alters the intrauterine environment and activates the detrimental signaling that is transferred to the fetus resulting in premature deliveries, IUGR babies and their related complications.

B-41 A RETROSPECTIVE CROSS-SECTIONAL STUDY OF PREGNANCY OUTCOMES IN DIABETES AND PREECLAMPSIA

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Background Diabetes mellitus (DM) is one of the more common pre-existing endocrine disorders in pregnancy and its prevalence in pregnancy will likely continue to rise as the average age of onset falls throughout the general population. Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. Approximately 7% of all pregnancies are complicated by GDM, resulting in more than 200,000 cases annually. Preeclampsia (preE) is a pregnancy-specific disorder affecting 3% to 10% of gestations and is a leading cause of maternal and fetal morbidity and mortality, accounting for nearly 60,000 maternal deaths per year worldwide. Preeclampsia is diagnosed in women presenting with new onset hypertension accompanied by proteinuria.

Objective The interaction between PreE and DM needs to be further examined despite the growing knowledge of pathophysiology in them. This study compared normal pregnancies to those complicated with preE, GDM, and/or pre-existing diabetes to assess the effects of hyperglycemia on placental development.

Methods A retrospective cross-sectional study (N=621) was conducted over a year of 2008 through 2011 at Baylor Scott and White Memorial hospital, Temple, TX. We distributed subjects into different groups: subjects without PreE or diabetes (N=350), PreE but no diabetes (N=118), GDM but no PreE (N=72), GDM and PreE (N=23), Pre-GDM but no PreE (N=21) and Pre-GDM and PreE (N=37). Average age of the patients who had PreE ranged from 26.9 to 31.6 years and patients who had any diabetes aged from 27.6 to 28.1 years. Maternal age, blood

pressures, gestational age at delivery, and infant birth weight were collected. Statistical analysis was performed using Duncan's post-hoc test and ANOVA.

Results Patients who did not develop preE showed no significant difference in mean age regardless of diabetes status. Women who had pre-existing DM or GDM that went on to develop preE were older on average than their non-diabetic preE counterparts. Despite nulliparity being a risk factor for both GDM and preE, our analysis showed no significant difference among groups for gravidity ($p=0.21$, using ANOVA) with the average gravidity of 2.7 (1.8 SD) for 621 subjects having a range of 1 to 14 pregnancies. Patients with preE delivered earlier in pregnancy compared to those without preE, regardless of diabetes status. The women with pre-existing DM who developed preE delivered even earlier than those with preE and GDM or preE alone, suggesting more severe condition. After adjusting birth weight for gestational age, we found a 4% (about 128 g) reduction in birth weight in those with preE alone which was not a significant difference for this sample size. The diabetic women with or without preE delivered larger babies than average.

Conclusions Our results demonstrate that as maternal age increases, the risk of having pre-existing diabetes or developing GDM increases, and to a significant degree in those with preE. In contrast to studies that have shown women with preE are twice as likely to be nulliparous as women without preE, we were unable to demonstrate that gravidity had a significant correlation to diabetes or preE status. These differing results may be attributed to a relatively small sample size of women in some groups, owing to a limited number of pregnant women with preexisting diabetes or concurrent preE and DM delivering within our hospital system. Development of Pre E in those with preexisting diabetes led to growth restriction.

C-38 COMPARISON OF NEONATAL OUTCOMES IN PREECLAMPTIC VS. NON PREECLAMPTIC PREGNANCIES VIA RETROSPECTIVE STUDY

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Background Preeclampsia (Pre E), a de novo development of Hypertension in consort with proteinuria after 20 weeks of gestation is the prominent cause of morbidity and mortality in mother and the neonates. It affects approximately 3–8% of overall pregnancies. Although, particular etiologies remain unknown, It has been reinforced by numerous studies that Pre E is not just a single disorder, but a syndrome of pertinent multiple pathophysiological factors.

Methods A retrospective chart review over a year of 2014 (January 2014 to December 2014) was conducted of all pregnancies occurred at Baylor Scott and White Health System, Temple, Texas. (N=3704). We distributed subjects into two different groups: Preeclampsia (N=299) vs. Non preeclampsia (N=3405) and compared their basic

characteristics such as sex, race, birth numbers, mode of delivery, APGAR score, gestational age, birth weight as well as occurrences of gestational age, birth weight, admission to Neonatal Intensive Care Unit (NICU), occurrence of bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), hypoglycemia, thrombocytopenia, intraventricular hemorrhage (IVH), length of hospital stay (LOS) and mortality between two groups using two separate analyses.

Results We learned amongst two groups, infants born to Preeclamptic mothers have significantly lower birthweight (Mean=2739, SD=845 grams) compared to Non Preeclamptic mothers (Mean=3200, SD=659 grams), significantly higher rates of C-sections (44%) compared to Non Preeclamptic (28%), significantly lower GA (Mean=36.4 weeks, SD=2.59 weeks) compared to Non Preeclamptic group (Mean=38.3 weeks, SD=3.38 weeks), significantly higher rates of multiple gestation (7%) compared to Non Preeclamptic group (3%), significantly higher occurrence of hypoglycemia (26%) compared to non Preeclamptic group (20%), significantly higher rate of thrombocytopenia (28%) compared to Non Preeclamptic group (17%) and significantly higher length of stay (Mean=19 days, SD=20 days) compared to Non Preeclamptic group (Mean=14 days, SD=20 days).

Conclusion Infants born to Preeclamptic mothers have higher risk of c/s, higher risk of multiple gestation pregnancy, lower birth weight indicating intra uterine growth restriction and the lower gestational age indicating preterm birth. The data indicate the higher rate of hypoglycemia, thrombocytopenia and requirement of increased length of hospital stay in infants born to Preeclamptic mothers compared to Non Preeclamptic mothers.

Pulmonary/Critical Care

A-1 ROLE OF MTORC1 ACTIVATION IN VENTILATOR INDUCED LUNG INJURY AND THE ACUTE RESPIRATORY DISTRESS SYNDROME

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Rationale Patients with the acute respiratory distress syndrome (ARDS) and respiratory failure frequently require life-support with mechanical ventilation (MV). Although life saving, MV can exacerbate underlying lung injury or induce de novo injury known as ventilator induced lung injury (VILI). Low tidal volume (TV) ventilation has been shown to decrease mortality in patients with ARDS, yet little is known about the molecular mechanisms by which the lungs sense and respond to pathologic stretch. mTORC1 is a multi-protein complex that plays a key role in the regulation of cell growth and response to stress, and has been shown to play an important role in the pathogenesis of a number of diseases. Biomechanical activation of mTORC1

has been described in skeletal muscle, however the role of mTORC1 activation following cell stretch in the lung has not been explored. We hypothesize that injurious lung stretch from mechanical ventilation activates mTORC1 and plays a role in the development of lung injury during ARDS. **Methods** C57BL/6 mice were anesthetized and tracheostomy was performed followed by MV with protective low TV (6 cc/kg) or injurious high TV (12 cc/kg) using a Flexivent rodent ventilator. Rapamycin (or DMSO vehicle) was administered via the intraperitoneal or intra-tracheal route at the time MV was initiated. Lung physiology parameters were measured at baseline and hourly thereafter. Lung capillary permeability was assessed by measuring total protein levels in bronchoalveolar lavage (BAL) fluid or by extravasation of Evan blue dye. Cytokine levels were measured in BAL fluid via ELISA. mTORC1 activation was measured by immunoblotting with an antibody specific for the phosphorylated isoform of the ribosomal protein S6 (P-S6). Immunostaining was performed with paraffin embedded lung sections from mouse tissue and human lung autopsy and biopsy specimens using the same antibody. Primary human epithelial cells were stretched in vitro using Flexcell FX-4000 cyclic stretch system for varying amounts of time and degrees of stretch. Protein was isolated from stretched cells, and immunoblotting was performed as described above.

Results Mice subjected to injurious high TV ventilation had increased markers of lung injury including increased lung elastance (i.e. stiffness), BAL protein, and BAL interleukin (IL)-6 levels that were not seen following low TV ventilation. mTORC1 activation (i.e. S6 phosphorylation) was increased in lungs of mice ventilated with injurious ventilation and immunohistochemical staining revealed that the primary site of mTORC1 activation was airway epithelial cells. Immunostaining of lung sections from autopsies of patients with diffuse alveolar damage (the pathologic pattern of ARDS) had increased mTORC1 activation in airway epithelial cells compared to those without ARDS. Cyclic stretch of primary human airway epithelial cells in vitro rapidly activated mTORC1 in a dose-dependent fashion and mTORC1 activity rapidly decreased to basal levels after the cessation of mechanical stretch. Injurious stretch increased cellular reactive oxygen species (ROS) levels and stretch induced mTORC1 activation required ROS release. Finally, treatment with an mTORC1 inhibitor (rapamycin) decreased mTORC1 activation in the lung and reduced the physiologic lung injury seen with injurious MV. **Conclusion** mTORC1 is activated in airway epithelial cells following injurious MV in mice and humans. mTORC1 inhibition may represent a novel strategy to treat or prevent lung injury in patients that require mechanical ventilation. Further studies are needed to determine the mechanisms of stretch induced mTORC1 activation in lung injury.

A-44 **SPHK1 DEFICIENCY IN SMOOTH MUSCLE CELLS PROTECTS AGAINST HYPOXIA- OR HYPOXIA PLUS SUGEN MEDIATED PULMONARY HYPERTENSION**

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Rationale Sphingosine kinase 1 (SphK1) regulates the synthesis of the bioactive sphingolipid sphingosine 1-phosphate (S1P), an important lipid mediator that promotes endothelial cell proliferation, migration and angiogenesis. Serum S1P activates YAP1 signaling pathways and YAP1 activation promotes cell proliferation. We previously reported that SphK1 mRNA and protein levels were significantly up-regulated in pulmonary artery smooth muscle cells (PASMCs) isolated from patients with pulmonary arterial hypertension (PAH). In this study, we investigated whether smooth muscle cell conditional SphK1 deficient (SM22 α Cre⁺SphK1^{fl/fl}) mice are protected from experimental models of pulmonary hypertension (PH) and whether YAP1 plays a role in SphK1-mediated PH development.

Methods SM22 α Cre⁺SphK1^{fl/fl} mice and their wild-type (WT) siblings were used in this study. The 7–8 week old male mice were exposed to normoxia or 10% FiO₂ for four weeks (n=10 per group). The same experiments were designed for hypoxia plus sugen mediated PH model, where four doses of sugen (20 mg/kg bw, once a week) were used. Right ventricular systolic pressure (RVSP) was determined with a Millar pressure transducer catheter. The right ventricle: left ventricle+septum (RV/LV+S) ratio was calculated to assess right ventricular hypertrophy (RVH). Pulmonary artery remodeling was assessed using Aperio image software. Mouse PASMCs isolated from SphK1^{-/-} and WT siblings were used to study cell proliferation via BrdU assays. S1P (100 μ M) was used to study whether S1P can induce YAP1 translocation to the nucleus and activate YAP1 dephosphorylation in hPASMCs. YAP1 siRNA was used to examine whether YAP1 silencing attenuates S1P mediated hPASMC proliferation.

Results Under normoxic or normoxia+sugen exposure, RVSP and RVH did not differ between SM22 α Cre⁺SphK1^{fl/fl} and WT siblings. After four weeks of hypoxic or HS exposure, SM22 α Cre⁺SphK1^{fl/fl} mice developed significantly less severe PH, as assessed by RVSP and RVH when compared to WT mice. Hypoxia or hypoxia plus sugen-induced pulmonary vascular remodeling was significantly attenuated in SM22 α Cre⁺SphK1^{fl/fl} mice. Isolated PASMCs from SphK1^{-/-} mice are less proliferative, compared to WT. In vitro, S1P treatment induced YAP1 activation and cell proliferation in hPASMCs. Silencing of YAP1 attenuated S1P mediated hPASMC proliferation.

Conclusion Smooth muscle cell conditional SphK1 deficient mice are protected against hypoxia or hypoxia plus sugen mediated pulmonary hypertension. This effect could be related to YAP1 signaling. Studies are ongoing to further elucidate the link between sphingolipid signaling, YAP1 activation and pulmonary vascular remodeling. Supported by NHLBI HL111656 to RFM, P01 H198050 to VN.

A-45 **PROTECTION AGAINST MRSA-INDUCED MURINE ACUTE LUNG INJURY BY FTY720 (S)-PHOSPHONATE**

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Introduction Acute lung injury (ALI) remains a significant contributor to mortality and morbidity in critically ill

patients. Novel therapies are needed to address the lung vascular endothelial cell (EC) barrier disruption that occurs in ALI and leads to respiratory failure. We have previously demonstrated that FTY (S)-Phosphonate (Tys) exerts EC barrier protective effects in vitro and in vivo. In this study, we explored the therapeutic potential of Tys in ALI caused by the clinically relevant stimulus of methicillin-resistant *Staphylococcus aureus* (MRSA).

Methods Pre-treatment study: Anesthetized (Ketamine/Xylazine), Wild type (WT) C57BL/6 female mice (8–12 wks, n=7–8) received FTY720 (S)-Phosphonate (Tys) 0.5 mg/kg IP or vehicle control one hour prior to challenge with live MRSA (Wild-type USA300 strain) intratracheally (IT) 1.25×10^8 CFU or an equal volume of PBS (vehicle) and then were allowed to recover prior to harvest 18 hours later. Post-treatment study: C57BL/6 WT male mice (8–12 wks, n=3) were challenged with live MRSA (IT, 0.75×10^8 CFU/kg) and after 1 hour, were treated with Tys (IP, 0.5 mg/kg). In both studies, lung injury indices were measured 18 hours after MRSA. Leakage of proteins into alveolar space was assessed by measuring the protein levels in the bronchoalveolar lavage (BAL). To assess lung inflammation, neutrophil cell counts were determined in BAL.

Results IT MRSA in female and male mice causes a significant increase in BAL protein and neutrophil levels compared to PBS (18 hours). Pretreatment with Tys significantly reduced BAL protein levels by 20% ($p < 0.05$) compared to the vehicle group. Tys pre-treatment also significantly reduced BAL neutrophil recruitment after MRSA by 28% ($p < 0.05$) compared to the vehicle control group. In the Tys post-treatment study, MRSA-induced BAL protein levels were significantly decreased by 36% ($p < 0.05$) compared to the vehicle group. Tys post-treatment also attenuated BAL neutrophil recruitment by 34% compared to the vehicle control group.

Conclusion These results demonstrate that FTY720 (S)-Phosphonate decreases ALI after live MRSA in mice. This intervention represents a potential therapeutic agent against ALI.

A-46 PROLYL HYDROXYLASE 2 AND HYPOXIA-INDUCIBLE FACTOR 2-ALPHA ASSOCIATED GENESETS DIFFERENTIATE PULMONARY ARTERIAL HYPERTENSION

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Rationale Pulmonary arterial hypertension (PAH) is caused by functional and structural changes in the pulmonary vasculature, which leads to increased pulmonary vascular resistance (PVR). Not surprisingly, Hypoxic-inducible

Factor (HIF) and its upstream regulator, Prolyl Hydroxylase Domain-Containing Protein 2 (PHD2), have been linked to the hypoxia response in vascular remodeling and the development of pulmonary hypertension. Previous studies showed that specific deletion of Phd2 in endothelial cells results in spontaneous severe pulmonary hypertension in mice and conditional knockout of HIF2 α , but not HIF1 α , in endothelial cells dramatically protect mice from hypoxia-induced pulmonary hypertension. This study focused on the geneset expression profile instead of looking into the expression level of Phd2/Hif2 α associated genes.

Methods Phd2, Hif1 α and Hif2 α conditional knockout mice were created and used in hypoxia-mediated pulmonary hypertension models. Right ventricle systolic pressures (RVSP), right ventricular hypertrophy by RV/(LV+S) ratios, and small pulmonary artery smooth muscle layer thickness were measured. To determine the molecular signaling events that contribute to the development of PH in Phd2^{EC-/-}, we used Affymetrix Mouse Gene 2.0 ST Array (Affymetrix, Inc., Santa Clara, CA) to profile the protein-coding gene expression level in Phd2^{EC-/-} mice.

Results In total, 459 genes were found to be commonly deregulated (FDR < 10% and FC > 1.3) in both hypoxia induced PH mice and Phd2^{EC-/-} mice. At whole-genome level, the correlation in log₂-transformed gene expression fold change (log₂FC) between hypoxia and normoxia mice and between Phd2^{EC-/-} and WT mice was computed. A significant positive correlation was observed between the two sets of fold changes (Pearson correlation test: $r = 0.274$ and $P < 10^{-10}$), which suggests that the deregulation caused by hypoxia could be remarkably mirrored by Phd2 deficiency. We also compared the geneset score of the TGF- β signaling pathway (defined by the KEGG database) between WT and Phd2^{EC-/-} mice and found that the geneset score of the Phd2^{EC-/-} mice was significantly higher than that of WT mice, which suggests that both HIF2 α and TGF- β signaling pathways are upregulated in lungs isolated from Phd2^{EC-/-} mice and may contribute to the development of severe PH. Finally, we found that, among the 19 GO terms that were downregulated in HIF2 α KD cells, seven were found to overlap with the upregulated GO genesets (t-test: $P < 0.05$) in Phd2^{EC-/-} mice compared to WT controls, which suggests the opposite effect of HIF2 α and PHD2 on PH pathogenesis.

Conclusion These findings unveil temporally and spatially functions for PHD2/HIFs signaling pathways in the development of pulmonary hypertension. Phd2^{EC-/-} mice exhibited a significant higher level of HIF-2 α and TGF- β signaling in comparison to WT mice. Hif2 α mediated genesets differentiate pulmonary arterial hypertension suggesting mechanism-associated genesets help bridge the mechanistic gap between gene expression and transcriptomic profiling. Our study further confirms a central role of PHD2/HIF2 α pathway in PAH pathogenesis and provides a novel and useful diagnostic method to differentiate PAH human subjects.

A-47 ALTERATIONS IN RIG-I EXPRESSION AFFECT MORTALITY IN INFLUENZA VIRUS INFECTION IN MICE

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RATIONALE: Influenza A virus (IAV), is a highly contagious infectious agent that causes upper and lower respiratory tract infection resulting in 200,000 hospitalizations and 36,000 deaths in the United States per year. The retinoic acid-inducible gene I (RIG-I) product is an important pattern recognition receptor (PRR) that regulates IAV-induced antiviral interferons (IFNs) and proinflammatory cytokines, which participate in clearing viral infections. **METHODS:** We generated a RIG-I transgenic (TG) mice strain that expresses the RIG-I gene product under the control of the lung-specific surfactant protein C promoter. We compared the mortality and host immune response of RIG-I knockout (KO) mice, RIG-I TG mice and their litter matched wild type (WT) mice following challenge with IAV. All mice were developed in or backcrossed into a C57BL/6 background strain. **RESULTS:** Surprisingly, both RIG-I KO and TG mice had a survival advantage over WT mice. Infected RIG-I KO and TG animals displayed a similar inflammation profile in the lung as did WT mice, in terms of the protein concentration, total cell count and inflammatory cell composition in the bronchoalveolar lavage fluid (BALF), and by histopathology. All three types of mice exhibited similar antiviral and inflammatory gene responses following IAV infection, with some exceptions. We found that nucleotide-binding oligomerization domain 2 (NOD2) mRNA and protein expression was greatly increased in infected RIG-I KO mice, which suggested that induction of the PRR NOD2 compensated for RIG-I deficiency and initiated the host immune response to IAV in the KO mice. In addition, we found that the BALF IFN- γ /IL-4 ratio of KO and TG mice was significantly lower than that in WT mice. This implies an important role for Th1/Th2 balance in survival in viral pneumonia. **CONCLUSIONS:** Together, our results demonstrate that RIG-I is not required for the innate immune response to IAV in mice, but augments survival in viral infection when knocked out or overexpressed in the lung, perhaps through optimizing Th1/Th2 balance.

A-48 INFLUENCE OF ALVEOLAR EPITHELIAL CELL-ALVEOLAR MACROPHAGE INTERACTIONS ON MECHANICALLY-INDUCED LUNG INJURY/ INFLAMMATION

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Introduction The acute respiratory distress syndrome (ARDS) is a life-threatening condition that involves disruption of the alveolar-capillary barrier, severe hypoxia and often requires mechanical ventilation (MV). Unfortunately, the mechanical forces generated during MV can exacerbate lung injury through the release of pro-inflammatory cytokines which propagate barrier disruption. Although cells within the alveolus, including alveolar epithelial cells (AECs, type I and II) and alveolar macrophages (AMs), may also be subjected to elevated pressures during MV, it is not known if physical interactions between AMs and AECs can alter mechanically induced inflammation within alveolar cells. Furthermore, most *in vitro* studies of pressure induced inflammation to date have only used a single cell type. In this study we developed a co-culture system consisting of human primary AECs and AMs to investigate how pressure during mechanical ventilation alters pro-inflammatory cytokine secretion and barrier permeability.

Methods Primary human AECs were obtained from CellBiologics (Chicago, IL) and primary human AMs were isolated via bronchoalveolar lavage from lungs deemed unsuitable for transplantation from the Lifeline of Ohio organ procurement agency. AECs were seeded at a density of 2.5×10^5 cells/well on top of 0.4 μ m pore transwell permeable support. 24 h later AMs seeded directly on top of AECs or directly in transwells without AECs. Basal media was changed 2 hrs after seeding AMs to allow for adherence, and apical media was removed at that time to allow cells to grow at air-liquid interface. Pressure experiments were conducted exposing 1) AECs alone, 2) AMs alone, or 3) co-cultures of AECs+AMs; to 20 cm-H₂O oscillatory pressure (0.2 Hz) for 16 h. Media was then collected and IL6 and IL8 levels were quantified using ELISA (BD Biosciences). Apical and basal compartments were then rinsed twice with warm PBS and permeability was assessed by measured flux of 4 kDa FITC-dextran from the apical compartment to the basal compartment.

Results Under no pressure control conditions, AECs exhibited significantly less IL8 secretion compared to AMs and co-cultures of AEC+AMs. However, oscillatory pressure resulted in increased IL8 secretion from all groups. Similarly, IL6 secretion was increased following application of pressure in all groups. Interestingly, when AMs were cultured in the basal chamber such that they were not in contact with AECs, oscillatory pressure did not increase IL8 secretion suggesting that the increase in pressure induced inflammation with co-culture is contact-dependent. There was no increase in permeability following application of pressure to AECs or AMs were alone. However, pressure induced an increase in permeability when AEC+AM were in direct contact suggesting that pressure induced barrier dysfunction requires cell-cell interaction.

Discussion Our results suggest that although AMs secrete significantly more pro-inflammatory cytokines than AECs, physical interactions between AECs and AMs does not significantly alter the magnitude of pressure-induced increases in pro-inflammatory cytokine secretion. However, physical interactions between AMs and AECs does alter the amount of pressure-induced changes in barrier permeability. Future studies will focus on identifying the potential mediators of AEC-AM communication and will investigate if targeting these mediators can alter mechanically induced injury.

A-49 DIAGNOSTIC DIFFERENCES BETWEEN SOFA SCORES AND SIRS CRITERIA IN A LARGE ICU COHORT

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Rationale The introduction of the Sepsis-3 Criteria for the diagnosis of sepsis and septic shock in 2016 caused significant changes to the accepted definition of sepsis, severe sepsis, and septic shock. Previous guidelines in 2001 defined sepsis as the presence of the systemic inflammatory response syndrome (SIRS) in addition to the suspected presence of an infection. The 2016 guidelines introduced the Sequential Organ Failure Assessment (SOFA) score as part of the diagnostic criteria of sepsis in the intensive care unit. According to the 2016 definition Sepsis is defined as an increase in SOFA score of greater than or equal to 2. Given the complexity of the SOFA score, there has been concern that adherence to SOFA could result in a delay in recognition of sepsis. Our research contrasts these two sepsis definitions in an ICU population. **Methods** We performed a retrospective chart review of 577 patients from 2012–2016 at the University of Illinois at Chicago Hospital with an admitting diagnosis of sepsis, severe sepsis, septicemia, or septic shock. We obtained baseline data, including patient demographics and laboratory values. Vital signs and laboratory data over the first twenty-four hours of admission were assessed. The time at which each patient met the definitions of sepsis, severe sepsis or septic shock was recorded based on SIRS criteria and SOFA score. Additional data points included length of stay, length of ICU stay, and time to first antibiotic. **Results** Our data set included 577 patients with sepsis, severe sepsis, and septic shock. The average age was 62.4 years. Fifty percent of patients were African-American or Hispanic. The most common source of infection was pneumonia. On average, SIRS criteria for a diagnosis of sepsis were met 51.8 minutes earlier than Sepsis-3 criteria. The average time to antimicrobial administration was 237 minutes after diagnosis by SIRS criteria and 180 minutes after diagnosis by Sepsis-3. Average SOFA score was 9.7. Average length of stay was 7.1 days, with an average of 3.4 days in the ICU.

Conclusion There was minimal delay in diagnosis based on the SIRS versus Sepsis-3 criteria for definitions of sepsis. The difference between time in meeting SIRS and SOFA criteria is most likely explained by the increased number of lab values required to calculate SOFA score. This delay is an important consideration in future research.

A-50 CONCENTRIC RV REMODELING REPRESENTS AN ADAPTIVE PHENOTYPE ONLY IN PATIENTS WITH ADVANCED PULMONARY ARTERIAL HYPERTENSION

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Background Concentric right ventricular (RV) remodeling is thought an adaptive response in patients with pulmonary arterial hypertension (PAH). We sought to correlate markers of RV remodeling to afterload and performance in patients before and after treatment with parenteral treprostinil.

Methods We prospectively analyzed 25 treatment-naïve patients with advanced PAH before and after 3 months of monotherapy with parenteral treprostinil. Patients were divided into three subgroups based on two criteria including post-treatment cardiac MRI derived RV mass/volume (M/V) values above and below the median (≤ 0.4 defined as eccentric and > 0.4 as concentric hypertrophy), as well as afterload (Ea, pulmonary artery elastance): Group 1 (M/V ≤ 0.4 , Ea ≤ 0.8), Group 2 (M/V > 0.4 , Ea > 0.8) and Group 3 (M/V ≤ 0.4 , Ea > 0.8). The latter Ea was based on its correlation from previously published mortality data. Single-beat method RV-PA coupling was based upon the ratio of contractility (Ees, end-systolic elastance) to Ea (Ees/Ea). MRI-derived RV ejection fraction (RVEF) was used as a surrogate for performance.

Results At baseline, Group 1 had lower pulmonary vascular resistance (PVR) than Groups 2 and 3 (see Table). RVEF was not different while Ees/Ea was preserved across all groups. After treatment, all groups demonstrated similar improvements in PVR and RVEF. While RVEF remained similar across all groups, Ees/Ea was highest in Group 1 and lowest in Group 3 (see Table). M/V slightly increased in Group 2 relative to Group 3 owing to increasing RV mass. After 22 ± 14.3 months follow-up, there were 1/11 (9%), 1/7 (14%) and 3/7 (43%) deaths in groups 1, 2, and 3, respectively.

Conclusions Compared to eccentric hypertrophy, concentric hypertrophy (high M/V) may represent a favorable adaptation to increased afterload based on potential association with improved survival. Eccentric hypertrophy (low M/V) may represent poor adaptation with reduced RV-PA coupling when associated with increased afterload as compared to decreased afterload.

A-51 USP11 STABILIZES E2 TRANSCRIPTIONAL FACTOR 1 TO DRIVE PEG10 GENE EXPRESSION AND ACTIVATE LUNG EPITHELIAL CELLS

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Background: Lung cell proliferation and migration are necessary for re-epithelialization and repair after injury. The paternally expressed imprinted gene 10 (PEG10) protein promotes cell migration and proliferation, and *Peg10* transcription is activated by E2F transcriptional factor 1 (E2F1). Here, we describe a pathway in which E2F1 is stabilized by USP11, thus promoting PEG10 expression and lung epithelial proliferation and migration. **Methods and Results:** Lung epithelial cells (A549) were used to examine E2F1 stability and lung epithelial proliferation and migration. We found that knock-down or inactivation of a deubiquitinating enzyme, USP11 mitigated *Peg10* gene expression and protein levels in A549 cells. *Peg10* gene regulation has been known by E2F1. We

confirmed the conclusion by showing that knock-down of E2F1 significantly reduced Peg10 mRNA and protein levels. Interestingly, we found that knock-down of USP11 limited both E2F1 and PEG10 protein without altering E2F1 mRNA levels, suggesting that USP11 may regulate E2F1 stability, therefore influencing *Peg10* transcription. Further, we examined the effect of USP11 on E2F1 ubiquitination and stability. Knock-down of USP11 increased poly-ubiquitination of E2F1 and reduced E2F1 stability, while over-expression of USP11 diminished E2F1 ubiquitination and promoted its stability. Further, we found that the effect of USP11 on E2F1 ubiquitination is due to its localization in nuclei, as a nuclear translocation signaling (NLS) deletion mutant of USP11 (USP11 Δ NLS) failed to deubiquitinate and stabilize E2F1. To investigate whether USP11 affects lung epithelial cell functions through regulation of E2F1 stability and PEG10 expression, cell proliferation and migration were measured by electric cell-substrate impedance sensing (ECIS) system and cell scratch assay. Down-regulation of USP11 significantly decreased A549 proliferation and migration, while these effects were restored by over-expression of E2F1. Conclusion: USP11 targets and stabilizes E2F1 by deubiquitinating E2F1, thus increasing *Peg10* mRNA and protein levels and promoting lung epithelial cell proliferation and migration. The effect of USP11 is dependent on its nuclear localization. This study reveals a role of USP11 in lung epithelial repair and remodeling after injury.

A-52 MITOCHONDRIAL DNA DAMAGE IS AN IMPORTANT REGULATOR OF LUNG FIBROSIS IN MICE AND IN PATIENTS WITH IPF

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Rationale Alveolar epithelial cell (AEC) injury and repair are crucial determinants of the fibrogenic potential of asbestos and other noxious agents. We have previously shown that AEC mitochondrial reactive oxygen species (ROS) mediate asbestos-induced AEC mitochondrial DNA (mtDNA) damage and apoptosis by a mitochondria-regulated (intrinsic) death pathway. We showed that overexpression of mitochondrial human 8-oxoguanine DNA glycosylase (mtOGG1) preserves mtDNA and prevents asbestos-induced AEC mtDNA damage in vitro whereas mice deficient in *Ogg1* have increased AEC mtDNA damage, apoptosis and lung fibrosis (Kim *et al.* JBC 2014, Cheresh *et al.* AJRCMB 2015). We reasoned that transgenic mice with enforced expression of mitochondrial OGG1 (mt-Ogg1-EE) would have decreased asbestos-induced mtDNA damage and lung fibrosis compared to wild type (WT). Further, we hypothesized that patients with IPF have increased lung cell mtDNA damage as compared to normal controls.

Objectives To determine whether mtOGG1 is protective against lung fibrosis by assessing whether mt-Ogg1-EE mice

are protected against asbestos-induced lung fibrosis and whether mtDNA levels are increased in the lungs of patients with IPF as compared to controls.

Methods Crocidolite asbestos (100 or 200 μ g/100 μ l) or TiO₂ (200 μ g/100 μ l, negative control) was instilled intratracheally in male 8–10 week old WT (C57BL/6J) or mt-Ogg1-EE mice. The lungs were harvested at 21 days. Lung fibrosis was quantified via Sircol assay (lung collagen levels) or fibrosis score (trichrome staining). DNA was extracted from formalin-fixed, paraffin-embedded lungs from mice and IPF and normal human lung biopsies. Mitochondrial DNA damage was assessed by a quantitative PCR-based assay.

Results Mt-Ogg1-EE mice, as compared to WT, were protected against crocidolite asbestos-induced pulmonary fibrosis as measured by Sircol lung collagen and fibrosis scoring. This was accompanied by reduced asbestos-induced lung cell mtDNA damage in Mt-Ogg1-EE mice as compared to controls. Furthermore, we show that mtDNA damage is increased in human IPF lung biopsies relative to those from normal lungs.

Conclusions We demonstrate that Mt-Ogg1-EE mice are protected against asbestos-induced mtDNA damage and lung fibrosis and that the lungs of IPF patients have increased mtDNA damage. These results extend our previous findings implicating an important role for OGG1 in the preservation of AEC mtDNA integrity following oxidative stress necessary for preventing lung fibrosis. We reason that mtDNA damage may be a crucial regulator of human lung fibrosis. Strategies designed to limit AEC mtDNA damage arising from excess mitochondrial ROS may be novel therapeutic approaches for preventing lung fibrosis.

B-42 IMATINIB BLOCKS AUTOPHAGIC FLUX IN LUNG ENDOTHELIUM

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Rationale Endothelial cell (EC) dysfunction underlies the pathogenesis of acute lung injury (ALI) caused by inflammatory stimuli such as bacteria and mechanical ventilation (ventilator-induced lung injury or VILI). Recent work by our group has demonstrated that imatinib, a pharmaceutical multi-targeted tyrosine kinase inhibitor used in the treatment of multiple cancers, exhibits pulmonary barrier protective effects in LPS-injured mice and lung EC; however, it exacerbates murine VILI and EC dysfunction in 18% cyclic stretch-challenged EC (18% CS, *in vitro* model of VILI). The mechanisms by which imatinib mediates these effects and regulates lung EC function remain largely unknown. Previous studies in cancer cells have demonstrated that imatinib induces autophagy, a self-degradative process involved in cellular homeostasis and inflammation. The aim of this study is to explore the effects of imatinib in the regulation of autophagy in lung EC under baseline conditions and after mechanical stimulation.

Methods Human pulmonary artery endothelial cells (EC) were treated with imatinib (Im, 10–40 μ M) for 1 or 24 h. In separate experiments, Im-treated cells were subjected to 18% CS (Flexcell strain unit) for 24 h. Cell lysates were analyzed for LC3B-II and p62 (autophagosome markers) by immunoblotting (IB). Apoptosis and cell death were assessed by IB (Cell Signaling apoptosis kit) and a cell viability assay (MTT). Autophagosomes were visualized by immunofluorescence (IF) after staining with LC3B. To explore mechanistically the effects of Im in autophagy, EC were additionally treated with U0126 (MEK-ERK pathway inhibitor) and GNF2 or GNF5 (specific c-Abl inhibitors). For *in vivo* studies, C57BL/6J mice were challenged with Im (75 mg/kg) or vehicle (water) and then exposed to VILI (30 ml/kg tidal volume) for 4 h. LC3B-II expression levels were measured in lung homogenates by IB.

Results A dose-dependent increase in LC3B-II and p62 levels is observed in lung EC after imatinib treatment (24 h), indicative of autophagosome accumulation. Upon treatment with imatinib, no induction of apoptosis or cell death is observed. An increase in LC3B-II occurs in 18% CS-EC, and this response is significantly enhanced (by ~50%) in Im & 18% CS-treated cells. IF confirms the presence of autophagosomes in Im-, 18% CS-, and Im & 18% CS -treated EC. *In vivo*, similar to the *in vitro* observations, Im exerts additive effects on VILI-induced LC3B-II levels. Mechanistically, imatinib induces ERK1/2 activation in a dose- and time-dependent manner, while inhibition of this pathway by U0126, reduces Im-induced LC3B-II. Specific c-Abl inhibitors (GNF-2 or GNF-5) do not cause LC3B-II induction, suggesting that the observed effects are mediated through other Im-targeted kinases.

Conclusions Our data demonstrate that imatinib blocks autophagic flux in lung EC, an effect that is dramatically enhanced in mechanically stretched cells. Autophagy dysregulation and autophagosome accumulation may represent a novel mechanism by which imatinib induces lung EC dysfunction in VILI.

B-43 PDLIM5 REGULATES HYPOXIA-INDUCED METABOLIC SHIFT AND PULMONARY HYPERTENSION VIA ENO1

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Rationale PDLIM5 is a member of PDZ and LIM domain protein family. We have shown that PDLIM5 levels are elevated in pulmonary artery smooth muscle cells (PASMC) isolated from patients with pulmonary arterial hypertension (PAH). PDLIM5 is also upregulated in mouse lungs and PASMC of hypoxia-induced pulmonary hypertension (PH). In addition, hypoxia induces PDLIM5 expression. Recent studies suggest that metabolic reprogramming plays a role in the pathophysiology of PAH and hypoxia is known to induce glycolysis. However, it remains unknown whether PDLIM5 contributes to PH via regulation of the metabolic reprogramming in PASMC.

Methods We have overexpressed PDLIM5 in mice and generated smooth muscle cell (SMC)-specific PDLIM5 knock-out mice and exposed them to normoxia and hypoxia to

investigate its effects on hypoxia-induced PH *in vivo*. We silenced PDLIM5 in human PASMC with small hairpin RNA (shRNA), exposed them to hypoxia (1% O₂) or normoxia for 24 hours, determined the global metabolite profiles by mass spectrometry, and identified the metabolites that is controlled by PDLIM5. We measured the mRNA and protein levels of the key enzymes that are responsible for the abundance of the identified metabolites. Co-Immunoprecipitation (Co-IP) was also performed to determine the association between PDLIM5 and these enzymes. We also utilized siRNAs or ENOblock to silence or inhibit Enolase, followed by the BrdU assay, LDH assay, cell viability assay, and the measurement of SMC contractile proteins.

Results We found that overexpression of PDLIM5 prevented hypoxia-induced PH, whereas deletion of PDLIM5 in SMC enhanced hypoxia-induced PH *in vivo*. As expected, hypoxia induced the metabolites involved in oxidative phosphorylation (OXPHOS) and aerobic glycolysis in PASMC. Silencing of PDLIM5 attenuated the hypoxia-mediated induction of lactate, fumaric acid, and succinate; however, enhanced production of 2/3-phosphoglyceric acid (2/3-PG). We found that silencing of PDLIM5 had a little effects on mRNA levels of LDHA, SDH, ENO2/3, but induced ENO1 mRNA levels. Interestingly, silencing of PDLIM5 inhibited hypoxia-mediated induction of ENO1 protein, the enzyme converts 3-PG to phosphoenolpyruvic acid (PEP). Silencing of ENO1 and ENO-block inhibited PASMC proliferation and induced expression of SMC contractile proteins in both normoxic and hypoxic conditions, suggesting the participation of ENO1 in PH. Moreover, we found that ENO1 directly interacted with PDLIM5.

Conclusions Our results suggest that PDLIM5 may contribute to PH by regulating ENO1 to alter metabolism during hypoxia and PH. How PDLIM5 regulates ENO1 and the subsequent metabolic change and PH warrants further investigation. Support: NIH HL123804.

B-44 CLASSIFICATION OF HUMAN AIRWAY MACROPHAGE AND DENDRITIC CELL SUBSETS

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Rationale The respiratory system is a complex network of many cell types, including subsets of macrophages and dendritic cells that work together to maintain steady-state respiration. Due to limitations in acquiring cells from healthy human lungs, these subsets remain poorly characterized transcriptionally and phenotypically.

Methods We set out to systematically identify these subsets in human airways by developing a schema of isolating large numbers of cells by whole lung bronchoalveolar lavage.

Results Six subsets of phagocytic antigen presenting cells were consistently observed from airway lavage. These cell subsets were confirmed as airway-resident by comparison to lavage and blood cell types from healthy volunteers. Aside from alveolar macrophages, subsets of Langerin+, CD14+ BDCA1+, CD14+ BDCA1-, CD14- BDCA1+, and CD14- BDCA1- cells were identified. These subsets varied in their ability to internalize *Escherichia coli*, *Staphylococcus aureus*, and *Bacillus anthracis* particles. All subsets were more efficient at internalizing *S. aureus* and *B. anthracis* compared to *E. coli*. Alveolar macrophages and CD14+ BDCA1- cells were overall more efficient at particle internalization compared to the four other populations. Subsets could be further separated into two groups based on their inherent capacities to upregulate surface CD83, CD86, and CCR7 expression levels. Whole genome transcriptional profiling revealed a clade of “true dendritic cells” consisting of Langerin+, CD14+ BDCA1+, and CD14- BDCA1+ cells. The dendritic cell clade was distinct from a macrophage/monocyte clade, as supported by higher mRNA expression levels of several dendritic cell-associated genes, including CD1, FLT3, CX3CR1, and CCR6. Each clade, and each member of both clades, were discernable by specific upregulated genes, which can serve as markers for future studies in healthy and diseased states. **Conclusions** Overall, our studies provide a functional and transcriptomic reference of six steady-state macrophage and dendritic cell subsets found in human airways. This work builds a schema for future investigations into lower respiratory tract infections, chronic lung diseases, and targeted-cell vaccines.

B-45 ONCOGENIC ROLE FOR LYSOCARDIOLIPIN ACYLTRANSFERASE (LYCAT) IN NON-SMALL CELL LUNG CANCER: REGULATION OF AUTOPHAGY AND MITOCHONDRIAL FISSION

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Non-small cell lung cancer (NSCLC) accounts for ~85% of all lung cancers with a 5-year survival rate of approximately ~16%. Lysocardiolipin acyltransferase (LYCAT) is a cardiolipin remodeling enzyme that regulates the 18:2 linoleic acid pattern of mammalian mitochondrial cardiolipin, and plays a crucial role in maintaining normal mitochondrial function and vascular development. Our previous investigation indicated that LYCAT expression is dramatically increased in human NSCLC tissues and cells, as well as in lung tissues from mouse model of lung cancer compared to control samples. Tail vein injection of NSCLC cell lines with stable knockdown of LYCAT gene suppressed lung tumors compared to injection of wild type cells in athymic mice. Microarray analysis indicated that knockdown LYCAT significantly regulated p53 signaling, senescence and autophagy pathways via regulation of CDKN1A/p21 expression. In H2122 cells, knockdown LYCAT expression

augmented the autophagosome formation and the expression of LC3II and CDKN1A/p21; however, in control Beas2B cells, overexpression of LYCAT inhibited the autophagosome formation and the expression of LC3II and CDKN1A/p21. Further, knockdown LYCAT in NSCLC H2122 cell line attenuated mitochondrial fragmentation via inhibition of Drp1 expression and increasing MFN2 expression; while in Beas2B cells, overexpression of LYCAT enhanced Drp1 expression. In vitro, knockdown LYCAT inhibited H2122 and H23 cell proliferation, migration, invasion and clonogenicity via regulation of mitochondrial integrity and membrane potential. These results suggest that LYCAT has an oncogenic role in lung cancer by regulating autophagy and mitochondrial dynamics, and development of targeted therapies to reduce LYCAT expression or activity in NSCLC should be beneficial. This work in part was supported by NIH HL98050 to VN.

B-46 SENSITIVITY AND SPECIFICITY OF ESTABLISHED AND NEW D-DIMER CUTOFFS IN THE EMERGENCY ROOM FOR MANDATING IMAGING FOR DIAGNOSIS OF PULMONARY EMBOLI

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Background In the emergency room (ER), nationally used D-dimer cutoffs are used to initiate imaging which effectively detects pulmonary embolism (PE), but incurs a large financial and medical burden on patients and hospitals.

Specific Aim In patients evaluated in the Jewish Hospital (JH) ER for PE, we assessed sensitivity and specificity for the D-dimer cutoff most appropriate for ordering CTPA or VQ scans to diagnose PE.

Methods Retrospective chart review provided 367 patients (289 patients with D-dimer results obtained in the ER, and 78 patients admitted from 2010–2014 with a diagnosis of PE). There was a total of 81 patients from both data sets with PE, 29 of whom had D-dimer measured. Duplicate patients, those not evaluated for PE, those without imaging, and those without D-dimer were excluded (n=276), leaving 91 patients (62 without PE and 29 with PE) included in the study. Receiver-operating characteristic curves (ROC) were used to identify D-dimer cutoffs which provided optimal sensitivity and specificity for the diagnosis of PE. Also, both the JH ER D-dimer cutoff of 229 ng/mL and the ACP cutoff of 500 ng/mL if age ≤50 or 10× age for age >50 were assessed.

Results Of the 81 patients with a PE, 29 had a D-dimer prior to their CTPA or VQ scan while 52 were directly imaged based on a high pre-test probability as established by the Wells criteria. In our cohort, the lowest D-dimer associated with a PE was 365 ng/mL. The D-dimer cutoff of 229 ng/mL used in the JH ER had 100% sensitivity, correctly identifying all 29 patients shown to have PE, while at the same time, it only had 23% specificity. The ACP cutoff had 83% sensitivity and 76% specificity. In our cohort of 91 patients, using a ROC curve for D-dimer cutoffs for the diagnosis of PE, plotting sensitivity against 1-specificity, the

area under the curve was .846. From the ROC curve, for a D-dimer cutoff ≥ 505 ng/mL, sensitivity was 86% and specificity 69%, for a cutoff ≥ 442 ng/mL, sensitivity was 93.5% and specificity 56%, for ≥ 417 ng/mL, sensitivity was 97% and specificity 55%, and for ≥ 365 ng/mL, sensitivity was 100% and specificity 52%.

Conclusions If the goal is to emphasize the highest sensitivity, missing as few patients with PE as possible, then the low JH D-dimer cutoff of ≥ 229 ng/mL is preferable despite resulting in many more CTPA and VQ scans performed. However, a higher D-dimer cutoff, ≥ 365 ng/mL, would achieve the same sensitivity (100%) while increasing specificity from 23% to 52%, thus reducing the frequency of imaging substantially. Using the ACP cutoff provided a more balanced sensitivity of 83% and specificity of 76%.

B-47 UNCOMMON CAUSE OF RESPIRATORY FAILURE IN OKLAHOMA

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Introduction Foodborne botulism is a rare paralytic disease caused by neurotoxins synthesized by *Clostridium botulinum*, a group of spore-forming anaerobic bacteria. The disease is rare in the United States with a mean annual incidence of 0.0068 cases per 100,000 persons 1. The presentation can be variable and sometimes pose a diagnostic challenge. The case below highlights the importance of considering botulism in patients with acute ptosis and respiratory muscle weakness. **Description:** An 83-year-old woman was brought to the emergency department (ED) after a family member found her crawling around on the floor. She was last seen normal 24–36 hours before presentation. In the ED, she was noted to have dysarthria but normal vital signs and level of consciousness. Computed tomography (CT) of the brain showed no acute process. The patient's mental status worsened 24–48 hours after admission secondary to acute hypercapnic respiratory failure that required invasive mechanical ventilation. As hypercapnia resolved, she became responsive and able to follow commands. Physical exam revealed bilateral ptosis, subtle proximal weakness and hyporeflexia in the upper extremities. The pupils were equal and reactive, without ophthalmoparesis, facial weakness or sensory deficits. No attached ticks found. Urine drug screen was negative. Brain magnetic resonance imaging and analysis of the cerebral spinal fluid were normal. Acetylcholine receptor, muscle specific receptor tyrosine kinase, and voltage-gated calcium channel antibodies were all negative. Family members later reported that the patient frequently ate canned food that was many years old and leftovers that were weeks old. Nerve conduction studies showed 84% electroincremental response, a finding specific for presynaptic neuromuscular junction disorder. Botulism was considered and heptavalent

antitoxin was administered. Botulism was later confirmed by a positive stool culture for *Clostridium botulinum* type A.

Discussion Our patient presented mainly with acute ptosis and respiratory muscle weakness, with only subtle proximal weakness and hyporeflexia in the upper extremities almost to the point of being normal. There was no evidence of ophthalmoparesis, pupillary findings, autonomic dysfunction, or noticeable proximal muscle weakness which could be expected in a typical case of botulism. Although cranial nerve involvement was minimal, it was associated with diaphragmatic weakness leading to respiratory failure. Botulism is rare but serious and potentially deadly disease. The presentation can be variable and early recognition is crucial as the decision for the administration of antitoxin therapy is based on clinical grounds. Botulism should be considered even in the absence of typical signs and symptoms.

B-48 ANTI-INFLAMMATORY EFFECTS OF DIPEPTIDYL PEPTIDASE-4 INHIBITION ON HUMAN LUNG MICROVASCULAR ENDOTHELIAL CELLS

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Introduction: Severe inflammation in the lung is one of the primary causes of the acute respiratory distress syndrome (ARDS). Pulmonary vascular endothelial cells function as one of the pro-inflammatory sources in ARDS. Dipeptidyl peptidase-4 (DPP4) inhibitors are widely used for treatment of diabetes mellitus, and have been shown to have not only blood glucose-lowering effects but also anti-inflammatory effects on several types of cells and tissues. However, the potential effects of DPP4 inhibitors on pulmonary vascular endothelial cells remain unclear. Therefore, we examined the effects of the DPP4 inhibitor widely used diabetic medication, sitagliptin, on human lung microvascular endothelial cells (HLMVEC) with the pro-inflammatory stimulus LPS. **Methods:** We cultured HLMVEC with sitagliptin (10–1000 μ M) for an hour, then for another 4–18 hours with LPS (1–2 μ g/ml) and investigated the conditioned medium and HLMVEC for inflammation markers. **Results:** ELISA analysis of the conditioned medium revealed that the concentrations of TNF α , IL-6, and IL-8 were increased after LPS challenge, while sitagliptin decreased these cytokine levels in proportion to its concentration, indicating anti-inflammatory effects of sitagliptin on HLMVEC. Quantitative PCR for the HLMVEC showed the mRNA expression levels of *TNF*, *IL1B*, *IL6*, and *CXCL8* increased after LPS challenge; however, they remained unchanged after sitagliptin treatment regardless of the concentration. In addition, we examined the effect of sitagliptin on HLMVEC monolayer permeability by TER measurement, and the effect of sitagliptin on HLMVEC cell toxicity with WST-8 assay to examine cell proliferation. TER assay revealed the permeability with 10 and 100 μ M Sitagliptin were similar to that with control, but TER was substantially decreased by 1000 μ M sitagliptin. WST-8 assay

demonstrated that LPS challenge promoted proliferation of HLMVEC, while sitagliptin suppressed it in proportion to its concentration. The results of the TER and WST-8 assays imply that 100 μ M or less of sitagliptin has no apparent influence on permeability, and are non-cytotoxic. Conclusion: These results suggest that sitagliptin has novel anti-inflammatory effects on HLMVEC through mechanisms other than control of gene expression level; however the detailed mechanism remains unknown. Therefore, appropriate treatment with sitagliptin or other DPP4 inhibitors might improve the pathophysiology of ARDS via anti-inflammatory effects without worsening permeability and toxicity on HLMVEC. These results indicate that DPP4 inhibition has potential as ARDS therapy.

B-49 SPHINGOSINE KINASE1 AND S1P TRANSPORTER, SPNS2, SIGNALING AXIS REGULATE THROMBIN-INDUCED ENDOTHELIAL BARRIER RECOVERY: ROLE OF PHOSPHOLIPASE D2

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Acute lung injury (ALI) and its severe form acute respiratory distress syndrome (ARDS) are characterized by hyper-permeability due to opening of endothelial cell junctions. Thrombin, an inflammatory mediator, disrupts endothelial adherens junctions (AJs) followed by resealing of the AJs and recovery of the barrier. Molecular mechanisms of thrombin-mediated barrier disruption have been well studied; however, regulation of resealing of the AJs and barrier restoration are yet to be fully defined. The aim of the present study was to delineate the role of phospholipase D (PLD) 2 in regulating sphingosine kinase (SphK) and sphingosine-1-phosphate (S1P) signaling axis and endothelial barrier recovery after thrombin treatment. Thrombin induced a robust increase in human lung microvascular endothelial cell (HLMVEC) permeability within 30 min, which was accompanied by a slow barrier recovery. Thrombin activated PLD2 and SphK1 in HLMVECs, and expression of catalytically inactive PLD2 mutant prevented co-localization of phospho Ser225-SphK1 with actin/cortactin in lamellipodia during AJ re-assembly phase 30 min post-thrombin. Inhibition of PLD2 or SphK1 activity or knockdown of Spns2, the S1P transporter prolonged VE-cadherin tyrosine phosphorylation at Y658 and partially prevented VE-cadherin redistribution to AJs post-thrombin challenge. Thrombin stimulated phosphorylation of Spns2 at serine/threonine/tyrosine residues was dependent on PLD2 activation by thrombin. These results support the importance of PLD2/SphK1/Spns2 signaling axis in promoting recruitment of VE-cadherin at AJs during the resealing and recovery phase after thrombin mediated endothelial barrier disruption. This work was supported by NIH grant P01 HL060678 Project 4 to VN.

B-50 TRAF2 STABILITY IS REGULATED BY DEUBIQUITINATING ENZYME USP48 IN LUNG EPITHELIAL CELLS

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Background Tumor necrosis factor receptor (TNFR)-associated factor 2 (TRAF2) is an adaptor protein in the TNF α signaling pathway and plays an essential role in immune responses. TRAF2 ubiquitination and deubiquitination have been well studied in regarding with regulation of its function, however, very little research has been performed to examine whether the stability of TRAF2 is influenced by deubiquitinating enzymes. Here we identify that USP48 deubiquitinates and stabilizes TRAF2.

Methods and Results Lung epithelial cells Beas2B were used to examine TRAF2 stability. Cycloheximide and TNF α combination treatment reduce TRAF2 stability, while the effect was attenuated by over-expression of the deubiquitinating enzyme, USP48. To further investigate the role of USP48 in regulation of TRAF2 stability, Beas2B cells were transfected with USP48 shRNA. USP48 shRNA transfection significantly reduced USP48 expression, as well as TRAF2 protein levels, without altering TRAF2 mRNA levels and TRAF1, TRAF3, TRAF4, TRAF5, and TRAF6 expression. These data suggests that USP48 specifically regulates TRAF2 stability. Further, *in vivo* ubiquitination assay were performed to examine the effect of USP48 on TRAF2 ubiquitination. Over-expression of TRAF2 eliminated TRAF2 ubiquitination, while knock-down of USP48 increased K48 linked poly-ubiquitination of TRAF2. Further, co-immunostaining showed that TRAF2 and USP48 were co-localized in the cytoplasm and co-immunoprecipitation showed that USP48 was associated with TRAF2. Next, we examined the effect of USP48 on TNF α -induced signaling pathways. Interestingly, we found that knock-down of USP48 significantly attenuated TNF α -induced phosphorylation of JNK and c-Jun, but not of p38 and I- κ B.

Conclusion USP48 targets and deubiquitinates TRAF2, therefore stabilizing TRAF2 and regulating TNF α -induced activation of JNK in lung epithelial cells. This is first study to reveal that TRAF2 stability is regulated by a deubiquitinating enzyme and that USP48 plays a role in TNF α signaling.

B-51 INHIBITION OF INTEGRIN β 4 PHOSPHORYLATION ATTENUATES LUNG ENDOTHELIAL CELL INFLAMMATORY RESPONSES

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We previously reported lung endothelial cell (EC) inflammation attenuated by simvastatin, an HMG CoA-reductase

inhibitor, is mediated by decreased integrin $\beta 4$ (ITGB4) phosphorylation. As statin drugs are recognized to have pleiotropic properties and to date have not proven to have significant clinical efficacy in lung vascular inflammatory syndromes including acute lung injury (ALI), we hypothesized that strategies aimed precisely at inhibiting ITGB4 phosphorylation may prove to be more effective in this context. **Methods** Initially, to confirm EC inflammatory responses are associated with ITGB4 phosphorylation, human pulmonary artery EC were pretreated with an ITGB4 blocking antibody (10 $\mu\text{g/ml}$) or control (IgG) 1 hr before LPS (500 ng/ml, 1 h). Cell lysates were used for Western blotting with an antibody specific for ITGB4 or p-Tyr. Subsequently, we utilized ABO (200 μM , 1 h), a small molecule that inhibits ITGB4 phosphorylation (Y1494) via binding to annexin A7, to assess the role of ITGB4 on EC cytokine expression and EC monolayer transwell permeability induced by either LPS or MRSA (2 $\times 10^8$ CFU, 1 h). Separate studies investigated the effects of LPS and MRSA on ITGB4 phosphorylation alone and after ABO. Finally, to examine effects of ABO on downstream ITGB4 signaling, human pulmonary artery EC were pretreated with ABO or vehicle prior to MRSA and cell lysates were then subjected to Western blotting for total and phosphorylated (Y397) FAK.

Results LPS treatment was associated with increased EC ITGB4 phosphorylation that was further augmented by pretreatment with an ITGB4 blocking antibody. Conversely, pretreatment with ABO was associated with both decreased cytokine expression (IL-6, IL-8) and decreased EC monolayer transwell permeability induced by LPS or MRSA, as well as decreased ITGB4 phosphorylation induced by either LPS or MRSA. Finally, increased FAK phosphorylation induced by MRSA was also attenuated by inhibition of ITGB4 phosphorylation with ABO.

Conclusions These findings confirm EC ITGB4 phosphorylation is induced by inflammatory agonists including LPS and MRSA. Moreover, inhibition of ITGB4 phosphorylation is associated with an attenuation of agonist-induced EC inflammatory responses and downstream ITGB4 signaling. Our results implicate ITGB4 as a potential novel therapeutic target for patients with diseases characterized by increased lung vascular permeability and inflammation including ALI.

B-52 **EPIGENETIC REGULATION BY FTY720 S-PHOSPHONATE ATTENUATES MRSA-INDUCED EPIGENETIC CHANGES AND BARRIER DISRUPTION IN ENDOTHELIUM**

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Rationale A significant and sustained increase in vascular permeability is a hallmark of acute inflammatory diseases such as acute lung injury (ALI), but effective therapies for

preserving or reconstituting the vascular barrier are lacking. Prior work has demonstrated that FTY720 S-phosphonate (Tysiponate/Tys), an analog of sphingosine 1-phosphate (S1P) and FTY720, has more potent pulmonary barrier protective effects than these agents in vitro and in the LPS- and bleomycin-induced models of mouse ALI. Moreover, Tys preserves expression of the barrier promoting S1P1 receptor (S1PR1), whereas S1P and FTY720 induce its ubiquitination and degradation. In this report, we focus on the epigenetic regulation of Tys in endothelial barrier disruption caused by methicillin-resistant Staph aureus bacteria (MRSA), a more clinically relevant stimulus.

Results Heat-killed MRSA (HK-MRSA) induced significant barrier disruption in both human pulmonary artery endothelial cells (HPAEC) and lung microvascular endothelial cells (HLMEC), while Tys showed significant barrier protective effects in both cell types. SA product alpha hemolysin also induced significant barrier disruption in EC in a dose-dependent manner, which can be significantly attenuated by Tys. Tys significantly inhibited HK-MRSA induced methylation of histone H3 lysine 4 in ECs. Although HK-MRSA alone didn't affect acetylation of histone H3 lysine 27 in ECs, treatment with HK-MRSA and Tys significantly increased acetylation of histone H3 lysine 27. Unlike p-FTY and HK-MRSA which markedly inhibited HDAC activity, Tys treatment had no significant effect on HDAC activity. Furthermore, HK-MRSA increased the expression of S1PR1 mRNA and protein, which was partially inhibited by p-FTY but not Tys. Tys and S1P also significantly increased acetylation of the actin-binding protein cortactin, which is an important EC barrier regulator. In MRSA-induced acute lung injury using a mouse model, Tys showed significant pulmonary barrier protective effects and inhibited methylation of histone H3 lysine 9 compared with MRSA treatment alone.

Conclusion Tys has potent pulmonary barrier protective effects in MRSA-induced EC barrier disruptions and acute lung injury in mice. The epigenetic regulation of Tys may play an important role in this barrier protection. These results provide additional mechanistic insights into the barrier-regulatory effects of this potential ALI therapy.

C-39 **UNEXPLAINED HYPOKALEMIA ASSOCIATED WITH ACUTE OVERDOSE OF BUPROPION, A SMOKING CESSATION PHARMACOTHERAPY**

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Background Smoking remains the leading cause of preventable death in the United States. Accordingly, there is increasing awareness to quit smoking among the public. Bupropion, a dopamine reuptake inhibitor in the brain, is a frequently-prescribed inexpensive smoking cessation medication. Unfortunately, due to its euphoric effects at high doses, it has also become a drug of abuse via nasal insufflation and intravenous injection of crushed tablets.

Bupropion has a narrow therapeutic margin with high risk of seizures and cardiac arrest, particularly in patients presenting with parenteral overdose. Unlike oral administration, parenteral administration of the drug bypasses first-pass metabolism of bupropion in the liver, thereby achieving toxic concentrations of the parent compound that can provoke cardiotoxicity if left untreated. Although the mechanism leading to cardiotoxicity is uncertain, it has been postulated that bupropion-induced inhibition of potassium channels in the heart may be involved even though hypokalemia is not a commonly reported adverse event associated with acute bupropion overdose.

Purpose To determine whether significant, unexplained hypokalemia is observed in patients presenting with acute bupropion overdose.

Methods A PubMed, Google and Google Scholar search was performed for publications in English using the key words overdose, bupropion, wellbutrin, hypokalemia, potassium, cardiac arrest, cardiogenic shock and resuscitation. Publications thus retrieved were reviewed for pertinent clinical and laboratory data related to acute bupropion overdose, cardiogenic shock, cardiac arrest and hypokalemia (serum potassium concentration, <3.5 mmol/L).

Results Eleven case reports of unexplained hypokalemia associated with acute bupropion overdose were retrieved from the literature and reviewed. Adequate clinical and laboratory data, including serum potassium concentration at presentation, were available in 7 cases. This group comprised of 4 females and 3 males 16.7 ± 7.3 years of age (mean \pm SD; range, 3–26 years). Serum potassium concentration at presentation to the emergency department was 2.8 ± 0.4 mmol/L (mean \pm SD; range, 2.4–3.3). Severe hypokalemia (<2.5 mmol/L) was reported in one patient. Four patients experienced cardiac arrest and were successfully resuscitated. One patient succumbed despite rigorous resuscitation and supportive care.

Conclusions Acute bupropion overdose is associated with appreciable, unexplained hypokalemia that can be life-threatening if untreated. Accordingly, serum potassium concentration should be determined at presentation and monitored closely in these patients. Larger studies should be done to determine the prevalence of hypokalemia in patients with acute bupropion overdose.

C-40 BREATHKING BRASSIERE – A MYSTERIOUS CASE OF DYSPNEA WITH A SURPRISINGLY SIMPLE EXPLANATION

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Dyspnea of unknown etiology can at times lead to an extensive and costly evaluation that still fails to illuminate the underlying cause. Here, we present a case of a 53 year old woman with obstructive sleep apnea, cervical spine degenerative disc disease, migraine headaches and a history

of a cerebrovascular accident who reported having dyspnea for the past few years. She first presented in our clinic in 2014 reporting dyspnea at rest. Exacerbating factors included minimal exertion such as performing household chores and running errands, talking loudly and forcefully, wearing tight clothes, standing still, and after eating. Her dyspnea was alleviated when resting after activity and stretching. The dyspnea was not associated with fever, cough, chest pain, weight loss, or night sweats. The patient's family history included sarcoidosis in her mother, and she did not have a history of cigarette use or other substance abuse. Her pertinent physical exam findings included a well-appearing woman with normal vital signs who was not in respiratory distress. Her lungs were clear to auscultation bilaterally, her heart was in a regular rate and rhythm, and she had no peripheral edema. Her hemoglobin was 13.4 g/dL. She underwent an extensive battery of diagnostic tests including multiple pulmonary function tests, methacholine challenge tests, six minute walk tests, echocardiograms, computed tomography scans, and cardiopulmonary exercise tests, all of which yielded normal results. However, despite these normal findings, her dyspnea persisted. Separately, the patient's primary care physician referred her to general surgery for mastalgia. She was told at her initial consultation with general surgery that her mastalgia may be partially due to the inappropriately small size of her brassiere. When the patient was professionally refitted for a new brassiere, her dyspnea instantly improved. It is therefore possible that this patient's dyspnea was due to restriction from her brassiere exerting extrinsic compression on her thoracic wall. This is a classic example of an extensive and expensive evaluation of dyspnea, that, in the end, was due to an etiology that is rarely considered but is simple and inexpensive to address.

C-41 OBSTRUCTIVE SHOCK INDUCED BY HEPATOCELLULAR CARCINOMA EXTENDING TO THE RIGHT ATRIUM

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In its advanced stages, hepatocellular carcinoma or tumor thrombus has been reported to extend through the inferior vena cava into right atrium (RA) or right ventricle (RV). One of the most severe consequences is a thrombus causing an obstructive shock which may not respond to pressors or intravenous fluids, carrying a high risk of mortality. We hereby present a case of hepatocellular carcinoma extended into RA in a 69-year-old man who presented with a fall and head trauma, found to have lobulated large hypodense mass with large tumor extension possibly with bland thrombus into the right atrium as well as small ascites and anasarca showed in three phase CT of abdomen. On bedside echocardiogram, an ill-defined, large, mobile mass was noted in the RA extending to RV with diastole. Patient developed obstructive shock secondary to liver mass/

thrombus embolization to the pulmonary artery and he was not responded to resuscitation. In HCC with or without RA extension, nonsurgical approaches are on the horizon. A combination of targeted therapies with Sorafenib, chemoembolization and radiotherapy may show some benefits or as bridge for surgical debulking of the intracardiac tumor.

C-42 OBSTRUCTIVE SHOCK INDUCED BY HEPATOCELLULAR CARCINOMA EXTENDING TO THE RIGHT ATRIUM

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In its advanced stages, hepatocellular carcinoma or tumor thrombus has been reported to extend through the inferior vena cava into right atrium (RA) or right ventricle (RV). One of the most severe consequences is a thrombus causing an obstructive shock which may not respond to pressors or intravenous fluids, carrying a high risk of mortality. We hereby present a case of hepatocellular carcinoma extended into RA in a 69-year-old man who presented with a fall and head trauma, found to have lobulated large hypodense mass with large tumor extension possibly with bland thrombus into the right atrium as well as small ascites and anasarca showed in three phase CT of abdomen. On bedside echocardiogram, an ill-defined, large, mobile mass was noted in the RA extending to RV with diastole. Patient developed obstructive shock secondary to liver mass/thrombus embolization to the pulmonary artery and he was not responded to resuscitation. In HCC with or without RA extension, nonsurgical approaches are on the horizon. A combination of targeted therapies with Sorafenib, chemoembolization and radiotherapy may show some benefits or as bridge for surgical debulking of the intracardiac tumor. In its advanced stages, hepatocellular carcinoma or tumor thrombus has been reported to extend through the inferior vena cava into right atrium (RA) or right ventricle (RV). One of the most severe consequences is a thrombus causing an obstructive shock which may not respond to pressors or intravenous fluids, carrying a high risk of mortality. We hereby present a case of hepatocellular carcinoma extended into RA in a 69-year-old man who presented with a fall and head trauma, found to have lobulated large hypodense mass with large tumor extension possibly with bland thrombus into the right atrium as well as small ascites and anasarca showed in three phase CT of abdomen. On bedside echocardiogram, an ill-defined, large, mobile mass was noted in the RA extending to RV with diastole. Patient developed obstructive shock secondary to liver mass/thrombus embolization to the pulmonary artery and he was not responded to resuscitation. In HCC with or without RA extension, nonsurgical approaches are on the horizon. A combination of targeted therapies with

Sorafenib, chemoembolization and radiotherapy may show some benefits or as bridge for surgical debulking of the intracardiac tumor.

Rheumatology/Immunology/Allergy

A-53 DISTINCT SINGLE CELL GENE EXPRESSION SIGNATURES OF MONOCYTE SUBSETS DIFFERENTIATE BETWEEN TNF-ALPHA INHIBITOR TREATMENT RESPONSE GROUPS IN RHEUMATOID ARTHRITIS

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Recent work from our group demonstrated that pre-treatment serum type I IFN- β/α ratio >1.3 predicts non-response to anti-TNF α therapy (TNFi) in RA patients. The cellular mechanisms that underlie the IFN- β/α ratio that predicts response are unknown. Effects of IFN on single cells and uncommon cell populations may be masked in whole blood or mixed cell populations. We used single cell analysis to investigate whether monocyte gene expression differs significantly between RA patients according to their pre-TNFi serum IFN- β/α ratio. Single classical (CL) and non-classical (NC) blood-derived monocytes were isolated from 15 seropositive RA subjects prior to biologic therapy. Subjects were grouped by pre-TNFi serum IFN- β/α ratio: IFN- $\beta/\alpha > 1.3$ (n=6) and IFN- $\beta/\alpha < 1.3$ (n=9). 87 target genes were analyzed. Genes that varied significantly between the groups by categorical analyses were tested in multivariate logistic regression models. *JAK1*, *IL1A*, *TLR2*, *CD32A*, *CD36*, *CXCR3*, *IL8*, *IRAK1*, and *TYK2* expression were retained in the mixed monocyte gene expression model for differentiating between groups. *JAK1* and *IL1A* were also retained in the models from monocyte subsets. *TLR9*, *STAT1*, and *FCER* were retained in the CL model. *STAT2* and *IFI27* were retained in the NC model. Regression models from the monocyte subsets provided increased discriminatory potential for treatment response group in Receiver Operator Curve analysis in comparison to the mixed monocyte model. Within-cell co-expression patterns demonstrate biological differences in monocyte subsets of RA patients with an IFN- $\beta/\alpha > 1.3$, the ratio of type I IFNs which predicts non-response to TNFi. When monocyte subsets were analyzed separately, differentiation by gene expression was strongest among the patient groups and distinct expression signatures were identified, suggesting that further study of monocyte subsets will illuminate molecular differences that determine treatment response to

TNFi in RA. A better understanding of molecular mechanisms that underly the IFN- β/α ratio that determines treatment response should allow us to focus down to a marker that may be easier to measure, and, may reveal other targets for therapy. This work will help to develop a more individualized approach to therapy in RA.

A-54 PEPTIDYLARGININE DEIMINASE 2 IS NOT REQUIRED FOR THE FORMATION OF NEUTROPHIL EXTRACELLULAR TRAPS

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Neutrophil extracellular traps (NETs) are extracellular structures composed of DNA and antimicrobial proteins that are intended to trap and kill pathogens, but have also been implicated in a variety of diseases including rheumatoid arthritis, pancreatitis, and cancer. Peptidylarginine deiminase 4 (PAD4), a citrullinating enzyme, has been shown to be required for NET formation. Upon neutrophil activation, PAD4 citrullinates histones allowing chromatin decondensation and ultimately NET formation. PAD2 is also expressed in neutrophils, but it is not known whether or not it is required for NETosis. It is important to understand the roles of the different PAD enzymes in immune cells since isoform specific PAD inhibitors are being developed to target the different PADs in disease. To determine if PAD2 is required for NET formation, we purified murine neutrophils from the bone marrow of PAD2^{+/+} and PAD2^{-/-} mice as well as PAD4^{+/+} and PAD4^{-/-} mice as a control. Neutrophils were stimulated with TNF α and lipopolysaccharide for 4 hours, fixed, stained with DAPI and anti-citrullinated histone H4, and imaged. In a blinded manner, the total number of neutrophils and NETs were counted for each image. We also determined if PAD2 deficient neutrophils were able to kill *Candida* using a modified XTT viability assay. We found no significant loss of NET formation in the absence of PAD2. As expected, no NETs were detected in PAD4^{-/-} neutrophils. PAD2^{-/-} neutrophils showed no reduction in *Candida* killing compared to the PAD2^{+/+} neutrophils. Thus, we conclude that PAD2 is not required for NET formation in mice.

A-55 RELIABILITY AND VALIDITY OF THE PROMIS-29 IN SYSTEMIC SCLEROSIS ASSOCIATED INTERSTITIAL LUNG DISEASE

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Background/Purpose PROMIS-29 is a generic health-related quality of life instrument. Our objective was to assess the reliability and construct validity of PROMIS-29 in participants with Systemic Sclerosis-Associated Interstitial Lung Disease.

Methods Ninety-four participants with SSc-ILD were recruited and administered PROs at baseline visit, including PROMIS-29, patient global assessment for disease severity on a visual analogue scale (VAS), Dyspnea 12, Modified Medical Research Council Dyspnea Scale (MMRC), Leicester Cough Questionnaire (LCQ), Short Form 36 (SF-36), and the Saint George Respiratory Questionnaire (SGRQ; respiratory disease impact measure). Participants also performed a pulmonary function test (PFT). Pearson correlation coefficients between all questionnaires and physiologic measures, as well as Cronbach's α , were calculated and interpreted.

Results Mean age of participants was 51.6 years and mean disease duration of 2.8 years after first non-Raynaud's symptom. Of the 94 participants, 60.6% classified as diffuse SSc, and 24.5% limited SSc. Mean FVC was 75.6 (S.D. 16.0) and DLCO was 51.4 (S.D. 22.7) and 88% had NSIP fibrotic pattern on HRCT. PROMIS-29 scores were 0.2 to 0.9 SD below the US population. Cronbach's α reliability was acceptable for all domains (ranged from 0.74 to 0.98). Correlation coefficients were highest with PROMIS-29 physical function scale (0.36 to -0.81 for all comparisons; $p < 0.05$). Correlations were higher for dyspnea scales compared to LCQ. PROMIS-29 showed none-to-small discriminatory ability in comparison with physiologic measures (FVC/DLCO).

Conclusion PROMIS-29 has adequate reliability and construct validity for evaluation in SSc-ILD. It has moderate-to-large correlations with measures of dyspnea, dyspnea-specific QOL, and cough, and complements physiologic measures.

B-53 A NOVEL HIGH THROUGHPUT METHOD TO QUANTIFY NETOSIS IN FLUORESCENT MICROSCOPE IMAGES

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Neutrophils are the most abundant type of leukocyte and act as primary responders in the inflammatory process. Recently a form of neutrophil death known as NETosis has been implicated in the pathogenesis of multiple diseases including rheumatoid arthritis, systemic lupus erythematosus, pancreatitis, and cancer. NETosis is the formation of neutrophil extracellular traps, or NETs, which form when neutrophils lyse and released their decondensed chromatin affixed with antimicrobial molecules. Current methods of quantifying NETosis are time-consuming, are susceptible to bias, require very expensive equipment, are non-specific, or are unable to quantify NETosis after neutrophil lysis. To address these issues, we designed a novel ImageJ/Java based macro to provide a rapid, simple, and objective approach to analyze NETosis in standard microscope images of

immunofluorescently stained neutrophils. To generate the images, stimulated and unstimulated purified human neutrophils were fixed, stained with Sytox DNA stain, and imaged. The macro was then run on each image, first calculating the area and integrated density (the sum of all the pixels) for each cell. Then the macro eliminates cells that are only small fragments or are clumped. A file is generated that includes information for each neutrophil such as chromatin area and fold increase of chromatin area compared to condensed nuclei. The file also contains averages for chromatin area and the percent of NETs per image. To validate this program, images were analyzed by eye in a blinded manner to determine total cell number and percent NETosis. Analyzing over 2000 neutrophils, the macro calculated a 27.4% rate of NETosis and 29.1% was determined by eye. Further, the macro calculated these values in about 15 minutes and determining the percent NETosis by eye required several hours. Thus, this macro provides a means to quantify chromatin decondensation and NETosis in a fast, accurate, objective, simple, high throughput, and cost-effective manner making it optimal to assess NETosis in a variety of disease states.

B-54 DONOR LUNG-DERIVED T CELLS DIFFERENTIATE INTO IL-17A-PRODUCING T CELLS AFTER LUNG TRANSPLANT INTO LYMPHODEPLETE RECIPIENTS

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Background Recipient T cell-mediated alloimmune responses after lung transplant promote rejection and obliterative bronchiolitis development. However, the lung is a rich source of donor-derived T cells that may also contribute to acute and chronic rejection.

Methods Using a murine minor mismatch orthotopic left lung transplant model, we investigated the role of donor-derived T cells in cellular rejection and fibrosis after lung transplantation by transplanting lungs into recombination activating gene-knockout (RAG^{-/-}) mice that lack T and B cells.

Results At day 35 after transplantation, syngeneic left lung allografts did not display any lymphocyte infiltration. However, allogeneic left lung grafts had moderate peribronchial and perivascular lymphocytic infiltration. Some of the contralateral native right lungs also had mild perivascular lymphocytic infiltrates in recipients transplanted with allogeneic allografts. The donor lymphocytes in the lung grafts were predominantly CD3+CD4+ T cells regardless of allogeneic or syngeneic graft. Donor-derived CD4+ and CD8+ T cells also populated the non-transplanted lung and the spleen. Allogeneic donor-derived CD4+ T cells had an increased frequency of IL-17A+ T cells compared to syngeneic donor-derived CD4+ T cells. However, lung allografts transplanted into RAG^{-/-} mice did not develop obliterative airway fibrosis.

Conclusions Allogeneic donor lung-derived T cells have a propensity to differentiate into Th17 cells relative to syngeneic lung-derived T cells but are not sufficient to induce obliterative bronchiolitis pathology.

C-43 ANCA-ASSOCIATED VASCULITIS IN PATIENTS WITH SLE

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Introduction Patients with systemic lupus erythematosus (SLE) who develop acute kidney injury (AKI) are classically found to have immune complex-mediated glomerulonephritis (GN) or thrombotic microangiopathy (TMA) from associated anti-phospholipid syndrome. In this report we present 2 patients with SLE and a more atypical etiology of AKI due to ANCA-associated vasculitis (AAV). Case 1 A 25 year old female with a 7 year history of SLE was evaluated for worsening proteinuria. She had been hypertensive over her last several clinic visits (systolic range, 140–150 mm Hg; diastolic range, 90–100 mm Hg). Her creatinine had been stable at 0.65 mg/dL. Urinalysis (U/A) revealed ≥ 300 mg/dL of protein and 20 RBCs. A spot urine protein/creatinine ratio was 2.29. Complements (C3/C4) were within normal range, and anti-dsDNA was elevated at 48 IU/mL (>10 is positive). The initial diagnosis of SLE was based on presence of arthralgia, malar rash, and photosensitivity, plus positive ANA (>1:160 speckled pattern), anti-dsDNA, and anti-Smith. She had been managed on hydroxychloroquine 400 mg daily and prednisone 30 mg daily. Renal biopsy demonstrated focal segmental necrotizing GN consistent with AAV. Of 7 total glomeruli, 2 had active segmental necrotizing lesions with fibrinoid exudates. ANCA was positive (1:160), and antibodies to myeloperoxidase (MPO) were >100 units (>3.5 is positive). Immune complex-mediated GN was also diagnosed based on the presence of granular deposits of IgG, IgA, IgM and kappa/lambda light chains within the glomerular basement membrane. The etiology of her AKI was attributed to AAV with superimposed class III and class V lupus nephritis. Case 2 A 32 year female with a 2 year history of SLE was hospitalized with AKI. She was normotensive, and had a creatinine of 3.79 mg/dL (1.1 mg/dL 6 months prior). U/A revealed 300 mg/dL of proteinuria and 96 RBCs. A spot urine protein/creatinine ratio was 5.04, C3 and C4 were within normal range, and anti-dsDNA was not detected. She was on no medication for SLE as per her preference. The initial diagnosis of SLE was based on presence of malar rash, arthralgias positive ANA (1:160 speckled pattern), and elevated SSA antibody of 103 units (>30 is positive), with an indeterminate anti-dsDNA. At diagnosis, U/A showed 100 mg/dL of protein and 3 RBCs; her creatinine was 0.6 mg/dL. Renal biopsy demonstrated a total of 26 glomeruli, 13 with global and 4 with segmental sclerosis, 9 with cellular crescents, and 1 with a fibrous crescent. There was no evidence of immune complex deposition. ANCA testing was positive (1:320), and antibodies to MPO were elevated at 253 units/mL (>26 is positive). The etiology of her AKI was attributed to AAV. **Discussion:** These 2 cases reflect patients with SLE and AKI for whom renal biopsies revealed an alternate diagnosis than classical lupus nephritis or even TMA. Both patients had necrotizing lesions and

serology consistent with AAV. The 1st patient had a mixed picture with immune complex deposition also present, whereas the 2nd patient had a more typical appearance of AAV without immune complexes. These 2 cases raise the question of the role of ANCA in SLE. ANCA positivity may be found in ~20% of SLE patients via indirect IF¹. Additionally, in a European study of 566 SLE patients, the prevalence of anti-MPO was 9.3%². A search of the current literature did not yield evidence that ANCAs are involved in the SLE disease process. However, our 2 cases and similar case reports support the co-existence of SLE and AAV as a possible explanation for AKI. Given this overlap, clinicians must have a high index of suspicion for co-existing AAV in patients with SLE, presenting with AKI and features atypical for immune complex-mediated GN, such as non-depressed serum complements.

C-44 14-3-3: AN ADHESIVE PROTEIN OF MEDIAL INFLAMMATION

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Large Vessel Vasculitis (LVV) is an autoimmune disease wherein large vessels such as aorta and its primary branches are inflamed which can lead to life threatening consequences. LVV is characterized by the presence of immune cells and granuloma formation in the medial layer of aorta. Recently, we reported novel auto-antigenic roles of 14-3-3 family of proteins in the human aortic tissues of LVV. Amongst the 7 isoforms of the 14-3-3 family, only two (zeta and epsilon) were found to be auto-antigenic. In medial layer of the LVV aorta, 14-3-3 proteins co-localized with infiltrating immune cells, granulomas and smooth muscle cells. This intrigued us to test the role of 14-3-3 in the immune cell adhesion in aortic tissue. We hypothesized that the presence of 14-3-3 at the inflammatory site may influence adhesion of immune cells. To test the above hypothesis, using monocytes and T-cells as immune cells, and immortalized cell lines as well as primary cells (smooth muscle cells, fibroblasts and endothelial cells) from aorta as stromal cells, we investigated if the presence of 14-3-3 in the immune active region is purely co-incidental or has any functional consequence. Our results suggest that 14-3-3 proteins play important role in the monocytic adhesion. Disruption of 14-3-3 significantly impaired monocytic adhesion to various stromal cells. However, 14-3-3 isoforms were differentially involved in this process. Significant variation was observed when 6 isoforms of 14-3-3 were compared for their ability to affect immune cells adhesion to a range of stromal cells including smooth muscle cells, endothelial cells, fibroblasts etc. Primary cells from control or LVV aorta showed differences in the expression levels of 14-3-3 isoforms. Altered expression of the levels of 14-3-3 epsilon or zeta specifically correlated with the immune cell adhesion. This effect was further

pronounced when inflammatory cytokines (IFN- γ and TNF- α) or pro-inflammatory signal (e.g. TLR3 ligand) were present. In spite of 14-3-3 proteins being present in monocytes, their contribution to adhesion was insignificant. Together, our results strongly suggest that 14-3-3 of the stromal cells is primarily responsible for the monocytic adhesion, suggesting that 14-3-3 of aortic wall contributes to the medial inflammation, a key feature of LVV.

C-45 RELAPSING POLYCHONDritis WITH LIMBIC ENCEPHALITIS

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Introduction Relapsing polychondritis (RPC) is a rare autoimmune disease that causes inflammation in cartilaginous structures and is occasionally associated with manifestations in the cardiac, renal or central nervous systems (CNS). RPC usually presents with local inflammation to ear pinnae, eyes, nose, airway and joints; less commonly presents with involvement with heart, kidneys and CNS.

Case presentation A 39 year old African American male with past medical history of RPC presented to the emergency room with worsening memory loss of 2 weeks duration. He noted that he was unable to recall recent conversations. Associated symptoms included subjective fevers and stinging bilateral ear pain. Vital signs were normal on presentation. On physical exam, the patient was found to be alert but oriented only to person and time. The pinna were thickened bilaterally and bilateral conjunctival hyperemia was also noted. The mini mental status exam showed that the patient was unable to recall 3 basic objects after 5 minutes. Pertinent laboratory findings included an elevated white blood cell count (13,000 cells/uL), slightly elevated sedimentation rate (30 mm/hr), normal C-reactive protein, a positive ANA (1:80) and a positive anti-ribonucleoprotein antibody (1.1). Hepatitis and viral panel were negative. VDRL test was nonreactive. Coincidentally, anti-N-methyl-D-aspartate receptor antibody, which is highly suggestive of autoimmune limbic encephalitis, was positive (1:10). Cerebrospinal fluid analysis demonstrated elevated protein (56 mg/dL) and leukocytes (46 mg/dL) with 13% segmented neutrophils. Additional workup included an MRI of the brain which showed a signal abnormality in the bilateral hippocampi and occipital lobes which was suggestive of acute encephalitis. The patient's symptoms improved significantly with 3 days of IV methylprednisolone. He was discharged home with a 30 day course of 60 mg prednisone and follow up with his rheumatologist for further management.

Conclusion Relapsing polychondritis is a rare condition and CNS complications of the disease, such as limbic encephalitis, are even more uncommon. Treatment is often difficult in RPC because relapse is common. Identifying the condition promptly will allow the physician to treat accordingly, thus avoiding serious complications of the disease.

C-46 PRIMARY CENTRAL NERVOUS SYSTEM VASCULITIS IN A PATIENT WITH RENAL GRANULOMATOSIS WITH POLYANGIITIS

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Introduction Primary angiitis of the central nervous system (PACNS) is a very rare condition that is defined as an inflammation of the cerebral vessels, spinal cord and/or meninges without involvement of other organs. Headache is the most commonly reported symptom, occurring in about 60 percent of patients. Other less common symptoms include cranial neuropathies, ataxia, seizure, and coma. Diagnostic criteria include presence of neurological deficits, histologic or immunopathologic findings of CNS angiitis, and the absence of systemic vasculitis. We present a rare case of PACNS in a patient with known diagnosis of renal granulomatosis with polyangiitis (GPA).

Case presentation The patient is a 44 year old Hispanic woman who presented with severe headache to an outside hospital. Previous history was pertinent for hypertension, chronic kidney disease and GPA with renal involvement. Initial neurological workup included CT and MRI of the head and brain which demonstrated acute subarachnoid hemorrhage, while the cerebral angiogram was normal. Laboratory values were unremarkable. Twenty four hours after discharge, the patient presented to our institution with persistent headache associated with nausea and vomiting. Her vitals were stable with mildly elevated blood pressure. No focal neurological deficits were found on physical examination. Imaging studies, including CT and MRI of head and brain, revealed bilateral ischemic lesions with bilateral occipital hemorrhages. Cerebral angiogram demonstrated vascular irregularities in the distal branches of the anterior, middle and posterior cerebral arteries consistent with a central nervous system (CNS) vasculitis. Rheumatological workup showed an elevated sedimentation rate (28 mm/hr) and C reactive protein (1.7 mg/dL), positive anti-serine protease 3 antibody (3.5 AI) with high cytoplasmic-ANCA titer (1:1,280). Antinuclear antibody, antiphospholipid antibodies and cryoglobulins were negative. Urinalysis was bland. The patient was given intravenous methylprednisolone, but she continued to have additional embolic and hemorrhagic strokes. Intravenous cyclophosphamide was then initiated, resulting in no further strokes. She was discharged home with steroids in addition to a long term plan for cyclophosphamide which will be followed by a steroid-sparing agent, such as azathioprine or mycophenolic acid.

Conclusion This case is particularly interesting because although our patient did have a history of GPA and PACNS is more rare than secondary CNS vasculitis, we believe that she most likely developed PACNS rather than secondary CNS vasculitis as her GPA was in remission based on the bland urinalysis and the absence of clinical manifestations of GPA. It is important to make this challenging distinction because unlike PACNS, patients with GPA require more frequent doses of cyclophosphamide. The patient will need a follow up MRI 4–6 weeks after the initiation of treatment to assess for progression of the disease and presence of

new lesions. For some patients, a response to treatment may only be indicated by symptomatic improvement rather than the resolution of MRI lesions.

C-47 NEED FOR CONTINUOUS IMMUNOSUPPRESSION TO PREVENT EXTRARENAL MANIFESTATIONS IN ESRD DUE TO ANCA GLOMERULONEPHRITIS

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Introduction Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are pauci-immune, autoimmune vasculitis syndromes affecting small vessels. AAV encompass microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis, and granulomatosis with polyangiitis. Multiple organs can be involved with frequent involvement of the kidneys. Other affected organ systems include skin, upper respiratory tract, and lower respiratory tract. Potential life-threatening manifestations include pulmonary hemorrhage. Treatment modalities used in AAV include cyclophosphamide, rituximab, plasmapheresis, azathioprine, methotrexate and glucocorticoid therapy. It should be noted that there are significant side effects associated with these therapies, such as infection and bone marrow suppression. This case describes a patient with ANCA-associated vasculitis initially limited to kidney involvement. Cyclophosphamide therapy was discontinued due to significant side effects and chronicity of disease, however, the patient later developed extrarenal manifestations in the form of pulmonary hemorrhage.

Case description A 67-year-old male with past medical history of hypertension initially presented to nephrology clinic for creatinine elevation to 4.31. He had subnephrotic range proteinuria, dysmorphic red blood cells on urinalysis and positive P-ANCA and MPO antibodies. He underwent a kidney biopsy that was consistent with pauci-immune glomerulonephritis. On the biopsy, a minority of glomeruli demonstrated fibrocellular crescents and rare capillary loops with fibrin thrombi and acute inflammation. Overall, the biopsy favored an ongoing process with acute and marked chronic features, particularly notable for marked interstitial fibrosis. He was diagnosed with chronic glomerulonephritis secondary to ANCA-vasculitis. Intravenous cyclophosphamide therapy and plasmapheresis were initiated, but his therapy was complicated by bone marrow suppression with thrombocytopenia, lymphopenia, and worsened anemia. Plasmapheresis was delayed although he was ultimately able to complete 7 cycles. The decision was made to stop further cyclophosphamide therapy given his extensive chronicity on biopsy, the side effect of bone marrow suppression, and the patient's lack of extrarenal manifestations at the time. He was given a steroid taper and prepared for future dialysis. The patient remained asymptomatic for eleven months, however, he then developed dyspnea and occasional hemoptysis. He was admitted to the hospital and hemodialysis was initiated. Given his hemoptysis, bronchoscopy was obtained with progressively

bloodier lavages concerning for pulmonary hemorrhage. No evidence of malignancy or infection was discovered, hence, it was concluded that his pulmonary hemorrhage was due to pulmonary involvement of his vasculitis. He was started on intravenous cyclophosphamide and pulse steroids. He was stable for discharge home with steroid taper and planned 4-month course of cyclophosphamide.

Discussion In the case above, cyclophosphamide treatment was held due to his marked chronicity of disease and the side effect of bone marrow suppression. The risks of treatment were thought to outweigh the benefits, but the patient later presented with extrarenal manifestations of ANCA-vasculitis in the form of pulmonary involvement. This case highlights the lack of information in this population to predict which patients are at risk of developing future extrarenal manifestations thus warranting full treatment despite no expected renal benefit. While there is insufficient data at this time to draw conclusions on which patients should be treated, we can conclude that there is a need for further studies in this population to better understand which patients may benefit from treatment.

C-48 CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME - A RARE BUT LIFE THREATENING CONDITION

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Introduction Antiphospholipid syndrome is an autoimmune disease characterized by thrombosis and pregnancy loss. Less than 1% of the patients with APS develop accelerated form of this syndrome resulting in multiorgan failure² called catastrophic antiphospholipid syndrome (CAPS), the majority of patient with CAPS end up in intensive care unit with multiorgan failure.

Case description 39-year-old African-American female with no significant past medical history presented with soreness of bilateral lower extremities, more pronounced proximally with difficulty in ambulation for the past 4 weeks, also reported that she had swelling of both of her hands. Vitals on admission significant for low grade fever (100.5), oxygen saturation 99% on 2 L oxygen. Macular rash on bilateral lower extremities, decreased breath sounds in bilateral lung bases. Labs on admission significant for WBC 20K, hemoglobin 9.6, platelet 484, MCV 73.2, CK 1121, CRP 23.9, ESR 71. Chest x-ray showed posterior left basal infiltrate and developing right infiltrate. On second day of hospitalization patient was transferred to the ICU owing to increased shortness of air, fever and decreased breath sounds, patient continued to have declining respiratory status and was placed on the ventilator. She developed hypotension requiring brief pressor support. Patient started to develop discoloration of her distal digits which was initially thought to be result of hypo perfusion during the hypotensive crisis. Working diagnosis at this point was pneumonia leading to sepsis and antibiotic coverage was broadened, though initial blood cultures and sputum gram stain remained negative. During ICU stay patient also developed acute renal failure with decreased

urine output requiring intermittent hemodialysis. ID and rheumatology were consulted. Patient's ANA came back positive, complement levels were low, antiphospholipid antibody and SSA Ab were positive, MRI brain obtained was concerning for multiple scattered punctate throughout the brain and cerebellum. Echo demonstrated pericardial effusion with tamponade, 600 cc of fluid was drained. pericardial fluid demonstrated ANA positive with 1:4 and speckled pattern. Patient underwent renal biopsy which demonstrated lupus nephritis WHO class IIB and III. Per rheumatology recommendation patient was started on Solu-Medrol, weekly Cytoxan and heparin drip. After prolonged hospital stay patient was weaned off from the ventilator she was maintained on prednisone for suppression of her SLE and anticoagulation in context of digit hypo perfusion. Two months Later (on second hospitalization) patient underwent thumb, index, middle, small finger right hand partial and great, second and fifth left toes amputation. Microscopic examination of upper extremity amputation revealed that there were thrombus in the medium-size artery. In light of histological manifestation of vessel occlusion, presence of antiphospholipid antibody, rapid progression of symptoms with multiple toes and finger involvement led diagnosis of catastrophic antiphospholipid syndrome. Patient subsequently was maintained on lifelong anticoagulation and immunosuppression.

Conclusion Establishing diagnoses of CAPS require a high index of suspicion unless we consider in differential diagnosis of severe hypercoagulability state, it can be completely missed which can result in fatal outcome of these patients. The most identifiable common trigger factor are infections and surgical procedures. In most cases the concept of “triple therapy” with anticoagulants, corticosteroid and either plasma exchange or intravenous immunoglobulin forms the backbone of treatment. Patient with SLE should additionally receive cyclophosphamide (as in our patient) unless there is contraindication.

C-49 SEVERE THROMBOCYTOPENIA IN SYSTEMIC LUPUS ERYTHEMATOSUS: TREATMENT WITH HYDROXYCHLOROQUINE ALONE

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Severe immune thrombocytopenia in systemic lupus erythematosus (SLE-ITP) is defined as having a platelet count below 50,000, and is often accompanied by other potentially life threatening events resulting from organ inflammation and/or hemorrhage. Standardized first line treatment of severe SLE-ITP usually begins with high dose corticosteroids as first line treatment. Long term responses to corticosteroids alone are quite variable, with relapses in many cases. The addition of second-line agents includes azathioprine, cyclophosphamide, danazol, intravenous immunoglobulin, rituximab, and hydroxychloroquine (HCQ). A 22 year old Caucasian female presented with one year of intermittent low grade fever, knee arthralgias, headaches, nausea, fatigue, facial rash, and photosensitivity.

Physical examination was remarkable for punctate red papules over the malar areas of the face, and pain without swelling on full range of motion of both knees. Initial laboratory tests revealed a platelet count of 42,000, normal WBC and Hgb, normal chemistry profile, and a positive anti-nuclear antibody (ANA) in a speckled pattern at a titer of 1:320. Other testing that was normal or negative included PT, PTT, anti-DNA, complement levels, and bone marrow biopsy. She was not taking any estrogen containing medication nor any over-the-counter supplements. No obvious bleeding was noted in any organs. A diagnosis of systemic lupus erythematosus (SLE) was made, and treatment begun solely with hydroxychloroquine (HCQ) 300 mg daily. Six months later, her platelet count was 76,000, and all other presenting complaints and physical findings had resolved. One year after initial presentation, her platelet count was 180,000, and it remained in the normal range during twenty additional years of follow-up. It proved necessary to continue HCQ dosage of 300 mg daily to sustain subjective and objective remission of her other SLE phenomena. SLE is an inflammatory autoimmune disease involving multiple organs, with a wide range of clinical manifestations. Immune thrombocytopenia in SLE (SLE-ITP) has often been associated with other clinical features including (but not limited to) neuropsychiatric and renal involvement, hemolytic anemia, low complement levels, and high titer double-stranded anti-DNA antibodies. Several studies have indicated that HCQ is effective in treating refractory severe SLE-ITP, with long-term responses reported. The required daily dosage of HCQ in this situation (and for SLE in general) is variable, but can be optimized by measuring serum concentrations. It is reasonable to assume that our patient could have been treated with a higher initial dosage of HCQ for the first six to twelve months to enhance her response. We know of no published studies utilizing HCQ alone as first-line treatment of severe SLE-ITP. A recent editorial has commented on the overreliance of CSs in a number of rheumatologic disorders, including SLE. Obviously, each individual case of SLE must be evaluated on its own merits to implement a reasonable and effective treatment regimen. We propose that in selective cases of severe SLE-ITP, uncomplicated by hemorrhage or other life-threatening manifestations, consideration should be given to initial conservative treatment with HCQ alone.

C-50 ISOLATED OPTIC NEURITIS IN A SYSTEMIC LUPUS ERYTHEMATOSUS PATIENT

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Systemic Lupus Erythematosus (SLE) is a chronic multi-systemic autoimmune disease that may affect any organ of the body. Neurological manifestations are fairly common but only a small number of SLE patients with neuro-ophthalmologic manifestations have been reported in the literature. Although these manifestations are uncommonly encountered in SLE, they are important causes of disability and impairment of quality of life.

Case Presentation A 24 year old male with a past medical history of SLE and lupus nephritis, presented with a two week history of progressive worsening vision in the right eye accompanied with pain. His visual loss began with focalities of blurriness that quickly progressed to loss of the upper half of his visual field and ultimately lead to complete loss of vision. The patient was diagnosed with SLE and lupus nephritis 9 months prior and had been on prednisone and mycophenolate mofetil. The prednisone was tapered to 20 mg over a course of 3 weeks and mycophenolate was discontinued due to lack of insurance coverage. A clinical diagnosis of acute optic neuritis was made. Cerebrospinal fluid analysis was unremarkable. ANA titer and Anti-dsDNA were mildly elevated (1:160 & 26 units/ml, respectively), C3 and C4 were within normal limits, and serum IgG was within normal limits. MRI of the orbits and the cervical spine demonstrated findings consistent with right-sided optic neuritis with no evidence of demyelinating disease. The patient received 1 gm of IV Methylprednisolone for 5 days followed by Prednisone 40 mg daily and Mycophenolate Mofetil 1000 mg twice daily. The patient's visual acuity improved significantly over the following month.

Discussion A rare neurological complication of Systemic Lupus Erythematosus is optic nerve disease. Optic neuritis often occurs in association with Multiple Sclerosis and Neuromyelitis Optica; however, it could also be a neurological manifestation of some rheumatologic diseases including SLE as seen in our patient. This case underscores a rare neuro-ophthalmologic manifestations of SLE. Fortunately SLE associated optic neuritis responded rapidly to corticosteroids favoring a good prognosis in our patient.

C-51 A DASTARDLY DILEMMA OF ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS (AGEP)

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Acute generalized exanthematous pustulosis (AGEP) is a rare, acute eruption characterized by the development of numerous nonfollicular sterile pustules on a background of edematous erythema. Fever and peripheral blood leukocytosis are usually present. In approximately 90 percent of cases, AGEP is caused by drugs, most often antibiotics (eg, aminopenicillins and macrolides), the calcium channel blocker diltiazem, and antimalarials. The eruption develops within hours or days of drug exposure and resolves spontaneously in one to two weeks after drug discontinuation. 46 y AAM with PMHx HTN, DM, Trisomy 21, DVT sent from NH for evaluation of PNA and cellulitis. Reports pain and swelling in RLE x few weeks with cough. No abdominal pain. Denies cp/sob/f/c/n/v/d. He was treated with cefazolin and vancomycin. Was found to have erythematous rash throughout the body with blisters on skin fold to cubital fossa, inguinal area bilaterally and abdomen without oral mucous involvement. The erythematous rash got worse and the patient was found to be hypotensive 2

days after admission. Antibiotics changed to Vanc/Aztreonam/Clindamycin. There was some concern for TEN. WBC was 39.8 with 2% bands. Was transferred to burn unit 3 days after admission and was intubated due to respiratory distress, and was given pressors due to septic shock with concomitant drug reaction. Wounds were debrided and bacitracin ointment was applied. Biopsy of skin lesions was performed and dermatology was consulted. Pathology reports: Spongiotic dermatitis with mixed dermal infiltrate, follicular plugging, and focal subcorneal pustules. The findings of STS/TEN were not seen. Most Consistent with AGEF. Pt extubated on day 7 after admission to burn unit. Leukocytosis improved but still above 25 k, may be reactive leukocytosis 2/2 antibiotics use. Antibiotics was discontinued on day 10 in the setting of negative urine culture, blood culture, skin culture. 2 weeks after admission to burn unit, WBC trend down to normal limit, ambulating with PT, voiding spontaneously, tolerating diet, wounds healing appropriately, no need for surgical intervention and discharged from hospital.

This case illustrates the potential for a severe drug reaction with the use of cefazolin. Particularly, this was a case with cellulitis and the use of Vancomycin which may cause the common side effect of red man syndrome. Concern for other similar adverse cutaneous reactions such as SJS/TEN or DRESS can cloud the clinical and diagnostic picture. Although AGEF seen in patients is rare, it can lead to secondary skin infections or may become lethal if not treated appropriately. Recognition of this syndrome is critical to institution of appropriate management and prevention of severe systemic infection as well as ruling out other Severe Cutaneous Adverse Reaction to Drugs (SCARs).

C-52 MEDICATION PRIOR AUTHORIZATION, IS IT WORTH THE RISK?

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Introduction Hydroxychloroquine is a disease modifying antirheumatic drug (DMARD) used to treat rheumatic disorders such as lupus and rheumatoid arthritis. Some of the more common side effects of hydroxychloroquine include gastrointestinal upset, photosensitivity, dizziness, and changes in hair and skin pigmentation. More severe side effects include agranulocytosis, vision changes, retinopathy, Steven-Johnson syndrome, and exfoliative dermatitis. Hydroxychloroquine can also cause worsening of porphyria and psoriasis. We present a rare case of hydroxychloroquine-induced exfoliative dermatitis in a patient with psoriatic arthritis. Clinical vignette: The patient is a 50 year old Lithuanian man with history of psoriasis and psoriatic arthritis who presented to the clinic with worsening generalized joint pain and stiffness. His psoriasis had been primarily managed by his dermatologist with corticosteroid ointments and ultraviolet phototherapy. As his condition progressed, 10 mg methotrexate per week was added to help with his arthritis symptoms but without relief. The patient was unable to tolerate methotrexate therapy due to severe nausea, therefore, the medication was discontinued. Shortly after, he presented to his

rheumatologist with worsening joint pain in symmetric distribution in his hands, elbows and knees. Etanercept was initially recommended, but it was not covered by his insurance due to the absence of failure with a second DMARD to treat his psoriatic arthritis. He was then started on 200 mg hydroxychloroquine twice daily. Three weeks after initiation of hydroxychloroquine, patient developed a severe, desquamating maculopapular rash present on his palms, torso, back and thighs which required hospitalization, but no definite diagnosis was made at the time. The patient was seen by dermatology as outpatient and he was diagnosed with an exfoliative dermatitis related to the use of hydroxychloroquine. The medication was discontinued and the rash resolved. Etanercept was then started by his rheumatologist in an effort to manage both his psoriasis in addition to his psoriatic arthritis.

Conclusion Reviewing the medical literature when considering medications is necessary for the best interest of the patient to prevent potentially lethal side effects. Insurance companies often mandate which medications are covered based on algorithms, cost and availability. There are only a few documented cases of exfoliative dermatitis associated with the use of hydroxychloroquine in patients with psoriatic arthritis. In some instances, it was even found to exacerbate psoriatic skin lesions. Therefore, the use of hydroxychloroquine should be avoided in patients with psoriatic arthritis to avoid this rare severe cutaneous side effect.

C-53 FROM TENDINITIS TO OCCLUSIVE SYSTEMIC VASCULITIS: A PECULIAR CASE

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Introduction Giant cell arteritis (GCA) is the most common systemic vasculitis. Clinical features and diagnostic recommendations have been well documented in the literature. Diagnostic work up for GCA is usually considered in someone who is greater than 50 years old with new-onset headaches, visual disturbances, jaw claudication and history of polymyalgia rheumatica. An estimated 10% of patients with GCA present only with constitutional symptoms. We present a case of biopsy-confirmed GCA with atypical clinical manifestations.

Case presentation 62-year old woman with past medical history of asthma and hypertension who presented with neck, shoulder and back pain after a lifting injury. MRI cervical and lumbar spine, bilateral shoulders showed degenerative changes and bursitis, adhesive capsulitis, rotator cuff and biceps tendinitis. Physical therapy, nonsteroidal anti-inflammatory drugs (NSAID), and steroid injections provided temporary relief. However, she later developed neck pain with chewing, proximal muscle weakness, and periodic dizziness upon standing. She did not report constitutional symptoms, vision changes, jaw claudication or headaches. She had an unremarkable right temporal artery biopsy at age of 47 for suspected GCA. On examination, both upper extremities were pale, cold to touch. There was no detectable blood pressure nor palpable radial/brachial pulses. Duplex scan showed >50% bilateral subclavian

artery stenosis. Aortography and angiography with axillary angioplasty showed aortic arch calcification and diffuse smooth 90% stenosis of left axillary artery with dissection. Suspicion for vasculitis was high given the atypical presentation. CT angiogram showed severe stenosis of bilateral subclavian artery, smooth stenosis of the superior renal artery, and diffuse wall thickening of the infrarenal aorta. C-reactive protein was 50.3 mg/L, sedimentation rate was 69 mm/hr. ANA, rheumatoid factor, hepatitis B, C, ANCA, IgG4 levels were normal. Left temporal artery biopsy confirmed diagnosis of partially treated GCA. Treatment with prednisone was initiated.

Discussion In patients with multiple co-morbidities, treatment of one condition can sometimes mask symptoms of

another. Since our patient had asthma, she was intermittently treated with steroid tapers. Since she was initially diagnosed with tendinitis, she was treated with steroid injections and NSAID. We believe frequent steroid and NSAID exposure, though not at the therapeutic dose for GCA, altered her clinical course. The learning objective in this case is that someone under chronic or intermittent steroid therapy may have atypical presentation of vasculitis. When diminished pulses and blood pressure are noted in patients on chronic steroid therapy, vasculitis should be considered in addition to atherosclerotic peripheral vascular disease. Lastly, regardless of steroid use, a previously negative temporal artery biopsy does not rule out GCA as it can present with skip lesions.