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Cardiology/Cardiovascular Disease

B01 ABSTRACT WITHDRAWN

B02 INTERVENTIONS TO REDUCE SEDENTARY BEHAVIOR AT WORK

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Objective Sedentary behavior is associated with all-cause and cardiovascular disease (CVD) morbidity and mortality, independent of physical activity. However, the biological mechanisms underlying the deleterious consequences of sedentary behavior are largely unknown. We hypothesized that obese subjects with sedentary desk jobs, when assigned use of a sit-stand desk, will reduce their daily sedentary time and demonstrate improvement in arterial flow-mediated dilation (FMD), an early indicator of CVD.

Methods Obese subjects without known CVD were recruited at our institution via electronic flyers and received an adjustable sit-stand desk at work. Activities were quantified objectively with an accelerometer for 7 days at baseline and during the intervention. Subjects were incentivized for accelerometer compliance. FMD of the brachial and femoral arteries and nitroglycerin-mediated dilation of the brachial artery, fasting lipids, HbA1c, CRP, and anthropometrics were measured at baseline and 12 weeks. Paired t-tests were used to compare measurements over time.

Results Ten participants were enrolled (90% female, mean age 40 ± 5 , mean BMI 34 ± 4). Mean sedentary time at work (Monday-Friday 8 AM–5 PM) decreased over the intervention period by an average of 114 ± 33 minutes per day ($p=0.003$, figure 1). This correlated with an increase in standing time at work (111 ± 39 to 205 ± 77 minutes per day, $p<0.005$). Femoral FMD improved an average of 3.6% (4.7 ± 1.8 to 7.1 ± 1.6 , $p=0.019$, figure 2) while there was a non-significant trend toward improvement in brachial FMD (7.7 ± 3.1 to 9.9 ± 1.9 , $p=0.07$). There was no change in (endothelial-independent) nitroglycerin-mediated FMD. A significant reduction in fasting triglyceride level was noted (mean reduction 35 ± 13 mg/dL, $p=0.005$). There was no significant change in body weight or other anthropometrics, HbA1c, CRP, work-day or 24-hour step counts or moderate and vigorous physical activity.

Conclusions A significant reduction in sedentary time during working hours was identified with utilization of a sit-stand desk for 12 weeks. Improvement in FMD provides insight into mechanisms of adverse health risk associated with sedentary behavior.

Ongoing enrollment in this pilot study, in addition to 24-week follow-up, may strengthen these findings.

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Abstract B02 Figure 1 Comparison of M-F 8am–5pm mean sedentary time: baseline to 12-week

Abstract B02 Figure 2 Comparison of femoral FMD %: baseline to 12-week

B03 ACUTE DECOMPENSATED HEART FAILURE SECONDARY TO METASTATIC OROPHARYNGEAL SQUAMOUS CELL CARCINOMA

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Background Unexplained cardiomyopathy is rarely found to be caused by infiltrative malignancy, occurring in only 0.49% of cases. Most cases are identified on post-mortem autopsy as only 10% of such patients present with symptoms. Any malignancy is capable of metastasizing to the heart, however, only 0.6% of cases are from oral cavity carcinoma.

Case presentation A 60-year-old male with a history of submandibular squamous cell carcinoma (SCC) status post resection and chemoradiation therapy presented after 23-months of remission with symmetric lower extremity edema and worsening dyspnea of five days duration. He was found to have bibasilar diminished breath sounds and jugular venous distention. Initial echocardiogram revealed reduced left ventricular ejection fraction with massive asymmetric posteroseptal hypertrophy with left ventricular mass. Cardiac MRI revealed a diffuse mass extending into interventricular septum involving both ventricles with encasement of the coronary arteries (figure 1). Whole body PET CT scan failed to show evidence of malignancy outside of the heart. Biopsy of cardiac mass revealed poorly differentiated SCC similar in morphology to prior oropharyngeal SCC. Our patient was treated with

diuresis and beta blocker therapy, with plans for palliative chemotherapy. Unfortunately, he died shortly after discharge.

Decision-making Our patient presented with New York Heart Association class IV heart failure secondary to metastatic infiltration of SCC. Cardiac metastasis is more likely to occur with disruption of lymphatic drainage from the heart, which creates favorable conditions for tumor growth. Neoplastic invasion leads to a loss of normal myocardium which alters contractility and compliance leading to restrictive physiology. Additionally, tumor invasion of electrical conduction pathways can lead to the development of arrhythmias. Treatment options are limited.

Conclusion We present a case of an extraordinarily rare cause of heart failure in a patient with a history of oropharyngeal SCC thought to be in remission. While it is an uncommon diagnosis with poor prognosis, it should be considered in patients presenting with new symptoms of heart failure and history of neoplasm.

Abstract B03 Figure 1 Cardiac MR with diffuse mass extending into interventricular septum involving both ventricles with encasement of coronary arteries

B04 THE EFFECT OF E-CIGARETTE VAPING ON CARDIAC FUNCTION IN MICE

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10.1136/jim-2018-000745.3

Objective The rapid increase in use of electronic-cigarettes (e-cigarettes), especially among youth, raises the urgency for regulating bodies to make informed decisions, guidance, and policy on these products. This study will evaluate the toxicity of e-cigarettes in animals, especially on the cardiac function.

Abstract A03 Figure 1 Platelet reactivity in patients with stemi is different from nstemi: all patients were given 325 mg aspirin at least 30 minutes prior to blood draw. Platelets were isolated and examined basally (0) or after stimulation with agonists for (A) the P2Y₁₂ receptor (ADP), (B) the thromboxane receptor (U46619), and (C) Protease-Activated Receptor 1 (PAR1) for 15 mins and activation assessed by FACS by P-selectin expression, Mean Fluorescence Intensity (MFI) ±SEM, all performed in quadruplicate in each group, n=12–17. *p<0.05 and **p<0.01 between STEMI end NSTEMI

Method We exposed C57BL/6 mice to e-cigarette vapor using an InExpose smoking system from SCIREQ. Bodyweight was measured every two days. The cardiac function was assessed using echocardiography. Cardiac tissues were collected at the end of e-cigarette exposure for pathological analysis.

Results Our experimental data showed that chronic exposure to e-cigarette vapor (1 h/day for 3 months) induced significant cardiac and renal fibrosis in mice. Exposure to e-cigarettes also decreased the tissue expression of microRNA-29 b-3 p (miR-29b), an anti-fibrotic microRNA. Interestingly, short-term exposure of e-cigarette vapor (3 h/day for 2 weeks) had no significant effect on tissue fibrosis but significantly increased angiogenesis in mouse heart tissue. We found that short-term e-cigarette exposure increased the angiogenesis marker CD31 by about 2 fold in female heart tissue and about 50% increase in male heart tissue. The e-cigarette exposure also significantly increased the expression of Flk-1, the receptor of VEGF. However, it did not change the plasma level of VEGF. In addition, e-cigarette exposure caused inhibition of weight increase in experimental mice, but had no significant effect on cardiac function as measured by ejection fraction.

Conclusion These results suggest that e-cigarette vaping could cause cardiac tissue remodeling and affect cardiac tissue angiogenesis.

A03 THE PLATELET PHENOTYPE IN PATIENTS WITH ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION IS DIFFERENT FROM NON-ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

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10.1136/jim-2018-000745.4

Objective We recently identified ERK5 in normal human platelets and in a murine myocardial infarction (MI) model as a mediator of dysregulated platelet activity and infarct expansion via matrix metalloproteinase-9 (MMP9). We investigated whether MI changes the human platelet phenotype, perhaps promoting unpredictable and off-target responses to antiplatelet medications which has been observed.

Methods Blood was obtained from consenting patients with non-ST-segment elevation MI (NSTEMI) and ST-segment elevation MI (STEMI) following aspirin therapy but prior to a P2Y₁₂ receptor antagonist at the time of emergency department (ED) arrival. Platelet activation was assessed by FACS (surface P-selectin) following agonist stimulation for the major platelet receptors. Platelet ERK5 and MMP9 activity were examined by Western blot and gel zymography, respectively,

and plasma MMP9 by ELISA. Receiver Operator Characteristic analyses evaluated biomarker performance.

Results Platelet activation through the thromboxane receptor was quite different between groups (3.4-fold NSTEMI vs. 6-fold STEMI over baseline, $p=0.007$) and the protease-activated receptor 1 (PAR1) signaling pathway (7.1 fold NSTEMI vs. 4.6-fold STEMI over baseline, $p=0.001$). P2Y₁₂ receptor activation curves were almost identical for NSTEMI and STEMI platelets (figure 1). Aspirin therapy by measured plasma thromboxane confirmed equal efficacy in STEMI and NSTEMI. Platelet ERK5 activation was greater in NSTEMI and STEMI compared to control subjects: 3.5-fold higher in NSTEMI ($P=0.0009$) and 1.9-fold higher in STEMI ($P=0.049$). ERK5 protein expression was decreased by 2-fold in platelets at the time of STEMI compared to control and NSTEMI platelets ($P<0.05$). ERK5 inhibition dose-dependently decreased PAR1-mediated platelet activation in patients with NSTEMI. MMP9 protein expression was 3-fold greater in NSTEMI and STEMI platelets vs. control. Plasma MMP9 in control subjects was 284 ng/ml, 395 in NSTEMI patients ($p=0.002$ vs. control), 638 ng/mL in STEMI patients ($p=7\times10^{-6}$ vs. control). Plasma MMP9 concentration in the first blood sample in the ED predicted STEMI at a cut-off of 357 ng/mL (AUC 0.80, $p<0.001$; sens. 80%, spec. 90%) in which some samples were troponin negative.

Conclusion NSTEMI and STEMI platelets have different phenotypes and function suggesting a personalized anti-platelet regimen may be considered. Platelet-derived and plasma biomarkers such as ERK5 and MMP9 appear to rapidly distinguish between NSTEMI and STEMI patients in the ED population. ERK5 appears to be a viable target for anti-platelet medication, especially for patients with NSTEMI.

A04

HDAC INHIBITION-ENHANCED AUTOPHAGY RESCUES MITOCHONDRIAL FUNCTION DURING CARDIAC ISCHEMIA/REPERFUSION (I/R) INJURY

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10.1136/jim-2018-000745.5

Objective Reperfusion injury contributes significantly to myocardial infarct size and mortality. Currently, there are no clinical therapies targeting reperfusion injury. Elucidation of mechanisms of reperfusion injury is urgently needed. Our lab has shown that cardiomyocyte autophagy induced by an FDA-approved anti-cancer Histone DeAcetylase (HDAC) inhibitor, SAHA, blunts I/R injury when give at the time of reperfusion. However, the mechanism underlying cardioprotection of SAHA is not clear. We hypothesize that SAHA protects myocardium through maintaining mitochondrial function and reduces Reactive Oxygen Species (ROS) production during reperfusion injury.

Methods Cultured neonatal rat ventricular myocytes (NRVMs) and human embryonic-stem-cell-derived cardiomyocytes (hESC-CMs) were treated with SAHA 16 hours before subjecting to simulated I/R. Total mitochondrial DNA (mtDNA) was measured by qPCR (COX2, D-Loop and ATP6). Intact mtDNA was detected by semi-quantitative long PCR. Mitochondrial mass (mitoTracker), mitochondrial membrane potential (MMP, TMRM dye) and cellular ROS level (H2DCFDA dye) were measured by fluorescent microscopy and flow cytometry.

Additionally, 9 mice were randomized into 3 groups: vehicle control, SAHA pretreatment (one day prior and at surgery), and SAHA treatment at the time of reperfusion only. Each group was subjected to I/R surgery (45min coronary ligation, 24 h reperfusion). MtDNA (by qPCR) and mitochondrial mass (by electron microscopy, EM) were measured in infarct, border and remote zones. ATG 7 knockdown by siRNA in NRVM and hESC-CM were used to test the dependency of autophagy.

Results

- SAHA pre-treatment in hESC-CMs increased total mitochondrial DNA (mtDNA) by ~50% and increased intact mtDNA by ~20% ($n=3$, $p<0.05$). I/R in mice reduced total mtDNA ~50% in the border zone. SAHA pre and reperfusion only treatment preserved total mtDNA at the normal level in the border zone after I/R injury ($n=3$, $p<0.05$).
- In hESC-CMs and NRVMs, the total mitochondrial mass detected by mitoTracker increased ~40% ($n=3$, $p<0.05$). By electron microscopy, the mitochondrial mass was significantly increased in the border zone after SAHA treatments.
- In both NRVMs and hESC-CMs, SAHA pre and reperfusion only treatment preserved I/R induced mitochondrial membrane potential (MMP) loss by ~50% and reduced ROS production by ~30% ($n=3$, $p<0.05$).
- SAHA pretreatment in NRVMs and hESC-CMs significantly increased the translocation of LC3II and Drp1 by ~50% indicating increased mitophagy. Knocking down ATG7 abolished SAHA's protective effects on both MMP and ROS production.

Conclusions The FDA-approved anti-cancer HDAC inhibitor, SAHA, preserves I/R induced mitochondrial dysfunction and reduces myocardial ROS production when given before the ischemia or at the time of reperfusion. The protective effects are dependent on autophagy/mitophagy. These results demonstrated that I/R-induced mitochondrial dysfunction is one major contributor to reperfusion injury and will enable us to design novel therapies to treat reperfusion injury.

A05

CYANOSIS AS A LONG TERM COMPLICATION OF PULMONARY VALVE SURGICAL VALVOTOMY

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10.1136/jim-2018-000745.6

Background Severe pulmonary valve (PV) regurgitation can result from surgical or balloon valvotomy. If left untreated PV regurgitation in the setting of right ventricular non-compliance may lead to progressive cyanosis and increased morbidity and mortality.

Case A 60-year-old white male with history of hypoxia requiring supplemental O₂ presented with acute dyspnea. He was diagnosed with chronic obstructive pulmonary disease (COPD). His medical history was notable for valvular PS treated with surgical valvotomy at age 27 for symptomatic valvular (PS) after which he was lost to follow-up. Initially, patient was treated for COPD exacerbation. His exam was notable for pulmonary wheezing, elevated JVP, hepatomegaly, and peripheral cyanosis with clubbing. Despite COPD treatment and improvement of wheezing, he continued to require high levels of oxygen supplementation. TTE revealed normal left ventricle function, severe pulmonary and tricuspid valve

regurgitation, dilated right ventricle, normal estimated right ventricular systolic pressure and stretched PFO with large right-to-left shunting.

Decision making Given longstanding COPD history, initial working diagnosis was end stage COPD resulting in severe pulmonary hypertension with right-to-left shunting leading to cyanosis. However, due to history of PV surgical valvotomy, invasive hemodynamics were obtained and showed normal pulmonary artery pressure and pulmonary wedge pressure confirming elevated right atrial pressures secondary to RV non-compliance, tricuspid regurgitation and PV regurgitation. He was taken to surgery for a redo sternotomy with pulmonic and tricuspid valve replacements with closure of PFO. He was discharged a week later with oxygen saturation above 95% on room air.

Conclusion Elevated right atrial pressure secondary to RV non-compliance and severe pulmonary regurgitation may progress to right-to-left atrial shunting if a PFO is present, leading to cyanosis. It is critical to realize that right-to-left shunting at the atrial level is a function of RV filling pressure, and not always secondary to elevated right heart systolic pressure. Right heart catheterization plays a pivotal role in diagnosis especially in patients with coexisting pulmonary disease.

A31 MYXOID DEGENERATION OF ASYMPTOMATIC ACCESSORY MITRAL VALVE TISSUE WITHOUT LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION IN AN ADULT: A CASE REPORT

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10.1136/jim-2018-000745.7

Objective Accessory mitral valve tissue (AMVT) is a rare congenital heart disease with an echocardiographic incidence of 1 per 26000. To date, only about 106 cases of AMVT have been reported in literature with less than 10 cases reported of patients being diagnosed in 7th decade. Myxoid degeneration of AMVT has not been reported in the literature and we present a first case of AMVT showing myxoid degeneration.

Case presentation A 68-year old male with no significant past cardiac history was found to be a candidate of coronary artery bypass graft (CABG) after a diagnostic angiogram showed multi vessel coronary artery disease. Intraoperative transesophageal echocardiogram (TEE) demonstrated a sub-aortic valve abnormality appeared to be attached on the anterior leaflet of the mitral valve on the ventricular side beneath the left coronary cusp with an accessory cord causing attenuation/wind socking of that portion of anterior leaflet. The abnormality was resected and sent for pathological analysis. We observed a unique histological characteristic that is traditionally been associated with Mitral valve prolapse (MVP). The resected specimen had myxoid degeneration on pathological analysis. The characteristic myxoid lesion is the proliferation of the spongiosa of MV leaflets, with mucopolysaccharide deposits and excessive water content causing leaflet thickening and redundancy. There is marked increase in collagen type III. So the accessory tissue can undergo same disease process that a normal mitral valve does in cases of MVP.

Conclusion AMVT can have a lifelong asymptomatic course and can be found incidentally in a patient being managed for some other cardiac disease. This idea also gives birth to the

possibility of multiple cases in population dying undiagnosed so the actual number of cases of AMVT in world can be higher than what have been reported in literature. If our patient was not scheduled for a CABG, then just based on transthoracic echocardiogram he would have remained undiagnosed. We also agree that in the absence of other indications, a patient with asymptomatic isolated AMVT not causing left ventricular outflow tract obstruction can be safely followed up at an outpatient basis and no surgical intervention is necessary.

Abstract A31 Figure 1

A32 ABSTRACT WITHDRAWN

A33 ACUTE MYOCARDIAL INFARCTION IN PATIENT WITH INFECTIVE ENDOCARDITIS OF HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY

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10.1136/jim-2018-000745.8

Introduction Coronary artery embolism (CE) is an uncommon cause of acute myocardial infarction (AMI). We present a case of infective endocarditis (IE) of the left ventricular outflow tract (LVOT) in a patient with hypertrophic obstructive cardiomyopathy (HCM) complicated by subsequent CE.

Patient presentation A 28-year-old man with history of HCM was initially admitted to an outside hospital (OSH) for *Haemophilus parainfluenza* bacteremia. He denied intravenous drug use. Transesophageal echocardiogram (TEE) was negative for intracardiac vegetations as well as interventricular pressure gradient and patient was discharged with intravenous antibiotic therapy for presumed IE. Two days later, he subsequently developed left-sided body weakness, left facial droop, slurred speech and returned to same OSH where immediate mechanical thrombectomy resolved his neurologic symptoms. On repeat TEE, a mobile vegetation was adherent to the septal portion of the LVOT and interventricular gradient was present.

Upon immediate transfer to our center, he developed severe chest pain with shortness of breath. Electrocardiogram was significant for lateral Non-ST Segment Elevation Myocardial Infarction with corresponding Troponin-I elevation of 120 ng/mL. Coronary angiography revealed septal emboli of proximal left circumflex and first obtuse marginal branch with Thrombolysis in Myocardial Infarction flow grade 3 present.

He was urgently taken to the operating room for saphenous vein bypass graft to the obtuse marginal artery, embolectomy of left circumflex artery, and myomectomy of the interventricular septum to remove mobile mass. He was discharged 14-days later and remained symptom free after one month.

Discussion AMI is typically caused by thrombotic occlusion of a coronary artery due to underlying atherosclerotic plaque rupture or erosion. The prevalence of non-atherosclerotic AMI is difficult to quantify in the acute clinical setting, although previous studies based on autopsy and coronary angiography findings have characterized the rate of non-atherosclerotic AMI to be 4–7%.¹ Few studies have characterized the prevalence of CE, however, in a 1978 autopsy study, 13% had CE **Infarcts**.² The prevalence of CE-related de novo AMI has been reported at 2.9%, and about 15% of patients had multi-vessel CE. The most common reported cause of CE is atrial fibrillation (73%) whereas septic emboli due to IE accounts for 4% of cases.³

IE is a rare complication of HCM. IE antibiotic prophylaxis (IEAP) had been previously recommended for HCM until 2007 when it was controversially retired citing significant morbidity associated with IEAP and a lack of evidence supporting IEAP efficacy.^{4,5} The estimated prevalence IE in HCM is 3.7 per 1000 patient-years with an incidence 18 to 28 times higher than the general population, respectively.⁶

LVOT obstruction (LVOTO), left atrial enlargement (>5 cm), and dental procedures have been associated with IE in HCM.^{6,7} The high velocity and turbulence of blood flow during systole and resulting mitral-septal contact causes micro-trauma to the mitral valve (MV), aortic valve (AV), and septal endocardium seeding microorganisms.^{6,7} Dilation of the left atrium may reflect severe hemodynamic impairment with increasing LVOTO, mitral regurgitation, and greater endocardium damage.⁶

Of patients with IE in HCM, the MV is the most common site of infection while *streptococcus* spp. are the most frequent causative agents.^{6,7} Septal IE occurred in only 5 of the 84 reported cases of IE in HCM, highlighting the unique nature of our case. Furthermore, dentistry evaluation revealed no evidence of dental infection in our patient.

Conclusion We present a rare case of septal IE in a patient with HCM complicated by CE-related AMI.

A34 PEA ARREST IN PATIENT WITH AL CARDIAC AMYLOIDOSIS

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Introduction Amyloidosis is the deposition of insoluble protein aggregates in extracellular tissue. Clinical manifestation of amyloidosis is dependent on the type of amyloid and the tissue affected. Here we describe a case of cardiac amyloidosis causing PEA arrest.

Case report A 66-years-old male presented with non-specific symptoms of fatigue, decreased appetite, weakness, orthostasis, and syncope. Initial laboratory evaluation showed elevated calcium, abnormal SPEP with faint monoclonal protein, and elevated liver enzymes. Bone marrow biopsy with flow cytometry showed abnormal plasma cell population and Fluorescence In Situ Hybridization (FISH) was negative for myeloma. Tissue samples from sigmoid mucosa and liver biopsy were positive for Congo red staining. A diagnosis of plasma cell dyscrasia with immunoglobulin light chain (AL) amyloidosis was made. Cardiac MRI showed diffuse subendocardial delayed enhancement and thickening of the left ventricular myocardium (figure 1) consistent with cardiac amyloidosis. Our patient underwent autologous peripheral blood

stem cell transplantation for AL amyloidosis treatment. During transfusion, he developed three episodes of Pulseless Electrical Activity (PEA) arrest with Return of Spontaneous Circulation (ROSC) after two minutes of CPR following each arrest. After hospital discharge, he continued to experience syncope from orthostatic hypotension and was started on Midodrine therapy with resolution of symptoms.

Discussion Cardiac amyloidosis is exceptionally rare disease and typically presents with symptoms of heart failure. The deposition of amyloid within the myocardium causes ventricular wall hypertrophy leading to restrictive cardiomyopathy with diastolic dysfunction. Advanced myocardial involvement is associated with conduction abnormalities resulting in sudden cardiac death. Exertional syncope in this patient population is associated with poor prognosis and has been shown to increase mortality at two months.¹ The most common arrhythmias in cardiac amyloidosis are PEA and ventricular arrhythmias.² Small clinical trials of prophylactic intracardiac defibrillator (ICD) implantation have not shown to significantly reduce mortality as the majority of deaths are secondary to electromechanical dissociation.³ However, in selected cases, ICD's have shown to prevent sudden cardiac death related to ventricular arrhythmias.⁴ Managing patients with cardiac amyloidosis continues to be challenging as there is limited evidence and consensus for treatment therapy.

Conclusion Sudden cardiac death is a major cause of mortality in AL cardiac amyloidosis and is often preceded by PEA arrest and ventricular arrhythmias. Patient who presents with exertional syncope should be evaluated on a case by case basis for the potential benefit of ICD insertion.

Abstract A34 Figure 1

A35 MYOSIN BINDING PROTEIN-H LIKE IS A NOVEL MYOFILAMENT COMPONENT IMPLICATED IN ARRHYTHMIA AND DILATED CARDIOMYOPATHY

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Objective Dilated cardiomyopathy (DCM) is a heritable disease and is a major cause of heart failure. Approximately 100

genes have been linked to DCM, nearly all of which exhibit autosomal dominant inheritance with variable expressivity and penetrance. Using whole-genome sequencing, we identified a premature stop variant (R255X) in the *MYBPHL* gene in a family with DCM and congenital conduction system disease. *MYBPHL* encodes a previously unstudied protein, myosin binding protein-H like (MyBP-HL), which is structurally similar to myosin binding protein H (MyBP-H), a skeletal muscle protein, and the cardiomyopathy-associated myosin binding protein C (MyBP-C). Using human induced pluripotent stem cells differentiated to cardiomyocytes from the affected family, we identified that the R255X variant results in a null allele. We characterized heterozygous and homozygous *Mybphl* mutant mice and found systolic dysfunction and atrial and ventricular conduction system abnormalities. We showed that MyBP-HL is highly expressed in human and mouse atria, and is expressed in a small percentage of ventricular cardiomyocytes (VCMs). Based on these findings, we hypothesized that loss of MyBP-HL alters the function of specific VCMs in a manner that allows the development of ventricular arrhythmias and reduced cardiac function.

Methods Adult mouse cardiomyocytes were isolated using collagenase digestion on a retrograde perfusion Langendorff apparatus. Frozen whole hearts were sectioned 5 μ m thick. Cardiomyocytes and sectioned tissue were stained using MyBP-HL, cMyBP-C, and Cntn2 antibodies. Immunofluorescence microscopy was performed with an epifluorescent or a confocal structured illumination microscope.

Results Loss of MyBP-HL results in arrhythmia; therefore, we hypothesized that MyBP-HL may be expressed in the ventricular conduction system (VCS). We evaluated MyBP-HL protein expression in hearts and isolated VCMs from *Mybphl* WT, Het, and Null mice. In WT hearts, ~1 in 200,000 VCMs expressed MyBP-HL while the frequency of MyBP-HL+ VCMs in Het samples was only 10% of WT levels. MyBP-HL+ cardiomyocytes were enriched in the right ventricular free wall of WT hearts, with a significant reduction of MyBP-HL+ cells in the whole heart and RV free wall in Het hearts. The VCS was evaluated with the marker contactin-2 (Cntn2) and co-stained with MyBP-HL. MyBP-HL was observed to be co-expressed in Cntn2+ VCMs in the transition zone between atrial and ventricular tissue around the AV node. MyBP-HL+ cells also were observed in a subset of Cntn2+ Purkinje fibers. Interestingly, many MyBP-HL+ VCMs were not in the VCS, suggesting an additional role for those cells in regulating ventricular contraction. As little is known about normal MyBP-HL incorporation in the myofilament, we used structured illumination microscopy to generate super-resolution images of myofilaments from atrial cardiomyocytes. MyBP-HL co-localized with cMyBP-C in the C-zone of these cardiomyocytes, but also occupied additional space towards the M-line of the sarcomere. This localization was not altered in atrial cardiomyocytes from Het hearts. This localization pattern suggests a distinct interaction of MyBP-HL with the coiled-coil tails of myosin thick filaments originating from the M-line.

Conclusions Following the discovery that loss of MyBP-HL is associated with cardiac dysfunction and conduction system abnormalities, we have now identified that MyBP-HL associates with the VCS and heterozygous loss of MyBP-HL dramatically reduces the total number of MyBP-HL+ ventricular cardiomyocytes. These data suggest that loss of MyBP-HL may

deregulate critical regions of the VCS through cardiomyocyte disruption, leading to arrhythmias and ventricular dysfunction.

A36

HIF-1 α IS REQUIRED FOR FLOW-MEDIATED REGULATION OF ENDOTHELIAL CELL METABOLISM

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Objective Endothelial cell (EC) dysfunction and activation is a characteristic feature of sepsis, a condition marked by cytokine storm and disturbed blood flow, which by itself can lead to further activation of ECs and increased pro-inflammatory changes. EC dysfunction caused by disturbed blood flow is also a hallmark of chronic conditions such as atherosclerosis. In contrast, laminar blood flow promotes endothelial health and maintains the vascular integrity. Thus, flow-mediated mechanical regulation of endothelial health plays a critical role in health and disease. Increasing evidence suggests that metabolic reprogramming may play a role in EC activation. However, how flow induces changes in EC metabolism has not been fully explored.

Method We subjected human aortic ECs (HAECs) to either disturbed or laminar flow via a cone-plate viscometer system and performed RNA-seq. Data were analyzed with gene-set enrichment analysis, Ingenuity Pathway analysis, and gene ontological methods. We also measured gene (qRT-PCR) and protein (Western blotting) expression of glycolytic enzymes and pro-inflammatory cytokines. Glycolytic and mitochondrial functions were assessed by bioenergetics measurements (Seahorse), and microscopy. ROS generation was measured using CellROX. We also obtained mouse and porcine aortas for further analysis.

Results We found that disturbed flow significantly induces transcriptomic pathways involved in glycolysis. Bioinformatic analysis was confirmed via Seahorse assays, which showed increased glycolytic and reduced mitochondrial capacity in HAECs subjected to disturbed flow compared to laminar flow. Importantly, these metabolic alterations were required for HAEC activation and upregulation of inflammatory genes. HIF-1 α knockdown reversed the effect of disturbed flow on metabolism and inhibited the upregulation of glycolysis and reduction in mitochondrial capacity, as well as disturbed flow-induced inflammation. By sequentially inhibiting metabolic entry points into the mitochondria, we found that the mitochondria capacity is limited by substrate availability via pyruvate dehydrogenase activity kinase-1, which controls pyruvate levels in mitochondria, and is induced by HIF-1 α . Mechanistically, we demonstrate that HIF-1 α is stabilized by NOX4-dependent ROS generation due to an increased availability of NADH, itself present at a higher level due to decreased mitochondrial utilization under disturbed flow. Lastly, we found that NOX4, ROS, and HIF-1 α levels are higher in disturbed flow regions of pig aortas, compared to laminar flow regions.

Conclusion These results demonstrate that flow mediated mechanical forces drive metabolic changes in ECs, increasing glycolysis and reducing mitochondrial function by a HIF-1 α dependent mechanism. These metabolic changes are required for EC activation.

A55 ACUTE ANGIOTENSIN-(1-7) ADMINISTRATION DOES NOT LOWER BLOOD PRESSURE IN ESSENTIAL HYPERTENSION

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Objective The renin-angiotensin system (RAS) is a critical hormonal regulator of blood pressure. Over-activation of the RAS, and in particular the hormone angiotensin II, contributes to hypertension and cardiovascular diseases via numerous mechanisms including vasoconstriction, sympathetic activation, oxidative stress, and inflammation. Emerging evidence suggests that the deleterious cardiovascular actions of angiotensin II are opposed by the counter-regulatory hormone angiotensin-(1-7). Deficiency of circulating angiotensin-(1-7) is found in animal models of hypertension and chronic restoration of this hormone produces vasodilation to lower blood pressure in these models. There are limited and conflicting clinical studies with angiotensin-(1-7), however, and it is unclear if this hormone contributes to blood pressure regulation in humans. We propose that difficulties in showing cardiovascular effects of angiotensin-(1-7) in previous clinical studies relates to arterial baroreflex buffering to prevent changes in blood pressure. The objective of this study was to test the hypothesis that angiotensin-(1-7) would produce negligible effects on blood pressure with intact baroreceptors, and that its cardiovascular effects would be unmasked following elimination of baroreflexes.

Method To test this, we examined the effects of acute intravenous angiotensin-(1-7) infusion (ascending doses from 0.5 to 20 ng/kg/min) on supine blood pressure in subjects with essential hypertension under intact conditions and following acute autonomic withdrawal with the ganglionic blocker trimethaphan in a randomized, open-label, crossover study. Blood pressure was restored to baseline levels following autonomic blockade with individually titrated phenylephrine doses.

Results Seven subjects with essential hypertension completed this study (6 male; 48±4 years of age; 29±2 body mass index). All subjects were withdrawn from antihypertensive medications for at least two weeks, and were placed on a fixed sodium diet for three days, before each study day. When comparing change from baseline to maximum dose, angiotensin-(1-7) did not alter systemic hemodynamics under intact conditions (systolic blood pressure: 3±4 mmHg; diastolic blood pressure: 3±1 mmHg; heart rate: 0±1 bpm). In contrast to our hypothesis, angiotensin-(1-7) did not elicit a blood pressure-lowering effect under autonomic blockade (systolic blood pressure: 10±8 mmHg, $p=0.299$ vs. intact; diastolic blood pressure: 7±3 mmHg, $p=0.512$; heart rate: -2±1 bpm, $p=0.166$). Plasma angiotensin-(1-7) was measured in four subjects and showed an approximate 10-fold increase with infusions [8±4 baseline vs. 93±7 pg/mL after Ang-(1-7)], to levels within a physiologic range.

Conclusion Our data suggest that angiotensin-(1-7) infusion does not acutely induce vasodilation to lower blood pressure in essential hypertension. While chronic studies are needed, these findings provide new insight into acute regulation of the cardiovascular system by angiotensin-(1-7) in human hypertension.

B37 ROLE OF VITAMIN D INSUFFICIENCY AND/OR DEFICIENCY IN PATIENTS WITH HEART FAILURE AND REDUCED EJECTION FRACTION

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Introduction Lower vitamin D level has been linked to increased adverse outcomes in patients with heart failure and reduced ejection fraction (HFrEF). However, its significance in predicting these outcomes has not been well-illustrated. Our study evaluates the role of vitamin D insufficiency and deficiency in predicting 30-day readmission rate and length of stay (LOS) in patients with HFrEF admitted for acute heart failure syndrome (AHFS).

Methods A retrospective analysis of 2,087 patients admitted between January 1, 2005 and December 31, 2014 for AHFS. Patients without vitamin D level measured as 25-dihydroxyvitamin D (25[OH]D) were excluded. Normal 25(OH)D levels, insufficiency and deficiency were defined as ≥30 ng/mL, 20-29 ng/mL, and <20 ng/mL, respectively.

Results Of 2,087 patients admitted for AHFS, 180 had HFrEF and documented vitamin D levels, of which 42 (23.3%) had normal 25(OH)D levels, 83 (46.1%) had deficiency and 55 (30.6%) had insufficiency. In HFrEF-25(OH)D deficiency group, average age upon admission for AHFS was 62.7 years versus 69.9 years in HFrEF-normal 25(OH)D ($p=0.007$). After standardizing medical therapy and comorbidities in each group, the 30-day readmission rate among HFrEF-25(OH)D deficiency group was 40% versus 16.6% in HFrEF-normal 25(OH)D (OR: 3.4, 95% CI: 1.3 to 9.3, $p=0.01$). Average LOS in HFrEF-25(OH)D deficiency group was 8.2 days versus 4.1 days in HFrEF-normal 25(OH)D level ($p=0.04$). Mortality rate did not differ between the two groups ($p=0.7$). In HFrEF-25(OH)D insufficiency group, average age upon admission for AHFS was 69 years versus 69.9 years in HFrEF-normal 25(OH)D ($p=0.9$). The 30-day readmission rate was 29% in HFrEF-25(OH)D insufficiency group versus 16.6% in HFrEF-normal 25(OH)D group (OR: 2.1, 95% CI: 0.8 to 5.6, $p=0.2$). LOS was 7.2 days in HFrEF-25(OH)D insufficiency group vs 4.1 in HFrEF-normal 25(OH)D group ($p=0.3$). Mortality rate did not differ between both groups ($p=0.9$).

Conclusion Vitamin D deficiency, but not insufficiency, seems to be a significant predictor for an early age of hospitalization, higher 30-day readmission rate and LOS among HFrEF patients admitted for AHFS. Further studies are warranted to evaluate vitamin D supplementation on outcomes.

B38 CORONARY ARTERY DISEASE AND THE IMPACT OF AUTOIMMUNE DISEASES (RA, PSORIASIS AND SLE) ON THE SEVERITY, TYPE OF PRESENTATION AND PREVALENCE: A RETROSPECTIVE ANALYSIS

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Background It is well-known that Coronary artery disease (CAD) is more prevalent among patients with various types of autoimmune diseases such as rheumatoid arthritis (RA), psoriasis and systemic lupus erythematosus (SLE) among others.

Aim Evaluating the extent and severity, type of presentation and prevalence of CAD among patients with SLE, RA and psoriasis.

Methods A retrospective analysis of 8,978 patients who had cardiac catheterization between 01/01/2005–12/31/2016. Patients with documented history of SLE, RA or psoriasis were compared, as one group then separately, with those without history of autoimmune disease.

Results Of 8,978 patients underwent cardiac catheterization, 86 (1%) had history of RA, psoriasis or SLE, of them 80 (87.2%) had CAD versus 7539/8892 (84.8%) without autoimmune disease (OR: 2.4, 95% CI: 1.04 to 5.5, $p=0.03$). Average age in CAD-autoimmune disease group was 60.2 years versus 61.5 years in CAD without autoimmune disease ($p=0.1$). Patients without autoimmune disease presented more as acute coronary syndrome (OR: 2.4, 95% CI: 1.4 to 3.9, $p<0.001$), while autoimmune disease patients presented more as stable angina (OR: 1.5, 95% CI: 1.1 to 2.3, $p=0.02$). In CAD-autoimmune disease, 47.7% of patients found non-obstructive CAD versus 26.6% in CAD-without autoimmune disease (OR: 2.6, 95% CI: 1.6 to 3.9, $p=0.001$). Separate comparisons between patients with no autoimmune disease versus those with RA, Psoriasis and SLE are illustrated in tables 1, 2, 3 respectively. Patients with CAD-autoimmune disease had higher ESR (50 mm/hr) and CRP (4.5 mg/dl) compared to <10 mm/hr and <1 mg/dl, respectively, in autoimmune disease without CAD ($p=0.01$, 0.03, respectively).

Conclusion Prevalence of CAD in patients with psoriasis, RA or SLE is higher than those without any. Majority of them were found to have non-obstructive disease with single vessel disease. Elevation in CRP and ESR can explain the underlying inflammatory process of CAD among those patients.

B39 EVALUATION OF THE EXTENT OF CORONARY ARTERY DISEASE AMONG PATIENTS WITH SOLID CANCER: A RETROSPECTIVE ANALYSIS

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Background As the number of cancer survivors continues to grow with advancement of available therapies, their risk of having cardiovascular complications, especially Coronary artery disease (CAD), needs to be further illustrated.

Aim Assessing risk and extent of CAD among patients with solid cancer, and the role played by chemotherapy and/or radiotherapy on that risk.

Methods A retrospective study of 8,997 patients who presented with chest pain and underwent cardiac catheterization between 01/01/2005 and 12/31/2016. Patients with history of solid cancer were identified by chart review.

Results Of 8,997 patients who had cardiac catheterization, 180 had documented history of solid cancer, of them, 150 (83.3%) had evidence of CAD versus 7,673/8,997 patients (85.3%) without history of solid cancer who had CAD (OR: 0.8, 95% CI: 0.5 to 1.3, $p=0.4$). Presentation as stable angina

noted in 122 (81.3%) patients in CAD-cancer group versus 5201 (67.8%) in CAD-no cancer group (OR: 2.1, 95% CI: 1.4 to 3.1, $p<0.001$). The average period between the diagnosis of cancer and CAD was 4.5 years (SD: ± 0.9). CAD-cancer group had higher rate of non-obstructive CAD compared to CAD-no cancer one (OR: 1.1, 95% CI: 0.7 to 1.6, $p=0.6$). No difference between the two groups in terms of single or multiple vessel disease (OR: 0.9, 95% CI: 0.7 to 1.3, $p=0.7$). In CAD-cancer group, those who received chemotherapy and/or radiotherapy had higher risk of obstructive CAD compared to those who did not (OR: 3.8, 95% CI: 2.1 to 7, $p<0.001$). In CAD-cancer group, 53 patients (35.3%) had prostate cancer, 43 (28.7%) breast, 8 (5.3%) colon, 4 (2.7%) gastric, 5 (3.3%) thyroid, 8 (5.3%) bladder, 5 (3.3%) lung, and 24 (16%) had other types of cancer. Prostate cancer patients had higher risk of CAD compared to non-prostate cancer group (OR: 4.7, 95% CI: 2.2 to 7.2, $p=0.03$) without age difference. Similarly, breast cancer patients had lower risk of CAD compared to non-breast cancer group (OR: 0.5, 95% CI: 0.3 to 0.8, $p=0.008$).

Conclusion Patients with solid cancer have about the same risk and severity of CAD compared to those without cancer. However, exposure to chemotherapy and/or radiation carried a significant higher risk of obstructive CAD. Furthermore, prostate cancer had the highest risk of CAD among all other solid cancers.

B40 UTILIZATION OF ROUTINE LABS TO DETERMINE LENGTH OF STAY, MORTALITY AND READMISSION RATES FOR PATIENTS ADMITTED FOR ACUTE HEART FAILURE SYNDROME

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Background Heart failure (HF) carries a huge burden on healthcare in The United States with a prevalence of around 5.7 million patients and an annual healthcare cost of approximately \$30.7 billion. With a 5-year survival rate of around 50%, HF is a leading cause of morbidity, mortality, and frequent hospital readmissions. Many strategies have been tested to subjectively monitor these patients; however, a more standardized, widely-accepted strategy to risk stratify HF patients would likely have significant beneficial effects on overall patient outcomes and healthcare costs. With this study, we attempt to gain further insight into the role of routine labs and its association with length of stay (LOS), readmission rate, and all-cause mortality during the same hospitalization.

Methods We randomly determined 2059 patients who were admitted to inpatient medicine between 2005 to 2014 with a diagnosis of acute heart failure. All patients irrespective of their ejection fraction were included in the study. A retrospective analysis was done on routine admission labs, such as CBC and electrolytes, to determine whether they carry any correlation to readmission, length of stay, and mortality rates. Binary logistic regression was utilized to determine the odds ratio.

Results Out of 2059 patients, 1118 (54.3%) were male and 940 (45.7%) were female; 1912 patients (92.9%) had an EF of 50% or less, and 146 patients (7.1%) had an EF of more than 50%.

Mean LOS for patients with sodium (Na) at levels less than 135, 135 to 150, and greater than 150 were 6.8385,

5.5683, and 5.5000 days respectively. We subcategorized data into Na levels less than 125 when compared with levels greater than 125, were found to have higher 24-month readmission rate [OR: 1.91, 95% CI: 0.99 to 3.69, $p=0.052$] and no significant association for 1-month, 6-month, and 12-month readmission rates or mortality during hospitalization.

Mean LOS for patients with potassium (K) at levels less than 3.5, 3.5 to 5, and greater than 5 were 7.2213, 5.4812, and 7.4313 days respectively. We subcategorized data into K levels greater than 5 and compared with less than 5, and found lower readmission rate at 24 months [OR: 0.764, 95% CI: 0.59 to 0.99, $p=0.043$], at 12 months [OR: 0.71, 95% CI: 0.54 to 0.92, $p=0.009$] at 6 months [OR: 0.69, 95% CI: 0.53 to 0.89, $p=0.005$] and 1-month readmission [OR: 0.53, 95% CI: 0.39 to 0.72, $p=0.000$].

Mean LOS for patients with Chloride (Cl) at levels less than 95, 96 to 110, and greater than 110 were 7.3446, 5.8048, and 4.9456 days respectively. We subcategorizing data based on Cl greater than 110 and compared with Cl less than 110, and found low readmission rate at 24 months [OR: 0.57, 95% CI: 0.39 to 0.82, $p=0.002$], at 12 months [OR: 0.52, 95% CI: 0.37 to 0.74, $p=0.000$], at 6 months [OR: 0.57, 95% CI: 0.40 to 0.80, $p=0.001$] and no significant association for 1-month readmission.

Patients with bicarbonate at levels less than 23, 24 to 32, and greater than 33 were found to have mean LOS of 6.2253, 5.5466 and 7.3793 days respectively, however did not demonstrate statistically significant correlation with readmission rates or mortality during hospitalization

Mean LOS for Hemoglobin (Hb) at levels 9 or less, and greater than 9 were 8.6345 and 5.5828 days respectively. Hb levels showed decreased risk of readmission at 24 months [OR: 0.95, 95% CI: 0.91 to 0.97, $p=0.006$], at 12 months [OR: 0.95, 95% CI: 0.91 to 0.95, $p=0.007$], at 6 months [OR: 0.93, 95% CI: 0.90 to 0.97, $p=0.001$] and at 1 months [OR: 0.94, 95% CI: 0.89 to 0.99, $p=0.015$]. We subcategorizing data based on Hb less than or equal to 9 and compared with Cl greater than 9, and found higher readmission rate at 12 months [OR: 1.396, 95% CI: 1.04 to 1.87, $p=0.026$], at 6 months [OR: 1.494, 95% CI: 1.11 to 2.01, $p=0.008$] and no significant association with 1-month and 24-month readmission, and mortality during hospitalization.

WBC at levels <4000, 4000–11,000, and >11,000 had a mean LOS of 5.8590, 5.6420, and 6.8757 days respectively. In the study population, platelets and WBCs were found to have no significant association with readmission and mortality. **Conclusions** As routine labs like CBC and electrolytes have a direct correlation with LOS and readmission rates, validating these results with multi-centric studies and identifying high-risk patients to ensure closer follow up during and after hospitalization may have a positive impact on improving the outcomes of patients with HF.

B41 VALIDITY OF THE ALIVECOR SOFTWARE IN DETECTING PAROXYSMAL ATRIAL FIBRILLATION: A SUB STUDY OF THE INTERMITTENT VS CONTINUOUS ANTICOAGULATION THERAPY IN PATIENTS WITH ATRIAL FIBRILLATION (iCARE-AF) PILOT STUDY

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Introduction The Intermittent vs. Continuous Anticoagulation therapy in patients with Atrial Fibrillation (iCARE-AF) randomized pilot study was a recent trial conducted at University of Oklahoma Health Sciences Center examining the feasibility of using the AliveCor Heart Rhythm monitoring device as a means of guiding anticoagulation during episodes of paroxysmal atrial fibrillation. We conducted a sub analysis of the study to determine the sensitivity and specificity of the AliveCor software in accurately diagnosing episodes of atrial fibrillation.

Method Patients with paroxysmal atrial fibrillation were blindly randomized to receive an iPhone-based rhythm-monitoring device and instructed to send a daily 30 second single lead ECG for evaluation. A random month from the iCARE-AF study was selected for analysis. Two blinded physicians then individually interpreted the ECGs submitted from that month. Any discrepancy in the interpretation of an individual ECG was sent to another physician for final interpretation. The AliveCor software was then used to interpret the ECGs. The AliveCor software algorithm utilized the RR interval and the presence or absence of P waves for detecting atrial fibrillation.

Results Fifty-eight total patients were enrolled in the (iCARE-AF) randomized pilot study. Twenty-nine patients were randomized to receive an iPhone-based rhythm-monitoring device. A total of 239 ECGs were analyzed. Eight total ECGs had a discrepancy between physician interpretation and were sent for further analysis before final interpretation. A total of 21 episodes of AF were detected. The AliveCor software had 100% sensitivity and 91% specificity for the detection of atrial fibrillation.

Conclusion The iPhone based rhythm monitoring device is valid means of detecting atrial fibrillation in patients with paroxysmal atrial fibrillation. Further study is needed before the device can be used to manage patients with atrial fibrillation.

B42 MENTAL STRESS-INDUCED MYOCARDIAL ISCHEMIA: A SYSTEMATIC REVIEW OF THE LITERATURE

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Background There is robust evidence that psychosocial factors play a central role in the development of ischemic heart disease, and the body of literature on mental stress-induced myocardial ischemia (MSIMI) is rapidly growing. With the development of mental stress testing, it is now possible to directly measure the impact of this particular type of stress on the heart. We conducted a systematic review on MSIMI, with a focus on the unique responses of men and women to mental stress.

Methods A systematic search of PubMed was conducted for articles published between 1996 and 2017. Peer-reviewed articles in the English language involving mental stress testing in adult patients with known or suspected heart disease (IHD) were selected for examination. The bibliographies of all articles were reviewed to ensure inclusion of the broadest possible scope of data. Studies using ECG assessment, transthoracic echocardiography, and radionuclide ventriculography for diagnosis were included.

Results 183 articles were identified, and 21 met inclusion criteria. Of these, 2 were randomized controlled trials, 18 were

prospective observational studies, and 1 was a case control study. MSIMI was defined variably as left ventricular segmental wall motion abnormality (n=5), perfusion defect (n=10), or reduction in left ventricular ejection fraction by $\geq 5\%$ from resting measurement (n=6). A public speaking task was the most commonly used mental stressor (n=10). Other forms of mental stress tasks included mental arithmetic in 2 studies, Stroop color test in one study, and a combination of stressors in 5 studies. 31.6% of studies utilized radionuclide angiography, 52.6% utilized nuclear perfusion, and 21.0% utilized echocardiography as the modality (or modalities) of choice to examine ischemia.

Of the 4156 patients in the selected literature, 1102 were women (26.5%). 4.7% of studies had no female participants. 96.7% of patients had stable ischemic heart disease, while the remaining 3.3% were either post-myocardial infarction patients or healthy subjects. The overall prevalence of MSIMI was 31.2%, with a prevalence of 28.9% among men and 36.6% among women. Five studies have investigated potential causes of this sex difference, with proposed mechanisms including microvascular dysfunction and unique psychological risk factors in women. Long term survival data was available in 865 patients. MSIMI was independently associated with reduced survival time in all six studies that measured this outcome. In one study, every 5% drop in left ventricular ejection fraction in response to mental stress was associated with a 5% increase in the probability of all-cause mortality and hospitalizations for cardiac causes over a median follow up period of 4 years. Studies on prevention and treatment of MSIMI have focused largely on antidepressant therapy or psychosocial intervention, but the effect of these modalities on survival has yet to be explored.

Conclusions MSIMI is common in patients with IHD, with a prevalence of over 30%. Women appear to be more susceptible to MSIMI, and the mechanism underlying this observation merits further exploration. Optimal treatment of MSIMI is not yet defined and should be investigated in prospective studies.

B43 A CASE OF CLOZAPINE INDUCED MYOCARDITIS

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Introduction Clozapine is an effective neuroleptic in the treatment of schizophrenia, however it is associated with life-threatening side effects including myocarditis and agranulocytosis. Myocarditis affects approximately 0.7% to 1.4% of patient being treated with Clozapine¹ and generally present acutely during initiation of Clozapine therapy. Here we present a case of myocarditis two weeks after initiating Clozapine therapy.

Case report A 33-years old male who was admitted for psychosis that was refractory to Valproic Acid, Risperidone and Haloperidol. Clozapine was started at 25 mg nightly and titrated up to 250 mg over a course of 14 days. Serum Clozapine level was 452 ng/mL on day 15. Our patient had persistent tachycardia without fever after three days of Clozapine therapy. On day 14 he developed chest pain. Electrocardiogram (ECG) revealed sinus tachycardia with less than 1-millimeter ST-segment elevation in leads II, V2, V3 and V5, and V6. Troponin was elevated at 3.455 ng/ml. Dual antiplatelet

therapy with Aspirin and Plavix was initiated along with therapeutic Lovenox anticoagulation. Echocardiogram revealed normal left ventricular function with no regional wall motion abnormalities and CT coronary angiogram showed widely patent coronary arteries. Prominent eosinophilia of 7.4% was found on laboratory data. Clozapine therapy was discontinued leading to resolution of symptoms.

Discussion Clozapine induced myocarditis is a rare event generally occurring within the first 4 weeks of initiating treatment. Myocardial damage is thought to be from an immunoglobulin-E mediated hypersensitivity reaction¹ given positive eosinophilic infiltrates on autopsy of fatal cases of Clozapine induced myocarditis.² In one study of 116 patients who developed myocarditis following Clozapine treatment, 74% of cases occurred in the first 4 weeks.¹ Although eosinophilia is associated with Clozapine-induced myocarditis, a definitive diagnosis can be difficult as the eosinophilic reaction can be delayed up to 7 days following troponin elevation.¹ For patients who develop persistent tachycardia with or without fever and chest pain while on Clozapine therapy, drug induced myocarditis should be considered in the differential diagnosis. The primary treatment includes the cessation of Clozapine and hemodynamic support which has been shown to reduce mortality.³

Conclusion Clozapine is an effective neuroleptic in the treatment of schizophrenia but clinical vigilance of the potential life-threatening side effects is paramount. If tachycardia, fever, or chest pain develop while on Clozapine therapy, immediate cessation of the drug is warranted until a precise diagnosis is made to prevent mortality.

B44 NEW ONSET CONGESTIVE HEART FAILURE WITH POLYCYTHEMIA VERA

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Polycythemia vera (PV) is a myeloproliferative neoplasm marked by increased hematocrit resulting in increased blood viscosity and hypercoagulability. It is traditionally associated with adverse cardiac events due to its propensity to trigger ischemic events. However, reports of acute congestive heart failure with dilated cardiomyopathy related to microinfarcts in PV are exceedingly rare (Konopka A, *et al.* 1998; Monyk BC, *et al.* 2016).

A 58 year-old male with no significant past medical history and no evidence of recent infectious illness presented to an outside hospital with symptoms and signs consistent with acute congestive heart failure and atrial fibrillation with rapid ventricular response. The initial echocardiogram revealed dilated cardiomyopathy with global hypokinesis and significantly reduced ejection fraction (28%). Coronary angiography was negative for significant coronary artery disease or signs of ischemia that would explain the patient's presentation. Atrial fibrillation was rate controlled on high dose beta-blocker. Heart failure was managed with diuresis, beta blocker and ACE inhibitor. Routine laboratory studies were positive for marked thrombocytosis, leukocytosis, and polycythemia. Peripheral smear narrowed our differential to myeloproliferative or myelodysplastic process. Bone marrow biopsy findings, presence of JAK2 V617F mutation, and low erythropoietin

level were suggestive of polycythemia rubra vera. The patient received therapeutic phlebotomy and was started on low-dose aspirin. At discharge, the patient was clinically asymptomatic and scheduled for outpatient follow-up for further workup of heart failure etiology.

To the best of our knowledge, we report the first case of PV-induced non-ischemic cardiomyopathy resulting in acute heart failure in the United States. Our patient did not have a past medical history of any risk factors for heart failure. After exclusion of common etiologies of acute heart failure, we believe that patient had PV-induced cardiomyopathy due to microinfarcts.

B59 ANTICOAGULATION FOR ATRIAL FIBRILLATION FOLLOWING GI BLEED IN PATIENTS WITH HIGH HASBLED AND CHADS2VASC SCORES

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Objective Physicians are often faced with the dilemma, to anticoagulate or not, when a patient with atrial fibrillation and high risk for stroke as well as major bleeding is admitted for GI bleed. We aim to compare outcomes in patients with high HASBLED and CHADS2Vasc Scores who were discharged on anticoagulation with those who were not.

Method A retrospective chart analysis was performed for all patients with nonvalvular atrial fibrillation on oral anticoagulation who were admitted for GI bleed with a HASBLED score more than or equal to 3 and CHADS2Vasc score >1. A total of 81 patients were included from January 2013 to January 2017. Patients were further divided in two groups, in group 1 (n=31) anticoagulation was restarted at discharge and in group 2 (n=50) anticoagulation was discontinued. Categorical data was analyzed using Chi square test or Fischer's Exact test and continuous variables were compared using Student t test.

Results Mean age in group 1 was 81.18 ± 7.29 years and in group 2 was 79.2 ± 8.84 years ($p=0.303$). 77.4% in group 1 were male vs 47% males in group 2 ($p=0.008$). The mean CHADS2Vasc score in group 1 was 4.52 ± 1.18 vs 3.96 ± 1.58 in group 2 ($p=0.0949$). Mean HASBLED score in group 1 was 3.77 ± 0.72 vs 3.44 ± 0.61 in group 2 ($p=0.0281$). Readmission for GI bleed was seen in 25.8% in group 1 compared to 20% in group 2, ($p=0.923$). Readmission within 1 year for stroke was not seen in any patient in group 1 compared to 6% in group 2 ($p=0.001$).

Conclusion Incidence of stroke was significantly higher in the group that did not continue anticoagulation at discharge. They also had a significantly lower HASBLED score. Our data suggests that when faced with a patient with high risk for stroke and bleeding based on CHADS2Vasc and HASBLED scores, patients are more likely to have worse outcomes if not discharged on anticoagulation.

B60 GALECTIN-3 AS A RISK PREDICTOR OF SUDDEN CARDIAC ARREST IN ISCHEMIC CARDIOMYOPATHY

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Objective Sudden cardiac arrest (SCA) is a common and catastrophic complication of ischemic cardiomyopathy. Currently, left ventricular (LV) function is the only parameter identifying patients at highest risk for SCA. However, many patients with ischemic cardiomyopathy develop SCA despite having preserved LV function. There are no known serum biomarkers that are predictive of SCA in these patients. We tested the hypothesis that serum galectin-3, implicated in cardiac fibrosis, can predict the risk of SCA and early (30-day) mortality after SCA in patients with ischemic cardiomyopathy.

Method We studied two different patient cohorts of coronary artery disease. The *first study group* included 204 patients with ischemic cardiomyopathy and severely reduced LV function (Ejection fraction <35%). These patients were followed up for 4.1 years to determine the incidence of emergent SCA. The *second study group* included patients with coronary artery disease who survived the first episode of out-of-hospital cardiac arrest. These patients were followed up for 30-days to determine the early mortality after SCA. We measured serum galectin-3 levels in both study cohorts comparing survivors vs. the patients who either developed SCA (*first study group*), or died within 30-days of emergent SCA (*second study group*).

Results After 4.1 years of follow up in the *first study group*, the incidence of SCA was 16.2%. Binary logistic regression analysis showed galectin-3 as a potential predictor of SCA in this cohort (galectin-3, *ng/ml*: survival, 9.4 ± 3.6 , N=108; SCA, 11.1 ± 5.6 , N=28, $p<0.05$). Among the survivors of out-of-hospital cardiac arrest (*second study group*), multivariate analysis showed galectin-3 as a strong predictor of 30-day mortality (galectin-3, *ng/ml*, survival, 26.7 ± 19.4 , N=23; death, 48.1 ± 21.8 , N=18, $p=0.002$).

Conclusion Elevated serum galectin-3 can predict SCA in patients with severe ischemic cardiomyopathy. In the survivors of out-of-hospital cardiac arrest, higher serum galectin-3 levels are associated with increased chances of death within 30-days of the first episode of cardiac arrest. These findings have implications for the early identification of patients at risk of SCA and consequent death, and need for automatic defibrillator implantation.

B61 ST-ELEVATION MYOCARDIAL INFARCTION LEADING TO EMPHYSEMATOUS CHOLECYSTITIS AND SEPTIC SHOCK

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Introduction ST-Elevation Myocardial Infarction (STEMI) is a well-known and serious medical dilemma often seen within the emergency room. Depending on the amount of myocardium involved and impact on systemic perfusion pressure, there can be many sequelae following STEMI including anoxic brain injury, shock liver, and acute tubular necrosis to name a few. However, to our knowledge, emphysematous cholecystitis (EC) has yet to be documented in literature as a secondary effect following STEMI. We present an unusual case of EC leading to septic shock following a STEMI.

Case presentation A 65-year-old man with hypertension, diabetes mellitus, and tobacco dependence presented to our hospital with sudden onset chest pain, nausea, vomiting, severe hypotension, and bradycardia. He was afebrile without leukocytosis and had unremarkable liver enzymes. ECG revealed inferior STEMI (figure 1) with corresponding Troponin-I of 4.984 ng/ml. He was loaded

with aspirin and ticagrelor and started on a dopamine drip before undergoing coronary angiography which revealed 99% acute thrombotic subtotal occlusion of a dominant mid-left circumflex artery with Thrombolysis In Myocardial Infarction (TIMI) 2 flow secondary to plaque rupture (figure 2). A Synergy 3.0 × 20mm drug eluting stent was placed resulting in 0% stenosis and TIMI-3 flow with resolution of his chest pain. Two days later, he developed fever, right upper quadrant abdominal pain, tachycardia, and recurrent hypotension. Laboratory data was significant for white blood cell count of $18.0 \times 10^3/\mu\text{L}$, lactic acid of 3.2 mmol/L, total bilirubin 27.6 mg/dL predominantly unconjugated, and hepatocellular injury pattern on liver enzymes. CT abdominal imaging revealed gas in the gallbladder (GB) wall with moderate pneumobilia (figure 3) and two intrahepatic gas containing foci (figure 4). He was urgently intubated, started on intravenous antibiotic and pressor therapies, and taken to operating room for open cholecystectomy. Within 48-hours of abdominal pain presentation, he developed multi-organ failure secondary to worsening septic shock due to *Methicillin-Resistant Staphylococcus aureus* (MRSA) bacteremia and *Clostridium perfringens* within the biliary tree. Despite continued hemodynamic support and appropriate anti-infective therapies, he continued to clinically deteriorate and expired soon after he was made comfort care.

Abstract B61 Figure 1 Electrocardiogram showing sinus bradycardia with inferior ST-segment elevation in leads II, III, aVF and anterior ST-segment depression in leads V1–V4

Abstract B61 Figure 2 Coronary angiogram show 99% occlusion of dominant mid-left circumflex artery

Abstract B61 Figure 3 CT abdomen with contrast showing gas in the gallbladder wall and lumen representing emphysematous cholecystitis with moderate pneumobilia

Abstract B61 Figure 4 CT abdomen with contrast showing 1 to 2 intrahepatic gas containing foci likely representing abscess formation

Discussion EC is an uncommon diagnosis caused by infection of the gallbladder wall by gas-forming organisms which accounts for 1–3% of all acute cholecystitis presentations. It is mostly commonly seen in diabetic men who are greater than 50-years-old with peripheral vascular disease¹. GB ischemia leading to necrosis is considered the key inciting event for this life-threatening condition which allows for secondary infection¹. There have been cases reported in patients undergoing hemodialysis given the large hemodynamic changes affecting visceral circulation, and no cases have been reported in current literature following a myocardial injury event. We believe that because of the reduced perfusion pressure to the

GB via the cystic artery, our patient developed an acute ischemic event leading to infarction and necrosis allowing spread of gas-forming organisms with resultant spread throughout the biliary tree and into the liver causing profound septic shock.

Conclusion This case highlights the challenging management of a common patient presentation leading to an uncommon and life-threatening diagnosis. While our patient was successfully treated for his myocardial infarction, all efforts at reversing his severe septic shock were not enough to prevent his passing.

C19 IMPACT OF CREATION OF NATIONAL HEART VALVE DISEASE AWARENESS DAY ON PUBLIC ENGAGEMENT ONLINE AND SUBSEQUENT CREATION OF WEBSITE/ IPHONE APPLICATION FOR PUBLIC AWARENESS

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Objective/background Internet-based tools allow individuals to gather and communicate their ideas and information. Use of internet by the general public has increased sharply over the past decade. Internet provides opportunity to health care professionals to create awareness, to educate people on health care issues & new advances in medical field. As many as five million Americans are estimated to have heart valve diseases, which occurs if one or more of heart valves don't work properly, but 2/3 people know nothing about these diseases at the time of diagnosis. Even after such widespread prevalence of these diseases and innovations in its management, public awareness about heart valve disease stays alarmingly low. It is for this reason that 21 national organizations joined together to establish the first-ever National Heart Valve Disease Awareness Day on Feb. 22, 2017. We planned to analyze the impact of creation of this day on public engagement and discussions online and how these trends changed over a period of one year. Subsequent online educational tool was created by a trainee led team.

Methods We analyzed and collected social media demographics with Captiv8 software to see public engagement related to heart valves from July 2016-June 2017 by searching for tags 'aorticvalve', 'mitralvalve', 'mitralvalveprolapse' and 'TAVR'. We searched similar tags on Google trends from July 2016-June 2017 to analyze the peak popularity of these searches and to

estimate if National Heart Valve Disease Awareness Day on Feb. 22, 2017 had any impact on search trends online. Online public awareness content for valvular heart diseases was analyzed for their simplicity and suitability for non-medical population and their quality of engagement and subsequent plans to create simple online tool (website/phone application) for public awareness of valvular heart diseases was initiated.

Results We found that all four search tags related to heart valves had peak popularity within February or just immediately after in March. Demographics data from online posts within last year also showed that the maximum engagement involved females, from USA of white ethnicity (figure-1). www.heartvalvediseases.com was created by a trainee led team with subsequent creation of iphone application (Currently in beta version), with goal to engage internal medicine resident clinic patient population and subsequently create more awareness of valvular heart diseases.

Conclusion Our analysis showed that the creation of National Heart Valve Disease Awareness Day in February this year resulted in increase public engagement and interest online. Further efforts are needed to encourage more engagement of people and more engaging content is needed to improve public awareness of these critical diseases. Trainee led public awareness efforts, through the creation of website, led to more patient engagement and education related to valvular heart diseases.

C20 SIGNIFICANCE OF 30-DAY READMISSION RATE IN PATIENTSWITH CORONARY ARTERY DISEASE ADMITTED FOR CARDIAC CATHETERIZATION

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Background Thirty day readmission rate has been a measure of quality affecting hospitals reimbursements. Reducing hospital readmissions has been made a national priority.

Aim Assessing significance of 30-day readmission rate among patients with coronary artery disease (CAD) admitted for cardiac catheterization.

Methods A retrospective study of 9,023 patients who underwent cardiac catheterization between 01/01/2005 and 12/31/

Google Trends Data	Mitral valve	Aortic valve	Mitral valve prolapse	TAVR
Peak popularity (Last 12 months)	March 5-11 th 2017	Feb 26-march 4 th 2017	Jan 29 th - Feb 25 th	Feb 12-25 th 2017 April 9-15 th 2017
Highest interest by region	USA Canada Australia	USA Philippines Australia	Russia USA Brazil	USA
Social media Demographics (Instagram)	#Mitralvalve	#Aorticvalve	#Mitralvalveprolapse	#TAVR
Total engagements	37000	52000	174000	72000
Gender	Female 64%	Male 36%	Female 55%	Male 45%
Top three countries	USA UK Turkey	USA Italy UK	USA Philippines UK	USA Russia Italy
Ethnic demographics	White 50% Asian 30% Hispanic 15%	White 53% Asian 25% Hispanic 18%	White 52% Asian 33% Hispanic 11%	White 55% Asian 33% Hispanic 12%

Abstract C19 Figure 1

2016. Thirty day readmission rate, 6-month mortality, severity of CAD and number of vessels affected were obtained.

Results Of 9,023 patients, who had cardiac catheterization, 1,109 patients (12.3%) had readmission in 30 days, and 31 patients (0.3%) had mortality in 6 months. Of 1,109 patients 30-day readmission, 1023 (92.2%) had CAD on cardiac catheterization. Average age of patients with 30-day readmission 59.3 years versus 59.4 in those without ($p=0.9$). Obstructive CAD was noted in 84.8% of patients with 30-day readmission versus 73.1% in those without (OR: 2.03, 95% CI: 1.7 to 2.4, $p<0.0001$). Multiple vessel disease was noted in 69.2% of patients with 30-day readmission versus 54.3% in those without (OR: 1.9, 95% CI: 1.7 to 2.2, $p<0.0001$). Presentation as acute coronary syndrome (ACS) was noted in 21.5% of patients with 30-day readmission versus 21.1% in those without (OR: 0.9, 95% CI: 0.8 to 1.1, $p=0.2$). Patients with 30-day readmission but without 6-month mortality had more obstructive CAD (86%) compared to those with 30-day readmission and 6-month mortality (76%) (OR: 0.6, 95% CI: 0.2 to 1.5, $p=0.3$). Patients with 30-day readmission without 6-month mortality were more likely to have multiple vessel disease (69%) compared to those with 30-day readmission and 6-month mortality (46%) (OR: 2.6, 95% CI: 1.2 to 5.7, $p=0.02$). However, the average age in patients with 30-day readmission without 6-month mortality was 61 years versus 68 in patients with both 30-day readmission and 6-month mortality ($p=0.001$).

Conclusion Obstructive CAD and multiple vessels disease were more prevalent among patients who had a 30-day readmission. No significant difference noted in 6-month mortality in relation to 30-day readmission rate. However, age was an independent risk factor for 6-month mortality among patients with 30-day readmission.

C21 URINARY LEVELS OF MARINOBUFAGENIN AND ANGIOGENIC FACTORS IN PREECLAMPTIC PATIENTS

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Objective Comparison of angiogenic factors, and marinobufagenin (MBG) in urine of pregnant patients with and without preeclampsia (PreE).

Method A prospective cohort of patients with normal pregnancies and of those with PreE were recruited to provide urine samples. sFlt-1, soluble endoglin (sEng), PlGF, TGF- β -1, VEGF, and MBG were assayed using ELISA and results corrected to units per mg creatinine. Patient characteristics were compared using Chi-square tests for proportions, Student's t test for parametric data, and Mann-Whitney U test for non-parametric data. $P<0.05$ was taken as significant. Variation associated with gestational age was examined using correlations and when appropriate linear regression equations were obtained. Receiver operator curves (ROC) were examined to establish criteria levels for those factors that varied with PreE.

Results In total, 40 patients with normal pregnancies were sampled between 22 and 39 weeks gestation and 25 patients with PreE were sampled between 28 and 39 weeks gestation. As expected groups differed ($p<0.02$) for blood pressure, gestational age at delivery, and age. They did not differ for weight ($p=0.28$), height ($p=0.38$), and creatinine levels ($p=0.29$). Groups differed in sEng ($p=0.016$), PlGF ($p=0.018$), sFlt-1 ($p=0.00066$), and MBG ($p<0.0001$). The PlGF levels were less in PreE pregnancies while sEng, sFlt-1 and MBG levels were increased. TGF- β -1 and VEGF did not differ between groups ($p>0.14$). Only urinary MBG was found to vary with gestational age in normal pregnancies ($p=0.0009$). MBG, sFlt-1, PlGF, and sFlt-1/PlGF ratio had significant ROC area under the curve measures ($p<0.02$) with criteria for PreE that provided sensitivities between 65 and 88% and specificities between 74 and 96%.

Conclusion Urinary levels of certain angiogenic and antiangiogenic factors as measured in urine demonstrated differences in patients with clinical diagnosis of PreE. Urine specimen procurement and assay are a less invasive and potentially more acceptable for assessment of PreE.

C22 CELIAC DISEASE AND RISK OF ATRIAL FIBRILLATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Objective Several studies have found that celiac disease may be associated with a variety of cardiac manifestations. Atrial fibrillation is one of the most common arrhythmias that can cause significant morbidity. However, the risk of atrial fibrillation in patients with celiac disease according to epidemiologic

Abstract C22 Figure 1

studies remains unclear. We performed this meta-analysis to assess the risk of atrial fibrillation in patients diagnosed with celiac disease compared to controls.

Method A systematic review was conducted in MEDLINE, EMBASE, Cochrane databases from inception through December 2017 to identify studies that evaluated risk of atrial fibrillation in patients with celiac disease. Effect estimates from the individual study were extracted and combined using random-effect, generic inverse variance method of DerSimonian and Laird.

Results 4 observational studies with a total of 64,397 participants were enrolled. Compared with controls, celiac disease was associated with significantly increased risk of atrial fibrillation with a pooled OR of 1.38 (95% CI: 1.01 to 1.88). We found no publication bias as assessed by the funnel plots and Egger's regression asymmetry test with $p = 0.54$. However, the heterogeneity of the included studies was high.

Conclusion Celiac disease is associated with 38% increased risk of atrial fibrillation compared to controls.

C27 NSTEMI IN ABSENCE OF CORONARY ARTERY DISEASE

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Introduction In 2016 American Heart Association (AHA) reported that 15.5 million people ≥ 20 years of age in the USA have coronary artery disease (CHD). While the reported prevalence increases with age for both women and men it has been estimated that approximately every 42 seconds, an American suffers myocardial infarction (MI). We describe a peculiar case of 55-year-old homeless veteran who was found to have significant troponin elevation without obstructive coronary artery disease (CAD).

Case presentation A 56-year-old homeless veteran presented to emergency department (ED) because he fell in the street and was having suicidal ideation. He was found to be in hypertensive emergency on admission with first blood pressure reading 250/140. While in ED, aggressive treatment with intravenous anti-hypertensives lead to hypotension with blood pressure in 70/40, at which time he developed left sided radiating chest discomfort with shortness of breath. Patient reported that this was not his typical chest pain which was usually substernal pressure, non-radiating and was always associated with emotional stress such as anger or frustration. ECG showed normal sinus rhythm but with voltage criteria for left ventricular hypertrophy (LVH) and T wave inversion in lateral leads. Initial laboratory investigations were consistent with cTnI 0.05. Given that patient had several social factors – suicidal ideation, significant fall risk, homelessness, possible compliance issues – there was a concern to proceed immediately to coronary angiogram as if an obstruction was found the resultant percutaneous intervention (PCI) would require patient to be on dual anti-platelet therapy and that could be a problem in the face of patient's social issues as listed above. As he was closely observed overnight, his cTnI bumped from 0.05 to 50.9 but still ECG did not reveal any dynamic changes. Next morning, he was consented and taken for left heart catheterization (LHC) where his coronary arteries were found to be non-obstructive. An ECHO was done to get a comprehensive picture which showed moderately reduced left ventricular (LV) cavity. Wall thickness was increased in a pattern of moderate

to severe LVH. The estimated ejection fraction was in the range of 70% to 75%. There was dynamic obstruction at rest in the mid cavity, with mid-cavity obliteration, a peak velocity of 454 cm/sec, and a peak gradient of 82 mmHg. With Val-salva the peak gradient worsened to 197 mmHg. There was dynamic obstruction at rest in the left ventricular outflow tract (LVOT), with a peak velocity of 486 cm/sec and a peak gradient of 94 mmHg. Systolic anterior motion of mitral valve (SAM) was also noted. Final impression was HOCM based on ECHO findings.

Discussion HCM or Idiopathic hypertrophic subaortic stenosis (IHSS) is the most common cause of sudden death in young adults and athletes. It can be either be inherited or acquired as a result of mutation. There are two types of HCM, a more common, obstructive type (HOCM, 70%) and a less common, non-obstructive type (HNCM). In all cases of HCM, testing should be performed to detect outflow obstruction at rest and/or on provocation, and to thereby determine whether HOCM or HNCM is present. The signs and symptoms of HCM are variable, and there is not a strong correlation between the presence or magnitude of LVOT obstruction, the extent of LV hypertrophy, and symptoms. Sudden cardiac death is the most serious complication of HCM. Maximal wall thickness of >30 mm is a risk marker for sudden cardiac death particularly in young and asymptomatic patients. ECHO can reliably be used to diagnose HOCM by unexplained increased in LV wall thickness ≥ 15 mm, SAM and LVOT. Guidelines recommend getting cardiac magnetic resonance imaging (CMR) to clarify a diagnosis of HCM or the extent of wall thickness in those patients in whom LV wall thickness measurements remain uncertain with two-dimensional ECHO. After correct diagnosis is made, risk stratification of patients with regard to the need for prophylactic implantable cardiac defibrillator (ICD), can be of life-saving importance.

Conclusion Evaluation for HCM by ECHO is mandatory in a patient prompted by family history, systolic ejection murmur or abnormal 12-lead ECG. Since most mutations have a high degree of penetrance, first-degree family members of an affected individual should be evaluated for possible inheritance of the disease.

C28 LP(A) AND ATHEROSCLEROSIS

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Objective Lipoprotein (a) [Lp(a)] first emerged as potential risk factor for atherosclerosis in the 1980s. Since then, it has been well established that Lp(a) is a causative risk factor for coronary artery disease. Screening protocols, desirable blood levels, and treatments for increased Lp(a) have yet to be established and require further investigation. Our objective was to sift through literature on Lp(a) and atherosclerosis and draw conclusions that are important for clinical practice.

Methods Pubmed, uptodate, JAMA, and NEJM online databases were searched for 'Lipoprotein (a),' 'Lp(a),' and 'treatment,' 'risk factors,' 'screening,' 'atherosclerosis,' and 'coronary artery disease.' Relevant and recent articles were selected, reviewed, and described in our text.

Results Important and relevant information about Lp(a) and atherosclerosis was obtained. Lp(a) is a large glycoprotein which has a region homologous with the plasmin binding

domain of fibrinogen. This impairs fibrinolysis and leads to increased clotting. It also promoted foam cell formation. Lp(a) levels are 90% genetically determined with an identified variant allele causing increased levels in affected patients. Many studies have shown that higher levels of Lp(a) are correlated with coronary artery disease with hazard ratios and relative risk ratios nearing 2.5 when compared to normal Lp(a) levels. The studies do not use universal cutoff points to distinguish between 'high' and 'low,' Lp(a), but show a linear correlation between Lp(a) and disease. Studies addressing the allelic variant of Lp(a) strongly suggest a causal relationship between Lp(a) and coronary disease. Current screening recommendations are not standardized, and treatment has been proven to decrease disease risk. Niacin and PCSK-9 inhibitors are known to decrease Lp(a) levels. Low dose aspirin has been shown to decrease risk of disease in patients with high Lp(a). Statins do not lower Lp(a) but still decrease disease. Lipid apheresis can decrease levels greatly and RNA antisense drug treatments that target Lp(a) mRNA are currently in early clinical trials.

Conclusion Lp(a) is a well described, casual risk factor for coronary artery disease. Appropriate screening, desirable blood levels, and effective treatments to mitigate disease burden have yet to be described. Niacin and PCSK-9 inhibitors represent reasonable adjunctive treatments for patients with high Lp(a), in addition to statin and aspirin therapy. Antisense RNA drugs are exciting future treatments that will hopefully decrease Lp(a) levels and coronary artery disease.

C29

POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME PRESENTING AS AN ST-ELEVATION MYOCARDIAL INFARCTION

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Introduction Posterior reversible encephalopathy syndrome (PRES) is an uncommon diagnosis secondary to cerebral injury. The exact pathogenesis remains unclear but it has been associated with hypertension (HTN) and immunosuppressive therapy. As a secondary consequence, PRES can lend to the development of stress induced cardiomyopathy. We present a rare case of PRES presenting as an ST-Elevation Myocardial Infarction (STEMI).

Patient presentation A 62-years-old woman with past medical history of hypertension, rheumatoid arthritis, and adrenal insufficiency on immunosuppressive therapy was found unresponsive by her husband and taken to an emergency department where she developed tonic-clonic seizures and was subsequently intubated for airway protection. CT head imaging was significant for a small area of hypoattenuation in the left parieto-occipital region concerning for subacute stroke. She was transferred to our facility for further stroke evaluation. Upon presentation, her ECG was significant for inferolateral STEMI (figure 1) with corresponding Troponin-I of 12.44 ng/ml. Urgent coronary angiography revealed widely patent coronary arteries while echocardiography was significant for stress induced cardiomyopathy with left ventricular (LV) apical akinesis with small apical thrombus, and preserved systolic function of basal segments (figure 2). A brain MRI was performed to further workup neurologic events which revealed an injury

pattern consistent with posterior reversible encephalopathy syndrome (PRES) with areas of infarction (figure 3). She was cleared for anticoagulation therapy to treat LV apical thrombus along with adequate blood pressure control.

Abstract C29 Figure 1 Electrocardiogram with inferolateral ST-segment elevation myocardial infarction

Abstract C29 Figure 2 Echocardiogram in end systole with left ventricular akinesis. White arrow indicating LV apical thrombus. (LV: left ventricle, RV: right ventricle)

Discussion PRES can be a consequence of HTN alone but one study has found that the rate for development of PRES in hospitalized patients with sudden HTN matched for non-hospitalized controls using age and HTN history found no increase in incidence for the development of PRES.⁸ Patients who present with PRES will often have significant HTN and possibly seizures, but other disease processes such as chronic immune suppressive therapy can also contribute. Of significance, our patient not only had a history of HTN and presented with seizure, but she was also chronically immunosuppressed with Leflunomide, Methotrexate, and Prednisone for her rheumatoid arthritis and adrenal insufficiency. Interestingly, our patient presented with clinical evidence of myocardial infarction for which urgent coronary angiography was negative.

The proposed mechanism of cardiac injury is hyper-catecholamine stress resulting in cardiac injury. Studies in animal models have shown that intracerebral damage caused elevated catecholamines and was associated with coronary microvascular

spasm and myocardial necrosis.² Myocardial injury due to acute cerebral infarction produces myofibrillar degeneration characterized by dense eosinophilic transverse bands with intervening granularity as opposed to coagulation necrosis seen in coronary thrombosis where myofibrillar structure is intact.^{3,4} Elevated troponin in the setting of acute cerebral infarction is also a poor prognostic indicator associated with higher risk of in-hospital death and non-fatal cardiac event.⁷

Conclusion ST-Elevation Myocardial Infarction with elevated troponins can be misleading in patients presenting with recent central nervous system damage and seizure. While it is paramount to rule out a significant myocardial event, one should also take into consideration the neurogenic impact on cardiac function as seen in this case with PRES.

Abstract C29 Figure 3 Brain MR with area of T2/FLAIR hyperintensity

C42

DEMOGRAPHICS INCLUDING AGE, GENDER AND IMMIGRATION STATUS IMPACT ON CORONARY ARTERY DISEASE: A RETROSPECTIVE ANALYSIS

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Background Coronary artery disease (CAD) is the leading cause of death worldwide. Several factors play a role in the risk and severity of CAD.

Aim To assess the effect of demographics including age, gender, and immigration status among patients with CAD.

Methods A retrospective, single-center analysis was applied to all patients admitted for chest pain and underwent cardiac

catheterization between 01/01/2005 and 12/31/2016. Our hospital serves one the most diverse populations in New York City. Information about age, gender, and immigration status was obtained from the chart. The term undocumented immigrant refers to foreign nationals residing in the U.S. without legal immigration status. The term legal resident refers to all other types of residence including but not limited to U.S. Citizens, permanent residents, tourist and student visa holders.

Results Of 8,917 patients who underwent cardiac catheterization, 4,537 (50.9%) were <60 years old versus 4,380 (49.1%) were ≥60 years old. CAD was more prevalent, severe, male-predominant and presented more as acute coronary syndrome (ACS) among patients ≥60 years old compared to those <60 years old. Table 1 of 8,917 patients, 2,547 (28.6%) patients were undocumented immigrants versus 6,370 (70.4%) who were legal residents. Undocumented immigrants displayed evidence of CAD at a younger age and had more severe CAD than legal residents. Table 2 CAD was more prevalent among males but females developed CAD at a younger age. Males had more severe CAD and presented as ACS more than females. Table 3.

Conclusion Older patients have a higher degree of CAD. Undocumented immigrants have less prevalence of CAD but they do have worse presentation and more severe CAD findings at earlier ages. Males have more CAD prevalence, severe CAD and worse presentation than females.

Abstract C42 Table 1 Age

	Age < 60 years old N=4,537	Age ≥ 60 years old N= 4,380	Statistics
CAD	3582 (79%)	3989 (91%)	OR: 2.2 95% CI: 2-2.5 <0.0001
Gender Male vs Female	2705 (75.5%)	2553 (64%)	OR: 1.7 95% CI: 1.6-2 <0.0001
Obstructive disease	2572 (71.8%)	2980 (74.7)	OR: 1.2 95% CI: 1.1-1.3 P=0.004
Multiple vessel disease	2168 (60.5%)	2665 (66.8%)	OR: 1.3 95% CI: 1.2-1.4 <0.0001
Acute coronary syndrome	895 (25%)	770 (19.3%)	OR: 1.4 95% CI: 1.2-1.5 <0.0001
Hispanic	519 (14.5%)	658 (16.5%)	OR: 1.2 95% CI: 1.02-1.3 P=0.01
Legal resident	1084 (30.3%)	982 (24.6%)	OR: 1.3 95% CI: 1.2-1.5 <0.0001

Abstract C42 Table 2 Legal resident vs undocumented

	Legal resident N= 6370	Undocumented N=2547	Statistics
CAD	5505 (86.4%)	2068 (81.2%)	OR: 1.5 95% CI: 1.3-1.6 P<0.001
Average age	61 years	58 years	<0.0001
Gender Male vs Female	3774 (59.2%)	1285 (50.4%)	OR: 2.1 95% CI: 1.9-2.4 P<0.0001
Obstructive CAD	4130 (64.9%)	1421 (68.7%)	OR: 1.2 95% CI: 1.1-1.3 P=0.001
Multiple vessel disease	3200 (58.1%)	1323 (64%)	OR: 1.3 95% CI: 1.2-1.4 P<0.0001
Acute coronary syndrome	1322 (20.7%)	342 (13.4%)	OR: 1.7 95% CI: 1.5-1.9 P<0.0001

Abstract C42 Table 3 Males vs females

	Females N=3304	Males N= 5613	stats
CAD	2515 (76.1%)	5059 (90.1%)	OR: 2.9 95% CI: 2.5- 3.2 p<0.0001
Average age	58.7 years	63.6 years	<0.0001
Obstructive CAD	1545 (46.8%)	3988 (73.7%)	OR: 2.8 95% CI: 2.4- 3.1 p<0.0001
Multiple vessel disease	1458 (44.1%)	3376 (66.7%)	OR: 2 95% CI: 1.8- 2.1 p<0.0001
Acute coronary syndrome	388 (15.4%)	1276 (23.6%)	OR: 2.2 95% CI: 2-2.5 p<0.0001

C49 DONOR TATTOOS ARE NOT ASSOCIATED WITH POOR OUTCOMES IN HEART TRANSPLANTATION

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Objective Cardiac donor's medical and social history is the second most common reason for non-recovery of hearts after

poor graft function. There is limited data that studied the significance of cardiac donor's history of high-risk social behavior on recipient post transplant outcomes. We sought to investigate the impact of the presence of tattoos in cardiac donors on recipient overall and graft survival.

Method We identified all adults who received heart transplantation between 2000 and 2015 in the United States. Patients were divided by the presence or absence of donor tattoos. Cox proportional hazard models were performed to identify impact on long-term outcomes.

Results We identified a total of 30,261 transplantations. Of those, 10,796 had organs from donors with tattoos (DwT). DwT were more likely to be younger (29 vs 33 years, $P<.001$), male (76% vs 68%, $P<.001$), and to have a history of heavy alcohol use (16% vs 9%, $P<.001$), and to use cocaine (21% vs 10%, $P<.001$). After adjusting for donor and recipient factors, donor tattoos was not associated with overall survival (Hazard Ratio 0.98 [0.93–1.03], $P=0.43$), or graft survival (HR 0.98 [0.93–1.03], $P=0.32$).

Conclusion Our study showed that presence of tattoos in cardiac donors has no impact on overall and graft survival. To the best of our knowledge, this is the first analysis that studied the impact of tattoos on heart transplantation recipients. Our results may be helpful by considering donors for heart transplantation who were labeled as having a high-risk social behavior.

Diagnosis or Treatment of a Disease Process or Clinical Syndromes

A07 EPIGASTRIC PAIN POST-PCI; A RARE ATHEROEMBOLIC COMPLICATION OF A COMMON PROCEDURE

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10.1136/jim-2018-000745.33

Objective/background The reported incidence of atheroembolic events after Percutaneous Coronary Intervention (PCI) varies from 0.6 to 0.9 % in retrospective studies to 1.4 to 1.9 % in prospective series.¹ The kidney is one of the principal end organs that may be affected by atheroembolic events followed by skin with incidence of 0.9% and 0.6% respectively in a prospective study.² Isolated splenic infarction is a rare atheroembolic complication and only a few cases have been reported in the literature thus far.^{3,4}

Method We present a case of isolated splenic infarction post cardiac catheterization.

Result 68 years old Caucasian Male with past medical history of angina, hypertension, and abdominal aortic aneurysm was admitted for elective PCI. PCI was performed via radial access. Angiography showed dominant Right Coronary Artery (RCA) with 95% stenosis, for which RCA was stented with a drug-eluting stent. The patient complained of mild epigastric pain post PCI but the periprocedural course was otherwise uneventful. The patient was discharged home about 6 hours after the procedure. Later that day, he presented to the Emergency Department with increasing epigastric pain. He had tried over the counter medications but with no relief. He denied any nausea, vomiting, or sweating. His vital signs were within normal limits (WNL). On physical examination was significant for epigastric tenderness and rest of examination was WNL. Laboratory finding for CBC, CMP, and lipase was

WNL. EKG was unremarkable with the rate of 73/min, and no ST-T wave changes. Troponins were negative. CT abdomen with contrast showed multiple small wedge-shaped defects in an enhancement of spleen suggestive of splenic infarcts; Focal aneurysmal dilatation of infra-renal abdominal aneurysm was stable at 3.5 cm. The patient was symptomatically managed for pain. Esophagogastroduodenoscopy was performed that showed a hiatal hernia without gastritis or esophagitis. The patient was discharged after 24 hours, continuing dual antiplatelet therapy, and close follow up with primary care physician. One year after, he has not had any complications related to splenic infarction and is doing well.

Conclusion This case illustrates that a symptomatic isolated splenic infarction can be a complication after cardiac catheterization. Management includes rest, analgesics, and follow up scans to confirm the resolution of infarction. Symptoms usually resolve with conservative management. The true incidence of splenic infarction after cardiac catheterization is difficult to determine because of its rarity. Splenic hemorrhage, rupture and abscess are the potential rare but fatal consequences of splenic infarction. Physicians should be aware of this potentially serious complication in patients developing abdominal pain post-cardiac catheterization.

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A08

BRIC: A RARELY CONSIDERED DIAGNOSIS IN THE EVALUATION OF INTRAHEPATIC CHOLESTASIS

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Intrahepatic cholestasis is a common disease entity internists see in their daily practice with a wide differential including Dubin-Johnson syndrome, infiltrative diseases, drug induced liver injury, and many others. Typical guideline directed workup includes first reviewing medications and obtaining a right upper quadrant ultrasound. Based on the presence or absence of ductal dilatation, one may proceed to ERCP vs. MRCP or obtaining anti-mitochondrial (AMA), anti-nuclear (ANA) and anti-smooth-muscle (ASMA) antibodies, respectively. One rare cause (prevalence not known exactly but fewer than 1 in 100,000 people worldwide) of intrahepatic cholestasis is benign recurrent intrahepatic cholestasis (BRIC), a disease process with a benign natural history of no risk for decompensation of synthetic liver function. It is not typically considered in the differential diagnosis of many internists and gastroenterologists, leading to expensive, repetitive and unnecessary testing.

A 24-year-old male with a history of unexplained hyperbilirubinemia and alcohol use presented to the hospital with progressive jaundice, pruritis and fatigue for the past 3 weeks. Patient reported only remote alcohol use 5–6 years ago and no history of intravenous drug use. He was not on any

medications, prescription or over the counter. He reported two previous week long hospitalizations in the last 18 months for similar issues. Labs on admission were notable for an elevated aspartate aminotransferase (55 U/L), alanine aminotransferase (73 U/L), alkaline phosphatase (289 U/L), total bilirubin (24.8 mg/dL), and direct bilirubin (16 mg/dL). He was extensively worked up in the past without any definitive diagnosis reached. Workup included hepatitis panel, ANA, AMA, ASMA, and ceruloplasmin levels. Liver ultrasound and CT of the abdomen had been unremarkable. Transjugular liver biopsy showed parenchymal lobules that exhibited mild unrest with core disarray, slight kupffer cell hyperplasia and subtle evidence of canalicular cholestasis. With the patient's worsening jaundice and escalating bilirubin, the aforementioned tests were repeated and once again were all negative (extremely low titers). Review of previous records revealed normalization of bilirubin 2 months after his last episode of jaundice. Given the typical recurrent pattern of direct hyperbilirubinemia with interval normalization, and the findings on the pathology report, a diagnosis of BRIC was made. The patient was educated on the benign nature of his disease and discharged with Ursodiol and Atarax for pruritic control. He was followed up in liver clinic and continues to do well with slowly improving bilirubin levels.

BRIC is a rare and subtle diagnosis, especially considering the prevalence of viral hepatitis in our patient population, as well as Wilson disease in this age group. BRIC, first described many years ago, is diagnosed by identifying 2 of 6 specific characteristics (noted below) of which our patient had all 6.¹ BRIC is not known to cause progressive liver injury or cirrhosis, and the mainstay of management is supportive care and symptom management as effective treatment modalities have not otherwise been established.² Familiarity with the below criteria and considering BRIC in patients with recurrent cholestasis can help prevent redundant, costly workup.

Diagnostic Criteria for BRIC:

1. At least two episodes of jaundice with asymptomatic interval of months to years
2. Laboratory investigations suggestive of intrahepatic cholestasis
3. Cholestasis induced severe pruritis
4. Cholangiography showing normal intra and extrahepatic bile ducts
5. Liver histology suggesting centrilobular cholestasis
6. Absence of other causes of cholestasis.

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A16

ABDOMINAL WALL ABSCESS SECONDARY TO CHOLECYSTOCUTANEOUS FISTULA: RARE COMPLICATION OF COMMON BILE DUCT STENT OCCLUSION

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A 68-year-old female with history of chronic obstructive lung disease, gastroesophageal reflux disease, choledocholithiasis s/p

endoscopic retrograde cholangiopancreatography (ERCP) with common bile duct stenting presented with chronic abdominal pain and subjective fever for three weeks. Physical examination was significant for blood pressure of 90/50 mmHg, heart rate of 114 beats/minute, fever of 38.6 Celsius, abdominal distention and palpable abdominal wall mass in right lower quadrant. Initial investigations showed white cell count of 29 k/mm³, Hgb of 10.7 g/dl, platelets of 540,000/mm³, INR of 1.2 and creatinine of 0.52 mg/dl. Abdominal computerized tomography showed enhancement of gallbladder wall and fistulous tract extending from gall bladder to right lower quadrant abdominal wall with an abdominal wall abscess. (Figure 1) A hepatobiliary (HIDA) scan showed radiotracer being excreted through the fistulous tract from the gallbladder into the right abdominal wall and stasis of the radiotracer within the CBD stent suggesting at least partial obstruction of the stent. (Figure 2) Patient was started on broad spectrum antibiotics, and incisional drainage of the abdominal wall abscess was performed. Later ERCP was performed that showed occluded biliary stent that was removed. (Figure 3) Hospital course was complicated with sepsis and recollection of the abdominal wall fluid for which wound vacuum was placed. Despite appropriate management patient progressively deteriorated and goals of care opted towards comfort measures.

A cholecystocutaneous fistula is an abnormal epithelial tract between the gallbladder and the skin. This is an extremely uncommon presentation that is usually seen as a complication of chronic biliary tract disease such as calculous cholecystitis, though cases have been reported with adenocarcinoma of the gallbladder as well.^{1,2} The obstruction of the cystic duct due to a calculus or a carcinoma, causes perforation and subsequent fistula formation.³ The most common presenting symptoms are fevers, sweats, abdominal pain, anorexia and associated lump under the skin indicative of an abscess.⁴ The initial imaging studies are ultrasound and computerized tomography that can show a thickened gall bladder, fistulous tract and abdominal wall abscess. In the presence of a fistula opening, a fistulography can be a useful diagnostic modality. ERCP

can be used as a diagnostic modality and for removal of a stone blocking the cystic or common bile duct. Treatment begins with antibiotics with surgical intervention as the definitive treatment. A laparoscopic vs a single-stage surgical approach can be determined based on comorbidities. An open surgical approach is preferred if there is an underlying malignancy of the gall bladder.^{3,4} To our knowledge, there has not been any other case of cholecystocutaneous fistula formation complicated by intraabdominal abscess secondary to occlusion of a previously placed common bile duct stent.

Abstract A16 Figure 2

Abstract A16 Figure 3

Abstract A16 Figure 1

A06

RECURRENT PANCREATITIS SECONDARY TO DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction Pancreatic lymphoma is uncommon, representing less than 0.5% of pancreatic tumors, with diffuse large B-cell lymphoma (DLBCL) being the predominant type. Acute pancreatitis secondary to pancreatic lymphomas is a rare presentation. We report a case of recurrent pancreatitis secondary to DLBCL.

Case presentation 57-year-old female with history of recurrent episodes of pancreatitis presented with complaint of upper abdominal pain. Physical examination was significant for tenderness in the epigastrium and left upper quadrant along with point tenderness at level of thoracic vertebra T8 – T9. Initial investigations showed a normal complete blood count, with an increased lipase of 149 units/L and a creatinine of 0.68 mg/dl. Abdominal computerized tomography showed stranding surrounding the pancreas reflecting acute pancreatitis. Magnetic resonance imaging of the back showed a large mass at T9 vertebral body surrounding the aorta and causing severe left neuroforaminal narrowing. PET scan showed hypermetabolic focus in head of pancreas with maximum dimension of 2.5 cm with multiple hypermetabolic osseous metastases largest being at level of T9 vertebra. An endoscopic ultrasound was performed with fine needle biopsy of the paraspinal mass. Pathology slides diagnosed the mass as Stage IV high Grade Diffuse Large B-Cell Lymphoma. Patient subsequently, underwent 5 cycles of R+DA-EPOCH regimen, one cycle of R-HCVAD mini B cycle and 6 cycles of intrathecal methotrexate alternating with cytarabine. Currently, he is being followed up in oncology clinic with significant symptom improvement.

Conclusion Secondary involvement of the pancreas by diffuse Large B-Cell lymphoma is a rare occurrence. Patients who present with pancreatitis specifically recurrent pancreatitis should be evaluated for this diagnosis. Pathological diagnosis is important to distinguish pancreatic lymphoma from pancreatic adenocarcinoma. Treatment usually consists of a combination of chemotherapy and radiation therapy, or stem cell transplantation. Most cases however respond very well to chemotherapy only.

Abstract A06 Figure 1

Abstract A06 Figure 2

Abstract A06 Figure 3

Abstract A06 Figure 4

Abstract A06 Figure 5

A39 PRIMARY DUODENAL ADENOCARCINOMA PRESENTING AS A GIANT DUODENAL ULCER

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Introduction Giant duodenal ulcer refers to a duodenal ulcer that is greater than 2 cm in diameter. In majority of the cases, the etiology is benign; however, primary duodenal carcinoma is encountered not infrequently, upto 15% of GDU. Despite this, there is no standard guideline in diagnostic approach or in surveillance. Here we present a case of refractory giant duodenal ulcer that was ultimately diagnosed as primary duodenal adenocarcinoma, 2 months after the initial presentation.

Case presentation 76 year-old female presented with epigastric pain and hematemesis. Patient was taking aspirin 81mg daily, however denied taking any other non-steroidal anti-inflammatory medications. Initial laboratory test was notable for hemoglobin of 4.1 g/dL. Upper endoscopy showed a large ulcer in duodenal bulb, approximately 20 mm in diameter with small adherent clot. No biopsy was taken as the ulcer appeared benign endoscopically. The etiology was attributed to aspirin and H. Pylori infection (positive stool antigen). Aspirin was subsequently discontinued and patient was discharged with 14-day course of triple therapy. Two months later, patient

presented again with massive upper gastrointestinal bleeding. Repeat upper endoscopy showed previously seen duodenal ulcer that had enlarged in size with worsened surrounding edema. Biopsies were taken from the edges of the ulcer; final histopathology revealed adenocarcinoma. A small hypodense liver lesion seen on the abdominal Computed Tomography was found to be a metastatic focus on liver biopsy. Patient was not deemed to be a surgical candidate. She progressively deteriorated with development of gastric outlet obstruction and ultimately decided on palliative management.

Discussion Giant duodenal ulcer accounts for 1–2% of all duodenal ulcers. As with any other peptic ulcers, the most common etiologies are H. Pylori infection and use of non-steroidal anti-inflammatory medications. Primary duodenal malignancy is rare in general. However, upto 15% of GDU was found to be primary duodenal adenocarcinoma in one series. There is no standard guideline about obtaining biopsies at index endoscopy or regarding surveillance. Newton, et al. suggested taking biopsies of all giant duodenal ulcer to rule out malignancy. In the case of gastric ulcers, biopsies are recommended for all ulcers to exclude malignancy and surveillance endoscopy to be performed in a selected group of high risk patients. Similar approach may be necessary for giant duodenal ulcers, as the cost of missed diagnosis of malignancy can be paramount.

A09

RHEUMATIC HEART DISEASE IN AN ADULT PATIENT PRESENTING WITH NON-SPECIFIC SYMPTOMS

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Introduction Rheumatic Heart Disease is cardiac inflammation and scarring triggered by an autoimmune reaction to infection with group A Streptococci. In the acute stage, this condition consists of pancarditis, with chronic disease manifested by valvular fibrosis. It is a serious complication of Rheumatic Fever which is rare before age 5 years and after age 25 years; and is most frequently observed in children and adolescents. We discuss a case of Rheumatic Heart Disease in a relatively healthy 34 year old man.

History and clinical findings A thirty four year old male presented with complaints of severe muscle aches, arthralgia, fatigue, generalized malaise, subjective fevers and loss of appetite going on for a few weeks; beginning while he was on vacation in California. The symptoms began in his lower extremities and gradually spread to the rest of his body making it relatively difficult to complete activities of daily life like changing gears and applying brakes while driving. The patient denied any sore throat and didn't have any signs and symptoms of pharyngitis.

Laboratory and diagnostic data On presentation, his ESR and CRP were very elevated and an extensive autoimmune workup was mostly inconclusive. His infectious workup was positive for elevated Antistreptolysin O antibody titres which were at five times the upper limit of normal (ULN). He underwent a transthoracic echocardiogram showing a small vegetation over the pulmonary valve thus leading to a clinical diagnosis of Rheumatic Heart Disease.

Management On admission, before the definitive diagnosis, the patient was started on Tylenol, gentle fluid and dietary

resuscitation. After the diagnostic workup, high dose Aspirin one gram every six hours and Amoxicillin 500 mg twice daily were initiated. With significant symptomatic improvement, the patient was discharged home to be started on penicillin prophylaxis on an outpatient basis for a total of ten years given he had valvular involvement.

Conclusion Rheumatic heart disease is a rare condition and requires a high degree of suspicion for diagnosis. It can present with non-specific symptoms like generalized malaise without a history of pharyngitis. The key is timely diagnosis and adequate antibiotic treatment followed by penicillin prophylaxis.

A56 UNUSUAL PRESENTATION OF SOLID PSEUDOPAPILLARY TUMOR OF THE PANCREAS WITH PYELONEPHRITIS AND WEIGHT LOSS

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Introduction A solid pseudopapillary tumor (SPT) is a rare exocrine pancreatic neoplasm that accounts for 2–3% of pancreatic neoplasms. In about 15% of patients, the neoplasms are incidentally detected. Most patients have nonspecific clinical features such as abdominal pain, poor appetite, or nausea, all of which can be related to tumor compression on adjacent organs. We present a unique case of a 20 year old female that initially presented with pyelonephritis and weight loss and was found to have SPT of the pancreas.

Case A 20 year old Jordanian female with history of type I diabetes mellitus presented to the emergency department with left sided flank pain that radiated into her groin, nausea, vomiting, dysuria for three days, and a subjective 20 pound weight loss over the past 3 months. Upon presentation, patient was afebrile, normotensive, and tachycardic with pertinent lab findings of leukocytosis. Urinalysis and culture were completed, and findings were consistent with pyelonephritis. On physical exam, left sided CVA tenderness was elicited, but no palpable abdominal masses were found. Patient underwent CT abdomen/pelvis to evaluate for possible nephrolithiasis. Imaging was negative for nephrolithiasis, but demonstrated a 7.5 × 7 cm mass in the pancreatic head with mass effect; suggestive of SPT of the pancreas or GIST tumor. GI was consulted and recommended outpatient follow-up after full resolution of the infection. Upon follow-up, EUS-FNA was performed, which revealed an epithelial neoplasm, most consistent with SPT of the pancreas. The tumor was compressing the gastric antrum and duodenal bulb causing partial gastric outlet obstruction. Surgery was consulted, and patient underwent pylorus preserving Whipple resection. Patient recovered well post-op and was discharged home in stable condition.

Discussion SPT of the pancreas is a rare tumor that was first described by Frantz et al in 1959 and accounts for less than 3% of all pancreatic tumors. Recently, there has been a 7-fold increase in the number of SPTs diagnosed since the year 2000, likely attributed to improvement of CT imaging and increased access to EUS. SPT predominantly affects females (82–92%) with a median age of 22 and are found in the head (34–40%) or tail (24–36%) of the pancreas in a majority of cases. The most common presenting signs are upper abdominal pain (38–47%), followed by mass effect or palpable

abdominal mass (36%), or no symptoms at all (15%). Among asymptomatic patients, the diagnosis is made incidentally or in cases of acute unrelated injury. In our case, the only presenting sign associated with the SPT was weight loss, which is rare as it represents less than 1% of SPT cases.

Diagnosis of SPT is made through a combination of imaging modalities and pathologic findings. CT scan is the most common initial modality of choice followed by diagnostic confirmation with EUS guided FNA. The advent of EUS guided FNA increased the diagnostic accuracy of SPT to 82.4% from 23.5% for CT scans alone and 41.2% for EUS alone. On average, SPTs are 6–8.5 cm in diameter and present with metastasis 9–15% of the time. Overall, patients have a favorable outcome with a 5 year survival of 94–97% following surgical resection. The recurrence rate is less than 5%.

Conclusion This case is a unique presentation of SPT involving a patient with pyelonephritis and weight loss. Routine CT imaging to evaluate for nephrolithiasis revealed an incidental finding of a 7.5 cm mass suggestive of possible SPT of the pancreas. Physicians should consider this neoplasm as a differential in patients, specifically females 20–30 years old, that present with unexplained weight loss and abdominal pain.

A57 ATYPICAL BRUGADA SYNDROME PRESENTING AS PERSISTENT VENTRICULAR TACHYCARDIA STORM REFRACTORY TO MAXIMAL MEDICAL AND INTERVENTIONAL MANAGEMENT

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Introduction Brugada Syndrome is an ECG abnormality with a high incidence of sudden death in patients with structurally normal hearts. First described in 1992 by the Brugada brothers, the disease has since had an exponential rise in the numbers of cases reported, to such an extent that the second consensus conference reported in 2005 that it was the second leading cause of death in males <40 (after trauma). We report a successful treatment of an unusual case of Brugada Syndrome which was refractory to all forms of medical, surgical and electrophysiological interventions.

Case report A 48-year-old quadriplegic male presented with VF/VT arrest at home. He was successfully resuscitated with DCCV, started on amiodarone drip and transferred to hospital where coronary angiogram failed to show any vessel obstruction. EF was estimated to be 55–65%. Electrolytes and blood glucose were within normal limits. His ECG findings were concerning for Brugada Type I pattern; hence an ICD was placed. Throughout his stay he continued to have recurrent PMVT/VF requiring multiple ICD shocks despite maximal dosage of quinidine, amiodarone and isoproterenol. He was taken for radiofrequency ablation which was unfortunately not successful and he had to be intubated and sedated to ride out the electrical storm. He was extubated a few days later. Next, Dr. Shivkumar at UCLA, the world's leading expert on using stellate ganglionectomy to treat electrical storm was contacted. He recommended bilateral stellate ganglionectomy all the way down to T4-T5. Hence, thoracic surgery team was involved and patient underwent uneventful surgery. Unfortunately, patient's response to surgery was sub-optimal. At this point in time, patient had developed PTSD due to persistent ICD shocks. We discussed goals of care with patients family and

offered our last option, renal sympathetic denervation, (RSD) as a final attempt to help patient's VT storm. RSD is a procedure not yet approved in US as a therapy, however there have been <20 case reports that it may suppress electrical storm. Patient then underwent successful ablation of left ventricle purkinje system and renal sympathetic denervation after which he had no further episodes of arrhythmia. His blood pressure remained labile post ablation, due to loss of autonomic system as he had to rely completely on his endocrine system for blood pressure maintenance. He was started on midodrine and pseudoephedrine to augment that response. He continued to improve clinically and was sent to a skilled nursing home on low dose amiodarone for rhythm control with close follow-up in clinic.

Discussion Brugada syndrome is due to a mutation in the cardiac sodium channel gene. There are 3 variants;

- Type 1 (Coved ST segment elevation >2mm in >1 of V1-V3 followed by a negative T wave).
- Type 2 (has >2mm of saddleback shaped ST elevation).
- Type 3 (morphology of either type 1 or type 2, but with <2mm of ST segment elevation).

Diagnosis is made on ECG finding along with clinical criteria such as documented VT/VF, syncope and family history of SCD among others. ECG changes can be unmasked by multiple factors: fever, ischemia, hypokalemia, hypothermia and medications (antiarrhythmic drugs, cocaine, alcohol). The only proven therapy is an implantable cardioverter – defibrillator (ICD). Quinidine has been proposed as an alternative in settings where ICD's are unavailable or where they would be inappropriate (e.g.: neonates).

Conclusion Brugada Syndrome has a classic ECG pattern which is potentially diagnostic but it might be missed on due to transient nature of ECG changes. Hence, it merits a high index for suspicion in patients presenting as VT/VF with family history of sudden cardiac death and normal coronary circulation. It is appropriate for patients with suspicious ECG changes to undergo electrophysiological evaluation to look for inducible VT/VF as undiagnosed Brugada syndrome has been estimated to have a mortality of 10% per year.

A58

POSTPARTUM INDUCED THROMBOTIC THROMBOCYTOPENIC PURPURA

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10.1136/jim-2018-000745.41

Objective Postpartum induced Thrombotic Thrombocytopenic Purpura (TTP) is a rare but feared complication of pregnancy. We present a 28-year-old gravida 1 para 1 female who recently had a full term normal spontaneous vaginal delivery who presented with severe acute thrombocytopenia and anemia in whom ultimately etiology of thrombocytopenia was found to be due to TTP.

Method A 28-year-old Gravida 1 Para 1 female with no significant past medical history, who recently had a full term pregnancy without any complications via normal spontaneous vaginal delivery presented with lightheadedness, nausea, and vomiting for 1 week. Upon presentation, she was hemodynamically stable. Her physical examination was unremarkable. Her blood work showed severe acute anemia with Hgb of 6.1 and severe acute thrombocytopenia with a platelet count of

27. Previous lab works showed mild thrombocytopenia. Creatinine was elevated at 2.15 and bilirubin elevated at 1.9. Her LFTS and PT/INR were within normal limits. Her peripheral blood smear showed 6–7 schistocytes. The clinical picture was concerning for TTP and a ADAMS13 level was checked and was found to be less than 5 %, this confirmed the diagnosis and she was immediately started on plasmapheresis. Patient underwent a total of 10 session of plasmapheresis. She received pre treatments with solumedrol and Benadryl before each plasmapheresis session. Her symptoms improved and her acute anemia and thrombocytopenia resolved. Her creatinine and bilirubin were also normalized and patient was discharged home with a short course of prednisone.

Result Postpartum induced TTP is a very rare yet, feared complication of pregnancy. Since the differences between causes of thrombocytopenia associated with pregnancy are subtle, it's very important to have correct diagnosis since the management are different. It is important to note that the classical pentad of symptoms associated with TTP may not be present in all patients. Our patient, had no neurological symptoms or fever upon presentation. Therefore a high index of suspicion for TTP is warranted in the setting of thrombocytopenia, microangiopathic hemolytic anemia and kidney dysfunction alone. Another important consideration is to check for ADAMS 13 level before starting Plasmapheresis since post plasmapheresis ADAMS13 values are not accurate. A value less than 10 % suggest TTP.

Conclusion There are numerous causes of thrombocytopenia associated with pregnancy, yet the differences between them are very subtle. This case report further illustrates the importance of diagnosing the cause of thrombocytopenia since treatment depends upon the diagnosis.

A38

METASTATIC GASTROINTESTINAL STROMAL TUMOR DISGUISED AS PANCREATIC PSEUDOCYST

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10.1136/jim-2018-000745.42

Objective Gastrointestinal Stromal Tumors (GISTs) are the most common non-epithelial benign tumor of the gastrointestinal tract. We present a patient with abdominal pain previously diagnosed with pancreatic pseudocyst in which etiology was ultimately determined to be due to metastatic GISTs.

Method A 59-year-old African American female with a past medical history of hypertension, and diabetes mellitus presented to the Emergency room with diffuse abdominal pain for a month. Patient also reported early satiety, nausea and 50 lbs weight loss over the past 2–3 months. She initially presented about a month ago to an out-of-state hospital with abdominal pain. Evaluation revealed a large pancreatic pseudocyst. She underwent, an endoscopic ultrasound-guided cystogastrostomy with the placement of stent. She continued to have abdominal pain, she was currently in town visiting family, but because of worsening abdominal pain she presented to the emergency room. Imaging of the abdomen had revealed a very large abdominal mass between the gastric body and pancreatic body and tail. There was also a lymph node lesion.

She underwent an endoscopic ultrasound, which revealed an ulcerated mass 3.5 cm in size in the proximal stomach along the lesser curvature. On the contralateral gastric wall, in the mid gastric body, there was the previously placed stent,

and an attempt to the scope through the stent was unsuccessful with marked friable tissue ingrowth. There was no cystic cavity. The endoscopic ultrasound noted a very large hypoechogenic mass at least 8 × 9 cm in size, appearing to arise from either pancreatic body or gastric wall with invasion into the gastric wall. There was also 2.3 cm hypoechogenic mass in the left lobe of the liver. All the above lesions have been biopsied and results showed a high-grade malignant spindle cell neoplasm consistent with GISTs. Patient was referred to Oncology and Surgery for further care and management.

Results GISTs are the most common non-epithelial benign tumor of the gastrointestinal tract. They are most commonly found in the stomach and small intestine. Our patient was previously diagnosed with pancreatic pseudocyst for which she underwent endoscopic drainage with a negative workup for malignancy. Tumor markers including CEA, CA19-9, and AFP were normal as well.

Conclusion This Case illustrates that GIST should be considered in the differential diagnosis when a patient presenting with pancreatic pseudocyst.

A60 SEVERE REFRACTORY HYPOXEMIA; A CASE OF UNTREATED EBSTEIN'S ANOMALY IN AN ADULT

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10.1136/jim-2018-000745.43

Background Ebstein's anomaly is characterized by deformities of the anterior leaflet of the tricuspid valve and atrialization of the right ventricle. Patients with severe tricuspid regurgitation are recommended to have tricuspid valve surgery with concomitant atrial septal defect closure. Most of the patients are treated through surgery in early childhood. Untreated cases often present with hypoxemia and other complications and early identification and subsequent treatment should be ensured. We present a case of young female who presented with refractory hypoxemia secondary to untreated ebstein's anomaly.

Case report A 30-year-old Spanish speaking female presented to the ED with shortness of breath since 1 day, and worsening pedal edema since 4 days, and was subsequently found to have Cr of 13 with anion gap metabolic acidosis. Patient was initially started on bicarbonate drip and subsequently underwent dialysis for refractory acidosis and volume overload. Upon further investigation, she was found to have history of ebstein's anomaly w/ ASD, was reportedly lost to follow up many years ago and also had history of CKD stage 5. On transthoracic echocardiography she had torrential tricuspid regurgitation, marked right heart dilation with systolic dysfunction. During dialysis patient developed hypoxia with pulse oximetry saturations in 60–70's range without any improvement on non-rebreather or 100% high flow oxygen. Rapid response sequences were called for the patient by the nursing staff although patient was clinically and neurologically intact without showing any signs of respiratory distress with these low oxygen saturations. Cardiology was consulted who recommended transfusing patient with blood to keep hgb in polycythemia range and congenital cardiology recommended surgical intervention for the patient. Detailed discussion was held with the patient to explain need for surgical intervention, but patient refused any surgical interventions. The history of patient's CKD was determined to be FSGS in the past by

nephrology, but the worsening was attributed to patient's untreated cardiac congenital anomaly. Patient was optimized with dialysis sessions and blood transfusions but stayed persistently hypoxic. She was eventually discharged with planned follow up in cardiothoracic surgical clinic. She was again lost to follow up, only to present again to the ED with cardiac arrest and very severe refractory hypoxemia and eventually died during that hospital admission.

Discussion Severe hypoxemia can be seen in patients with untreated congenital heart diseases and often it is refractory to oxygen supplementation due to underlying cardiac shunting. In patients with untreated ebstein's anomaly, severe tricuspid regurgitation and an associated ASD results in right to left shunting of blood causing severe hypoxemia. Transfusion of blood products can temporarily improve oxygenation but surgical treatment is the only permanent cure. Patients with untreated ebstein's anomaly with severe tricuspid regurgitation should be recognized and prompt surgical treatment should be pursued to prevent their clinical decline.

A61 PULMONARY ARTERY ANEURYSM AND PERICARDIAL EFFUSION: HEART TEAM APPROACH IN MANAGING AN UNCOMMON CASE

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Background Pulmonary artery (PA) aneurysm is rare in clinical settings. Early recognition and careful treatment should be considered to avoid fatal complications of this condition.

Case report A 66-year-old male presented to an outside hospital with left sided chest pain and dyspnea. Chest CT angiography showed small pericardial effusion and severe PA dilation (7.5 cm). He was discharged on naproxen for possible pericarditis. Nineteen days later, he presented with worsening symptoms. C-reactive protein was >68.5mg/l and EKG showed atrial flutter with rapid ventricular response. Repeated CT angiography showed enlarged pericardial effusion. After stabilizing the patient, he was transferred to our cardiac ICU. Transthoracic echocardiography showed ejection fraction (EF) of 45%, severely dilated PA, elevated right ventricular systolic pressure, moderately dilated inferior vena cava, along with stenosis and moderate regurgitation of pulmonic valve. Cardiac MRI showed aneurysmal PA (8 cm). Chest MRA showed aneurysmal ascending thoracic aorta (4.1 × 4.1 cm) and confirmed the aneurysmal main PA with the left and right pulmonary arteries measuring 4.5 and 5.4 cm, respectively. Right heart catheterization showed mildly elevated PA pressures with wide pulse pressure and pulmonary angiogram showed severely dilated aneurysmal PA. 750 cc of serosanguineous fluid were removed by pericardiocentesis and EF improved to 60% and 75% the next day and four days after pericardiocentesis, respectively. Fluid analysis showed exudative effusion with negative culture and cytology. Patients' symptoms improved and he was discharged to follow up with pulmonary and cardiothoracic surgery for evaluation for possible pulmonic valve replacement based on his symptoms and progression of his pulmonary regurgitation.

Conclusion This case demonstrates the vital role of early diagnosis and a heart team approach in management of rare and challenging cases with potential serious complications such as PA aneurysm.

A62

DELAYED MANAGEMENT OF MICROSCOPIC POLYANGIITIS LEADS TO CATASTROPHIC DIFFUSE ALVEOLAR HEMORRHAGE AND PROLONGED ICU STAY

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Introduction Microscopic polyangitis (MPA) is a necrotizing vasculitis, predominantly affecting small and medium-sized vessels, commonly involving the kidney and lung. We present a case of MPA that presented with subtle initial manifestations which rapidly progressed to diffuse alveolar hemorrhage (DAH) and generalized skin rash leading to intubation and prolonged ICU stay.

Case report A 71-year-old female with a history of hypertension on hydralazine presented to the ED with dry cough and mild skin rash on her right lower extremity, both started around 5 days. On physical exam, the patient was found to have normal oxygen saturation but bibasilar crackles and violaceous purpuric rash with a bullae formation on medial right ankle. Chest X-ray showed scattered interstitial opacities. D-dimer was >1000. CT angiogram of the showed small bibasilar areas of pulmonary consolidation but no pulmonary embolism. CRP at that time was 1.5. The decision was to send her home on Levofloxacin for five days for a presumed pneumonia.

Two weeks later, she came back with worsening dyspnea. Physical exam was notable for oxygen saturation of 89% on room air, bilateral crackles and worsening skin rash involving bilateral lower extremities, back and shoulders and face (figure 1). Her labs showed hypoxemia with PaO₂ of 55 on room air. Chest x-ray showed progressive diffuse bilateral heterogeneous interstitial opacities. CRP was 18.5. Patient was subsequently admitted to the intensive care unit and intubated for acute hypoxemic respiratory failure. CT chest was concerning for alveolar hemorrhage which was confirmed on bronchoalveolar lavage by bronchoscopy. Extensive workup revealed P-ANCA, MPO positive antibodies. Results were confirmed by skin biopsy and findings were consistent with ANCA associated Vasculitis.

Abstract A62 Figure 1

Empiric high dose Methylprednisone was initiated followed by a total of 4 doses of Rituximab and 7 sessions of plasmapheresis once the diagnosis was confirmed. Patient responded to therapy well and was ultimately extubated.

Conclusion The etiology for MPA flare remains a medical dilemma. Hydralazine in our case is a known culprit to cause ANCA vasculitis. Close attention and review of medications is necessary when there is a concern or uncertainty in the diagnosis. Second, there should be a high index of suspicion to prevent such dramatic and life-threatening scenarios.

B32

A UNIQUE PRESENTATION OF ACUTE SARCOID MONOARTHRITIS IN A PATIENT WITH SARCOIDOSIS

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Sarcoidosis is a multisystem disorder of unknown etiology that is characterized pathologically by the presence of non-caseating granulomas in affected organs. It predominantly affects the lungs and intrathoracic lymph nodes, but up to 30 percent of patients present with extrapulmonary manifestations. We report an interesting case of a sarcoidosis patient presenting with acute monoarthritis found to have sarcoid arthropathy.

A 49 year old male with past medical history of sarcoidosis presented with acute on chronic left knee pain. The pain was located diffusely across his anterior knee, worse towards the end of the day, limiting his ability to ambulate. He rated the pain as 10 out of 10 in severity. He was taking oral methylprednisolone 8 mg daily for his sarcoidosis, and hydrocodone/acetaminophen 10/650 mg four times daily over the week before presentation for his increased knee pain. He denied the use of Disease Modifying Antirheumatic Drugs (DMARDs) in the past. The patient denied other symptoms including fevers, weight loss, vision changes, cough, dyspnea, or rashes.

On presentation, his blood pressure was 109/63, temperature was 97.9 degrees Fahrenheit, pulse was 93 beats per minute, respiratory rate was 20 breaths per minute, and pulse oximetry was 98% on ambient air. Physical exam was remarkable for left knee warm effusion without erythema and full range of motion with moderate pain. A semi-firm, 5 cm × 1 cm, mobile, mass was palpated at the left, medial, distal thigh. Lab tests showed white blood cells were 9.5 10³/uL with no left shift, hemoglobin was 13.4 g/dL, and platelets were 164,000/mcL. Basic metabolic panel and liver function tests were normal. Left knee x-ray revealed tricompartmental joint space narrowing, osteophytes, and suprapatellar effusion. On ultrasound of the lower extremities, a non-vascular structure was found in the left, medial, distal thigh. MRI of the left knee with and without contrast shows a large complex joint effusion with internal enhancing synovium, numerous nodules and debris, and mass effect on left medial musculature without discrete mass.

An arthrocentesis of the left knee was performed and ten cc's of clear-yellow fluid was aspirated. On synovial fluid analysis, there was 4,890 /mm³ white blood cells with 49% neutrophils. No crystals were identified and no growth on bacterial culture seen.

The patient was given a left knee intra-articular corticosteroid injection with relief of his pain and discharged home. The patient had a whole body PET/CT scan to evaluate extent

of sarcoidosis which showed focal uptake in his left knee. He was started on corticotropin subcutaneous injections with good control of his pain and inflammation.

Acute monoarthritis is a common initial presentation of many joint disorders. The most common causes include osteoarthritis, crystalline disease, and infection. In patients with a history of sarcoidosis, or hilar adenopathy and erythema nodosum, sarcoid arthritis should be considered if the initial work up is inconclusive. Sarcoidosis may mimic or occur concomitantly with many rheumatologic diseases. About 10–15 percent of sarcoidosis patients have an associated arthropathy. Due to the fact that it can mimic rheumatologic diseases, delayed diagnosis and/or misdiagnosis can occur. Therefore, in patients presenting to a rheumatologist with musculoskeletal system findings, it should definitely be considered in the differential diagnosis. Acute sarcoid arthritis is treated with anti-inflammatory medications such as NSAIDs or oral corticosteroids. Most symptoms tend to resolve spontaneously.

A40 SPONTANEOUS ATRAUMATIC SPLENIC RUPTURE IN A PATIENT WITH STREPTOCOCCAL PNEUMONIA

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Introduction Spontaneous atraumatic splenic rupture is a rare but dramatic occurrence that is most commonly attributed to infection or neoplasia. Deciphering the etiology can be challenging with many cases remaining unclear despite full investigations. We describe a case of such splenic rupture secondary to streptococcus pneumoniae infection.

History and initial laboratory data A fifty nine year old male with a past medical history of peptic ulcer disease and hypertension presented with nausea, vomiting and subjective fevers going on for a week. He was admitted for pneumonia; his nasopharyngeal swab was positive for Coronavirus and his urine was positive for Streptococcus pneumoniae antigen. He was started on appropriate antibiotics and during the hospital stay, while being evaluated for acute blood loss anemia, he was incidentally found to have spontaneous atraumatic splenic rupture and intraperitoneal bleeding.

Management He had an emergent splenectomy done, and received post splenectomy immunizations. His hospital course was complicated by pulmonary embolism post operatively and then an incidentally found descending aortic pseudoaneurysm with ulceration requiring thoracic endovascular aortic repair (TEVAR). It wasn't clear if the splenic rupture was related to the descending aortic pseudoaneurysm from a pathophysiological stand point. His further workup including testing for Cytomegalovirus, Epstein-Barr virus, Human Immunodeficiency virus, viral hepatitis, syphilis infection were negative. His connective tissue diseases' workup including Rheumatoid factor, ANA, c-ANCA, p-ANCA, cryoglobulin level were negative as well. His splenic histopathology was negative for any malignancy and showed necrotic foci with inflammation. His hospital course was further complicated by deconditioning which improved significantly with physical therapy and he was discharged home with close outpatient follow up.

Conclusion Spontaneous splenic rupture is a rare phenomenon which has been associated with malignancies and certain infectious etiologies. Our patient appeared to have streptococcal infection which despite ample antibiotic treatment, lead to

splenic rupture. This case also explains how important optimum post-operative care is to prevent long term deconditioning and morbidity.

B33 MULTICENTRIC MYELOID SARCOMA WITH TESTICULAR INVOLVEMENT

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10.1136/jim-2018-000745.48

Objective Myeloid sarcoma is a rare presentation of Acute Myeloid Leukemia (AML) that can present either as an isolated extramedullary disease or in association with AML. It is more commonly seen in the pediatric population and can involve any organs of the body; specifically, skin and lymph nodes are the two most common sites. Testicular involvement is extremely rare and often poses diagnostic and management dilemmas. Here, we report a rare case of newly-diagnosed AML with multicentric myeloid sarcoma involving testes.

Method Both authors cared for the patient, reviewed and summarized data from previously published cases, and drafted the manuscript. Written informed consent for case publication was already obtained.

Abstract B33 Figure 1

Results A previously healthy 29-year-old man presented with a one-month history of fatigue and epigastric discomfort. On examination, he had ptosis of the right eye and bilateral testicular enlargement with 1-cm hard mass adjacent to the left testis. Complete blood count showed elevated white blood cells of 78,000 cells/mm³ with anemia and thrombocytopenia. Radiological studies confirmed multiple masses involving the right orbit, left lower lung, abdominal viscera, and testes (figures 1 and 2). Findings on peripheral blood smear and flow cytometry were consistent with AML (figure 3). Multicentric myeloid sarcoma was presumed, and the patient subsequently received induction chemotherapy, with an improvement of circulating blasts, eyelid swelling, and testicular enlargement.

Conclusion This case report highlights an atypical presentation of myeloid neoplasms that physicians should be aware of. The recommended treatment for myeloid sarcoma is systemic chemotherapy with induction regimen used to treat AML. Testicular myeloid sarcoma and epididymal myeloid sarcoma are extremely rare. As systemic chemotherapy may not have adequate testicular penetration, orchiectomy for tissue diagnosis and symptom control followed by local radiation therapy and systemic chemotherapy has been most commonly used.

Abstract B33 Figure 2

Abstract B33 Figure 3

A37

CHILADITI'S SYNDROME ASSOCIATED WITH ACUTE COLONIC PSEUDO-OBSTRUCTION: A RADIOLOGICAL DIAGNOSIS

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Chilaiditi's syndrome is a rare radiological anomaly of hepato-diaphragmatic interposition of bowel associated with clinical symptoms. We report a case of Chilaiditi's syndrome associated with acute colonic pseudo-obstruction.

Abstract A37 Figure 1

Abstract A37 Figure 2

Abstract A37 Figure 3

A 90-year-old male presented with hypertensive emergency. Physical examination showed distended abdomen and right upper quadrant tenderness. Chest radiograph demonstrated marked elevation of the right diaphragm and interposition of the hepatic flexure of the colon between the diaphragm and the liver. Patient improved clinically with conservative management.

Awareness of this syndrome and its association with acute colonic pseudo-obstruction is important to opt towards a more conservative management instead of unnecessary interventions including surgeries.

B63

PRIMARY GASTRIC HODGKIN'S LYMPHOMA

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Objective Hodgkin's Lymphoma is a B-Cell lymphoma that arises from germinal center or post-germinal center B cells. It accounts for 10% of all lymphomas and approximately 0.6% of all cancers diagnosed in the developed world annually.¹ While the gastrointestinal tract is the predominant site in extra nodal Non-Hodgkin's lymphoma, primary gastrointestinal involvement is rare in Hodgkin's lymphoma. We report a case of primary gastric Hodgkin's lymphoma.

Case presentation A 70 year-old female presents with a few weeks of subjective fever, 40 lb weight loss and fatigue. On exam, patient was febrile to 100.6 F and appeared cachectic with evidence of temporal wasting; rest of the exam was unremarkable. Laboratory test was significant for microcytic hypochromic anemia with hemoglobin level of 8.2 gm/dL. Contrast-enhanced computed tomography of the abdomen showed thickened gastric wall along the greater curvature and multiple enlarged peri-gastric lymph nodes. An upper endoscopy revealed an ulcerative lesion in the proximal body (a). Biopsies showed clusters of lymphocytes and occasional atypical cells with an 'owl's eye' appearance, resembling Reed-Sternberg cells (b). Immunohistochemical stains were positive for CD 30, weakly positive for PAX5 and negative for CD 45, confirming Hodgkin's lymphoma (c). Positron emission tomography showed distant involvement of pulmonary lymph nodes. Patient was started on chemotherapy with ABVD regimen (Adriamycin, Bleomycin, Vinblastine and Dacarbazine). Patient tolerated well five cycles of the chemotherapy, but refused further therapy. At completion of the 5th cycle, patient was asymptomatic with appreciable weight gain; PET scan revealed no evidence of residual disease.

Discussion Stomach is the predominant extra-nodal organ involved in lymphoma, usually as a secondary site. Occasionally, non-Hodgkin's lymphoma such as MALToma or diffuse large B cell lymphoma can present as primary gastric lymphoma. However, primary gastric Hodgkin's lymphoma is extremely rare. Diffuse mucosal involvement of the stomach and absence of prominent extra-gastric disease suggest primary gastric Hodgkin's lymphoma. Biopsies may not show the typical Reed-Sternberg cells; immunohistochemical stain is necessary for a definitive diagnosis. Prognosis is largely unknown with no clear guidelines for treatment, because of its rarity. Similar to prior reports, our patient responded favorably to chemotherapy and remains asymptomatic at 10 months.

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B56

CROSSING A BRIDGE TO HEARTBREAK

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Objective To describe an atypical cause of myocardial ischemia, in a patient presenting with chest pain and elevated troponins.

Introduction Myocardial bridging was first described by Reymann in 1737, as muscle overlying the intramyocardial segment of an epicardial coronary artery which was characterized by systolic compression of the tunneled segment. In the vast majority of cases, it remains clinically silent. We present a classic case of acute coronary artery disease caused by myocardial bridging.

Clinical presentation Patient is a 33 year old AAM with no known medical history who presented with sudden onset localized left sided chest pain for one week. Pain is intermittent and intense, rated as a 9/10. It lasts for an hour with no aggravating or alleviating factors. The patient denies nausea, vomiting, diarrhea, constipation, fever, vision problems, urinary symptoms, shortness of breath or syncope. No prior history of similar presentation. No family history of heart disease or sudden death. He denies any use of illicit drugs or smoking. Vitals are stable on admission. His exam was significant for left sided chest wall point tenderness. His electrocardiogram showed T wave inversions in the lateral leads, in conjunction with an elevated troponin of 7.41. The subsequent troponin was 6.35. Urine drug toxicology was unremarkable. Patient was treated as non-ST elevation myocardial infarction with heparin infusion, aspirin and plavix. He was taken to the cath lab the following day and was found to have myocardial bridge with compression of left anterior descending artery. All vessels were deemed patent. Patient was discharged with medical treatment.

Discussion The hemodynamic changes brought upon by myocardial bridging are rarely clinically apparent, however as this case demonstrates can have potentially severe consequences. As the coronary artery courses through the myocardium, systolic compression can result in angina, arrhythmias, myocardial ischemia and subsequent acute coronary syndrome. Recent studies suggests that myocardial bridges are present in approximately one-third of adults, with 75% of the cases being superficial bridges. These instances involve the myocardium crossing over the LAD in a perpendicular or nearly perpendicular fashion. Conversely, the remaining 25% occur when the myocardium crosses the LAD in another orientation, typically stretching from the right ventricle into the interventricular septal fibers. Even though the anatomical defect of myocardial bridging has been long known, the advent of newer imaging techniques such as coronary computed tomography angiography and intravascular ultrasound have allowed for better understanding of the disease process itself. It has been noted

that atherosclerosis frequently develops immediately proximal to the tunneled section of the vessel, likely due to a change in applied tangential forces. The compressed segment itself is more commonly spared. First-line therapy includes beta-blockers and non-dihydropyridine calcium-channel blockers, while nitrates are contraindicated. Surgical myotomy, stent placement, and CABG surgery exist as alternatives if a patient remains symptomatic despite optimal medical management.

Clinical implication With regards to anginal chest pain, myocardial bridging is a rare etiology that has become better understood coinciding with the improved sensitivity of cardiac imaging, CT angiography and IVUS have been vital in understanding the pathophysiology of a tunneled coronary vessel. Other forms of imaging such as magnetic resonance tomography, doppler-flow catheterization, and transthoracic Doppler echocardiography have been used to detect bridging, but their definitive role has yet to be established. With advancements in various imaging modalities, the bridge between an underlying structural anomaly and its clinical implication will only be further strengthened.

B57

LIQUID BIOPSY DISTINGUISHES RECURRENT GBM FROM RADIATION NECROSIS IN PERIPHERAL BLOOD OF PATIENTS WITH GBM

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Objective Glioblastoma is the most aggressive brain cancer and is very difficult to distinguish from conditions such as radiation necrosis. The objective of this study is to present a reliable test to differentiate glioblastoma from pseudoprogression and radiation necrosis using a minimally invasive blood-based liquid biopsy.

Method A 4mL aliquot of peripheral blood from human patients is subjected to Ficoll gradient and PBMC purification followed by flow cytometry on magnetically purified CD14⁺ cells stained using CD14, HLA-DR and novel surface biomarker VNN2 fluorochrome-conjugated antibodies to quantify Monocytic Myeloid-Derived Suppressor Cells (Mo-MDSC) and CD14⁺ VNN2⁺ cells in GBM or radiation necrosis patients (RN).

Results The quantification of Mo-MDSC and CD14⁺ VNN2⁺ cells on 18 GBM and 6 RN patients showed that GBM patients have a high number of Mo-MDSCs compared to RN patients (Median 33% vs. Median 6.5% respectively, $p=0.0008$) while a low proportion of CD14⁺ cells expressing VNN2 (Median 5.7% and 32% respectively, $p=0.0003$). In both GBM and RN patients, the quantity of Mo-MDSC and CD14⁺ VNN2⁺ cells was combined into a unified index designed DR-Vnn2 Index or DVI. Values ≥ 1 are indicative of GBM diagnosis, while values <1 are indicative of RN ($p=0.0004$).

Conclusion This novel, fast and minimally invasive test was able to successfully differentiate GBM from RN patients with a high degree of certainty and reliability.

B58

PAROXYSMAL AUTONOMIC INSTABILITY AND DYSTONIA FOLLOWING A MOTOR VEHICLE ACCIDENT

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Objective We were consulted on a patient in the surgical ICU (SICU) following new onset spells concerning for seizures. Our objective was to properly diagnosis the patient and provide adequate treatment for his condition. Our patient was a 20-year old male who presented following a motor vehicle accident, 7 days prior. He initially presented with a Glasgow coma score of 5, diffuse axonal injury, intra-parenchymal hemorrhage (left basal ganglia), increased intra-cranial pressure, right sided pneumothorax and fractures of ribs 6 and 7, right scapula and vertebral end plates of T3-T6. In the interim the patient had been intubated, had an intraventricular shunt placed and removed after 5 days and finished a 7-day course of Keppra prophylaxis. He had been stable until the morning we were consulted.

Methods On observation the patient was found to have episodes extensor posturing, diffuse dystonia and high frequency, low amplitude tremors. He was also noted to have autonomic instability limited to these spells with unstable vital signs including hyperthermia up to 39.3 °C, tachycardia up to 153 bpm and tachypnea up to 46 breaths per min. On exam the patient was found to have 3+ reflexes bilaterally at the patella, biceps and brachioradialis. Brain stem reflexes including gag, cough and corneal were intact. The patient would respond to painful stimuli (nail bed pressure) with increased extensor posturing and increased rigidity but no withdrawal. We obtained a video EEG that showed generalized rhythmic delta activity, lateralized rhythmic delta activity in the right frontal and temporal regions and epileptiform discharges in the left frontal regions. Lab results were non-specific except for an elevated CK level, which had been previously trending down.

At that time our leading diagnosis was new onset seizures following traumatic brain injury (TBI) and intraparenchymal hemorrhage. Due to the concern for possible seizures and the epileptiform activity on EEG the patient was loaded with Keppra and continued a maintenance dose. He was further treated with as needed diazepam. These treatments failed to control the patients dystonic tremor, dystonia, posturing and only minimally helped his autonomic instability. Due to the inadequacy of our treatment we continued to look for other possible causes of our patient's condition. We conducted a brief literature search to help us arrive at our final diagnosis.

Results We arrived at the diagnosis of paroxysmal autonomic instability and dystonia (PAID) syndrome. We treated our patient with clonazepam 1 mg twice a day, Gabapentin 300 mg twice a day, baclofen 10 mg every 6 hours and 10 mg of propranolol three times a day. This treatment gave us great results with stabilization of the autonomic system and resolution of the dystonia and dystonic tremor. The patient did continue to have a few breaks through paroxysms but was under better control. His CK began to drop and the patient began to respond to commands for hand gripping and eye opening.

Conclusions PAID syndrome is a rare syndrome that most commonly affects young persons following severe TBI. The

physiology behind the condition is thought to involve disinhibition of the sympathoexcitatory regions of the CNS causing cortically provoked catecholamine surges leading to paroxysms of autonomic instability. The dystonia likely arises from disruption of the pontine and vestibular nuclei. PAID syndrome should be thought of in the differential diagnosis young TBI patients who are not responding to typical treatments for seizures who have signs of autonomic instability. In our experience PAID syndrome responds well to a regimen of clonazepam, gabapentin, baclofen and propranolol.

B62

LIFE THREATENING: CARDIAC TAMPONADE FROM ACUTE BLEEDING SECONDARY TO APIXABAN

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Background Direct oral anticoagulants (DOAC) including direct factor X-a Inhibitor, Apixaban are indicated for the prevention of embolic events in non-valvular atrial fibrillation and for treatment for venous thromboembolism (VTE) including Deep Venous thrombosis (DVT) and Pulmonary Embolism (PE).¹ As compared to vitamin K antagonists the bleeding risk is low and with the advent of new reversal agents, they have a promising future.² However, hemopericardium is a life-threatening emergency rarely reported with anticoagulants. There are quite a few case reports of hemopericardium reported with dabigatran and rivaroxaban, however, data in case of apixaban is limited.^{3,4} We report a case of cardiac tamponade secondary to Apixaban use requiring acute surgical intervention.

Case description 62-year-old African American male with the history of Hypertension, Atrial fibrillation, deep venous thrombosis, metastatic renal cell carcinoma on Apixaban presented with progressively worsening peripheral edema and shortness of breath. Physical examination showed blood pressure of 88/50 mmHg with the heart rate of 130 beats/minute, bilateral pitting edema, positive jugular venous distention, negative Kussmaul sign with pulsus paradoxus difference of 8–10 mmHg. Laboratory values were remarkable for a drop in hemoglobin from 10 g/dl to 8.2 g/dl, platelets of 62,000/mm³, Creatinine of 1.82 mg/dl, potassium of 4.7mEq/L and mild elevation of troponin to 1.7 with no specific electrocardiographic findings. Chest radiograph showed enlarged cardiac silhouette. Echocardiogram showed a large pericardial effusion up to 3.89 cm. Subsequently, cardiothoracic surgery was involved and the patient had pericardiocentesis with 800 cc fluid drainage, along-with pericardial window formation, and pericardial biopsy. The pathology of the pericardial fluid and pericardium was negative for any malignant cells. Apixaban was held. The patient had an extensive intensive care unit stay and passed away secondary to cardiorespiratory failure.

Conclusions Reports of life-threatening hemopericardium should warrant clinicians to use DOACs carefully assessing risks versus benefits in the patients. This also emphasizes the need to look for possible interventions to control acute bleeding secondary to DOAC use. Hemopericardium should also be on our differential when patients treated with anticoagulants, including DOACs, present with clinical and radiographic signs suggestive of cardiac tamponade.

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Abstract B62 Figure 1

B64

RETROPERITONEAL FIBROSIS- AN UNCOMMON CAUSE OF ACUTE RENAL FAILURE

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Objectives Retroperitoneal fibrosis is an uncommon cause of acute renal failure, which leads to obstruction of retroperitoneal structures, typically affects ureters. We present a 41-year-old male who presented with acute renal failure; ultimately etiology was found to be retroperitoneal fibrosis.

Methods A 41-year-old African American Male with past medical history of dyslipidemia presented to the Emergency Room with Left lower quadrant aching pain not associated with food or bowel movements that is radiating to the back for the past three weeks.. He also endorsed fourteen pound unintentional weight loss in the past 2 months and night sweats and chills. Ibuprofen made the pain better and nothing made the pain worse. He work as correctional officer and denied any recent travel or exposure to TB. He is current half a pack day smoker and social drinker. His Physical examination was benign with mild generalized abdominal pain to deep palpation.

CBC was unremarkable other than mild macrocytic anemia and CMP showed BUN of 21 and Creatinine of 1.67. ESR was 48 and CRP was 6.1. Thyroid Stimulating hormone and urine analysis was unremarkable ANA screen and Quantiferon TB test was negative. A CT of the abdomen was done which showed lower abdominal aorta surrounded by soft tissue mass like density, which suggested retroperitoneal fibrosis and left urethral obstruction. MRI of the abdomen and pelvis further suggested the diagnosis. An IR guided stent was placed for his

urethral obstruction. His kidney function improved and subsequently he was discharged home and referred him to Interventional radiology for biopsy.

Results Retroperitoneal fibrosis is an uncommon cause of acute renal failure, which is due to the inflammation, and fibrosis of the retroperitoneal organs. More than two thirds of the cases of retroperitoneal fibrosis are idiopathic. Other one third of the cases are due to secondary causes such as drugs, malignancies infections radiations and or smoking.

Most of the patients present with non-specific symptoms. Physical examination findings are not specific. Laboratory exams may show an elevated BUN and Creatinine due to the obstruction. Most of the patients also have elevated ESR and CRP. The diagnosis is usually made during imaging studies due to the non specific nature of symptoms and physical exam findings. CT with contrast is the image of choice. A CT guided core biopsy or open biopsy confirms the diagnosis. All Patients diagnosed with retroperitoneal fibrosis should be thoroughly evaluated for malignancies, infections and previous exposure to radiation and drug history.

Conclusion Retroperitoneal fibrosis is a rare cause of acute kidney injury. Although most common cause is idiopathic other secondary causes such as infectious, malignancy, exposure to radiation and drugs should be ruled out.

C01 A PACEMAKER THAT WAS AVOIDED

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10.1136/jim-2018-000745.56

Objective Thyroxine is an essential hormone in human body and exerts many effects on the cardiovascular system. Low metabolic state in hypothyroidism causes bradycardia and reduced cardiac contractility leading to reduced cardiac output, severe bradycardia and Atrio-Ventricular (AV) blocks. We present a case of severe hypothyroidism causing high grade AV block which was successfully treated with thyroxine hormone replacement without requiring cardiac pacemaker placement.

Method 87 years old man with past medical history of hypertension and hypothyroidism was told by his cardiologist to present to Emergency Department (ED) after he was found to have abnormal electrocardiogram (EKG) findings on Holter monitor. Patient denied chest pain, palpitations, shortness of breath, headache or dizziness at the time of presentation to ED. Physical examination findings were as follows: Pulse 36 beats /min, respiratory rate 16/ minute, Blood Pressure 180/70 mmHg, percentage oxygen saturation was 96% on room air. EKG showed New onset atrial fibrillation with slow ventricular response, frequent episodes of bradycardia to less than 40 bpm and Left Bundle branch block (figure 1). The patient was not taking any AV nodal blocking agents such as beta blockers, calcium channel blockers or digoxin. Thyroid stimulating hormone (TSH) was elevated to 74.03 IU/ml (reference range 0.39–4.08 IU/ml), with free T4 decreased to 0.53 mg/dl (0.58–1.64 mg/dl). The patient reported that he was on levothyroxine 25 mcg daily for at least 3 years and he had been taking it on an empty stomach daily. Echocardiogram showed EF 46–50%, mild diastolic dysfunction and increased pericardial fat. Patient was admitted and levothyroxine dosage was

increased to 50 mcg per oral daily. Telemetry review on day one showed high degree AV block with 2.9 second sinus pause. However, subsequent telemetry review showed complete resolution of high degree AV block and pauses were no longer seen few days after increasing the dose of levothyroxine. Permanent pacemaker insertion was avoided and patient was discharged on levothyroxine 50 mcg daily, apixaban 20 mg daily for new onset atrial fibrillation and was advised to follow up with PCP for repeat thyroid function testing in 4–6 weeks.

Results Cardiac dysrhythmias have been reported with hyper as well as hypothyroidism. Bradyarrhythmias are typically associated with hypothyroidism. Kazim et al. reported a study on AV blocks in patients with thyroid disease. A subgroup analysis of the study shows that 7 out of 29 patients (24%) who had hypothyroidism and AV blocks had complete resolution of AV blocks after treatment with levothyroxine. However, the sample size was too small to draw any definitive conclusion. AV blocks due to hypothyroidism in most texts is considered to be reversible, however, literature is controversial and few studies showed that most patients with AV block need permanent pacemaker placement. ACC/AHA/HRS 2008 guidelines for device based therapy of cardiac rhythm abnormalities recommend permanent pacemaker implantation in patients with advanced second degree and third degree AV blocks who have symptoms (Class I recommendation, level of evidence C). However, the guidelines also give Class III recommendation in favour of deferring a pacemaker placement in patients who are asymptomatic and have a benign reversible cause of AV blocks such as Lyme disease, drug toxicity, or transient increases in vagal tone (Level of evidence: B). There is no clear guideline regarding how to manage patients with high degree AV blocks with severe hypothyroidism and there is a lot of controversy in the literature. Our patient had a baseline first degree AV block and was found to be in new onset Atrial fibrillation with slow ventricular response and high degree AV block. AV block improved with supplementation of thyroxine.

Conclusion Advanced second degree and third degree AV block with symptoms is considered to be an indication for pacemaker placement as per the latest guidelines by AHA/ACC. However, the decision to insert a permanent pacemaker should be individualized, especially, in patients with a reversible cause of heart block such as hypothyroidism. In our patient, there was complete resolution of advanced second degree AV block within days after increasing the dose of his levothyroxine. Further studies may show better insight for role of permanent pacemaker in AV blocks in patients with thyroid dysfunction.

Abstract C01 Figure 1

C13 EPIGLOTTITIS IN AN ADULT: A TRUE EMERGENCY FOR THE INTERNIST

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10.1136/jim-2018-000745.17

Objective Epiglottitis in adults can be unpredictable and sometimes catastrophic. It is of utmost importance to be able to quickly assess such cases for airway compromise.

Method I present a case of adult epiglottitis in which the patient's condition deteriorated rapidly requiring emergent tracheostomy.

Results A 47 year old man with a 2 week history of sore throat presented to the ER with worsening of pain, fever and painful swallowing for the past 1 day. At the time of presentation he denied any change in voice or trouble breathing. Physical exam was significant only for pharyngeal erythema. Labs were remarkable for WBC of 25,000. CT with contrast showed epiglottitis. No critical airway stenosis was noted. Patient was started on ceftriaxone, dexamethasone and was admitted to a telemetry unit for observation. In the next 16 hours the patient reported difficulty with swallowing secretions and later difficulty breathing. Stridor was noticed on physical exam. Fiberoptic assessment of the airway revealed significant inflammation and airway obstruction to the extent that intubation was deemed not possible and the patient was taken to OR for emergent tracheostomy. Videolaryngoscopy examination in the OR showed severe epiglottic edema with limited visualization of the glottic opening. Awake tracheostomy was performed and the patient was later transferred to the ICU. Dexamethasone was discontinued on day 4, Patient was decannulated on day 5 and was eventually discharged to home on day 7.

Conclusion With the advent of immunizations against Haemophilus influenzae serotype b, epiglottitis in the pediatric population has declined rapidly in the past several decades. As a result, most cases of epiglottitis now occur in adults. Interestingly some studies show that the incidence of epiglottitis is increasing in those aged 45 to 64 and in those older than age 85. Patients with epiglottitis usually presents with symptoms of sore throat and painful dysphagia. Presence of stridor, dyspnea and a short duration of symptoms prior to presentation (less than 24 hrs), are all described as predictors of airway loss. Treatment is centered on airway management. Antibiotics are the mainstay with steroids as adjuncts. In conclusion, epiglottitis in adults can be unpredictable and sometimes catastrophic and any clinical suspicion of epiglottitis warrants an aggressive approach. An Internist can sometimes be the first responder in inpatient units and it is of utmost importance to be able to quickly assess such cases for airway compromise.

A59 HYPERTRIGLYCERIDEMIA LEADING TO ACUTE PANCREATITIS IN A THIRTY ONE YEAR OLD MALE

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10.1136/jim-2018-000745.58

Introduction Pancreatitis is an inflammatory process in which pancreatic enzymes auto-digest the gland. The gland sometimes heals without any impairment of function or any morphologic changes; this process is known as acute pancreatitis. Long-

standing alcohol consumption and biliary stone disease cause most cases of acute pancreatitis, but numerous other etiologies are known. In 10–30% of cases, the cause is unknown, and hypertriglyceridemia has been shown to be a relatively rare etiology. We discuss a case of acute pancreatitis associated with hypertriglyceridemia.

History and clinical findings

A thirty one year old male with history of depression and anxiety presented with sharp epigastric pain going on for four days. The pain was associated with cramping, diarrhea, nausea and non-biliary vomiting. He denied alcohol abuse and reported drinking around twice a month, had no history of gallstones or biliary colic, illicit drug abuse or use of medications known to cause pancreatitis or hepatitis. He denied any family history of premature sudden cardiac deaths, hyperlipidemia or diabetes. On physical exam, he appeared to be an overweight gentleman in mild distress. He had epigastric tenderness and tachycardia.

Laboratory and diagnostic data Initial investigations showed increased serum lipase levels, mildly increased white blood cell counts and a Computed Tomography scan of the abdomen showing peri-pancreatic fluid with parenchymal stranding concerning for inflammation along with severe fatty liver disease disproportionate to the patient's age. The patient's fasting lipid profile showed a triglyceride level of 882. His liver enzymes were not elevated and bilirubin was mildly raised at 1.8. He was also found to be hyperglycemic with a raised hemoglobin A1C. His acute hepatitis panel, serum alcohol level, serum calcium level and urine drug screen were negative. Abdominal ultrasonography was negative for gallstones or biliary obstruction.

Management The patient was started on intravenous normal saline, was kept nil per os (NPO) and since the patient didn't appear to be septic, antimicrobial therapy was withheld. He was also started on low dose atorvastatin, multiple dose insulin injection therapy with outpatient follow up for newly diagnosed diabetes mellitus. With symptomatic improvement, the patient's diet was restarted and he was counselled about familial hyperlipidemias.

Conclusion Hypertriglyceridemia is a relatively rare cause of pancreatitis and requires a high index of suspicion for diagnosis. The treatment of pancreatitis itself in these cases is similar to that of other etiologies with the primary management being supportive.

C14 TIME DOES NOT HEAL ALL WOUNDS

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Introduction This is a case of pyoderma gangrenosum presenting 14 years after procto-colectomy for ulcerative colitis. Response to oral steroids and wound therapy was suboptimal warranting use of anti-TNF therapy.

Case presentation A 61 year old female with past medical history significant for ulcerative colitis s/p procto-colectomy in 2003, orthotopic liver transplant for primary sclerosing cholangitis (maintained on sirolimus) and chronic kidney disease presents with a non-healing ulcerated wound on the left medial calf. The wound started as a blister and progressed to a 20 × 10 × 2 cm ulcer with elevated violaceous borders. Despite initial concerns for infectious cellulitis, response to

multiple prolonged courses of antibiotics was marginal. Given history of inflammatory bowel disease and wound characteristics, pyoderma gangrenosum was suspected. Vasculitis, calcific uremic arteriolopathy and brown recluse spider bite were put forward as differential diagnoses. Wound biopsy showed vascular thrombosis with extensive necrobiotic changes and foci of acute inflammation which was nonconclusive. Sirolimus was held to allow for better wound healing. Poor wound healing persisted despite three weeks on high dose prednisone. Patient was then started on infliximab, and the wound showed marked improvement after a few weeks of therapy. However thereafter, family decided to proceed with hospice care, mainly because of decline in mental status of unclear etiology.

Discussion Pyoderma gangrenosum is a rare cutaneous manifestation of ulcerative colitis and Crohn's disease. It seems to have a course independent of the underlying disease activity. Traditionally treatment consisted largely of local wound care and topical and systemic steroids. Topical tacrolimus and oral cyclosporine have also been used as single agents or more commonly as combination therapy with steroids. Surgical debridement may actually worsen disease and is best avoided. Recently the role of biologics has been explored. PG is associated with the upregulation of several pro-inflammatory cytokines including IL-8, TNF, IL-1 β , IL-6, and interferon gamma, among many others, which may explain the response anti-TNF agents. Level of evidence supporting use of these various agents is variable. Randomized controlled trials support the use of prednisolone, cyclosporin, and infliximab. Decision on using a particular agent will depend on wound extent, local expertise and associated comorbidities (for patients with concomitant active inflammatory bowel disease for example, anti-TNF agents may be an attractive option).

C15

DIABETIC KETOACIDOSIS COMPLICATED BY PSEUDOHYPONATREMIA AND SEVERE DYSLIPIDEMIA

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10.1136/jim-2018-000745.60

Introduction Diabetic ketoacidosis remains a life threatening emergency with multiple complications. Here we present a case report of diabetic ketoacidosis with multiple severe metabolic abnormalities, and was a diagnostic challenge.

Case report A 53-year-old Caucasian male presented to the emergency department with a small subcutaneous abscess in his right thigh. His past medical history was significant for coronary artery disease, hypertension, dyslipidemia with hypertriglyceridemia and morbid obesity. He underwent an incision & drainage in the ED. Routine laboratory evaluation revealed significant hyponatremia (Sodium 106 mEq/L), hyperglycemia (Glucose 600 mg/dl) with elevated anion gap metabolic acidosis (Anion gap 20) and an elevated beta-hydroxybutyrate. He was clinically asymptomatic without any mental status changes. One month prior to admission, patient had a HbA1c of 14 with hypertriglyceridemia (TGL 1900 mg/dl). Patient denied knowledge of being diagnosed with diabetes but reported being compliant on atorvastatin 80mg and a healthy diet to lose weight.

Interestingly his serum was reported to be very lipemic, with significant hypercholesterolemia and hypertriglyceridemia which was reported too high to quantify. Patient's serum was too lipemic to quantify serum creatinine. His serum osmolality was normal (304 osmol/kg) supporting a diagnosis of pseudo-

hyponatremia secondary to hyperlipidemia and hyperglycemia. He was diagnosed with diabetic ketoacidosis precipitated by a subcutaneous infection resulting in significant lipolysis and resultant metabolic abnormalities. Endocrinology was consulted and he was started on an insulin drip, fenofibrates and statins.

He remained hemodynamically stable without any clinical symptoms. His keto-acidosis resolved within 12 hours, and he was tolerating an oral diet but his insulin drip was continued in view of evident lipolysis. Upon resolution of hyperglycemia his serum sodium increased to 116 mEq/L, and after 48 hours of remaining on the insulin drip his serum sodium increased to 130 mEq/L. He was subsequently transitioned to a subcutaneous insulin regimen and was discharged home.

Discussion Diabetic ketoacidosis (DKA) is an acute metabolic complication that occurs mainly in type I diabetes but has been increasingly reported in type 2 diabetes mellitus. Insulin deficiency increases free fatty acid (FFA) and amino acids release from adipose tissue and muscle, and increased counter-regulatory hormones causes increased gluconeogenesis and glycogenolysis in the liver. Elevated FFA taken up by liver leads to increased production of very low density lipoprotein (VLDL) resulting in hypertriglyceridemia. Pseudo-hyponatremia is a common complication of DKA with severe hypertriglyceridemia. Serum triglycerides (TG) >2,500 mg/dL, can decrease measured electrolytes by over 5% due to intracellular movement of serum lipid components.

Although moderate hypertriglyceridemia in DKA is common, TG levels exceeding 1,000 mg/dL, increases the risk of devastating consequences such as acute pancreatitis or lipemic retinalis warranting early recognition and appropriate treatment.

Hypertriglyceridemia is an uncommon cause of acute pancreatitis accounting for 1–4% of cases, especially when the serum concentrations exceeds 1,000 mg/dL. High plasma TGs, are hydrolyzed by lipase in the pancreatic capillaries and causes activation of trypsinogen resulting in pancreatitis. The common clinical scenario of hypertriglyceridemia-induced acute pancreatitis involves poorly-controlled diabetes mellitus with type IV hyperlipidemia, or chronic alcoholism.

First line therapy for hypertriglyceridemia comprises of insulin and lipid lowering agents, most importantly fibrate therapy. Plasma exchange has also been very effective in treating severe hypertriglyceridemia and in preventing complications. Compliance with lipid lowering agents and insulin is critical in prevention of recurrence.

Conclusion Hypertriglyceridemia and pseudo-hyponatremia are common complications in DKA. This case report demonstrates the severity of these metabolic abnormalities. The prompt recognition of these metabolic complications and rapid initiation of appropriate treatment can prevent multiple life threatening complications.

B45

ADDISON'S DISEASE IN A PATIENT WITH NECK TRAUMA

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10.1136/jim-2018-000745.61

Objective Addison's disease is the insufficient function of adrenal cortex due to destruction or dysfunction of 90% or more of both adrenal cortices. A rare disease, around 40–60 cases are reported per 1 million US population. Failure or delay in

diagnosis can be life-threatening. Concomitant endocrine problems increase the risk for debilitating illness.

Method Case report.

Results A 38-year-old female presented to our office in October 2017 with worsening of the following symptoms: light-headedness, anxiety, fatigue, cold intolerance, brain foginess, dry skin, hair loss, depression, abnormal labs, decreased appetite, unintentional weight loss (since Jun 2016), amenorrhea without pregnancy (since April 2017), depression and insomnia. She had been diagnosed with Hashimoto's disease (positive thyroid peroxidase antibodies and anti-thyroglobulin antibodies) in May 2017 and was on levothyroxine 100 mcg every morning. Her symptoms began in summer 2016 ever since she was accidentally hit in the right side of her neck by a baseball. She initially had a bruise and neck pain for a short period of time followed by all the symptoms mentioned above. Her mother has a history of Addison's disease, thyroid issues, ovarian or cervical cancer. On examination, she looked cachectic and tanned, and had a goiter. Her lab work was significant for very low cortisol (<0.8 microg/L). She was immediately started on Hydrocortisone 10mg oral tablet in increasing doses. She has since reported a decrease in her symptoms and an overall improvement.

Conclusion In patients with thyroid related symptoms overlapping with adrenal insufficiency features, Addison's disease should be considered and treated on time.

B46 IMMUNE THROMBOCYTOPENIC PURPURA- NOT NECESSARILY A DIAGNOSIS OF EXCLUSION

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10.1136/jim-2018-000745.62

Objective To describe a case of thrombocytopenia due to ITP that was obscured by presence of decompensated liver disease and massive splenomegaly.

Method We describe a case of 68 year old male with past medical history of alcoholic liver disease who was admitted for worsening ascites. Laboratory findings were significant for pancytopenia with a platelet count of 47×10^9 per liter. During the hospital course patient's platelet count dropped to as low as 9×10^9 per liter. Patient received multiple units of platelets without any significant improvement in platelet count which was thought to be secondary to sequestration from massive splenomegaly.

Results Eventually a trial of intravascular immunoglobulin was given and patient's platelet count improved to 90×10^9 per liter. A diagnosis of ITP was thus made.

Conclusion Immune thrombocytopenic purpura is generally a diagnosis of exclusion. We should be cognizant of the fact that ITP could be simultaneously present with more obvious causes of thrombocytopenia. A trial of IVIG may be worthwhile in a patient with low platelets refractory to transfusion.

C30 SEVERE BRADYCARDIA REQUIRING TEMPORARY PACING IN THE EMERGENCY SETTING: THE VICIOUS TRIAD OF AKI, HYPERKALEMIA AND AV NODAL BLOCKER TOXICITY

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Background In the emergency setting, physicians are often required to make quick decisions with limited available information. Severe bradycardia with shock is one of the true medical emergencies. Hyperkalemia is a frequent cause of cardiac rhythm disturbances and severe bradycardia can be seen with hyperkalemia and acute kidney injury, but in concomitance with AV nodal blockers, it may be even more profound and difficult to treat. We present a case of a patient who presented with refractory bradycardia and shock in unclear circumstances requiring urgent temporary transcutaneous pacing en-route to the hospital, it was subsequently found that underlying driving factor was severe hyperkalemia, acute kidney injury and beta blocker toxicity.

Clinical presentation 62 year old male with past medical history of Hepatitis C cirrhosis, end stage liver disease, alcohol abuse, CKD (stage 1), HTN and Osteoarthritis who was brought to the ED after he had a syncopal episode while eating dinner at his skilled nursing facility. Patient was reportedly unresponsive after that syncopal episode. On EMS arrival he was noted to have wide complex bradycardia with critically low heart rate ~20s and hypotensive 64/48 which prompted transcutaneous pacing at 70 beats/minute. In the ED patient was intermittently interactive, disheveled and poorly kept. Patient had no previous history of cardiac problems and the most recent echo 3 months ago had normal ejection fraction and no evidence of any structural abnormalities. Turning the pacemaker off resulted in asystole on monitor (figure 1), and thus patient was completely dependant on transcutaneous pacing in light of his bradycardia of unclear cause. Patient was given bicarbonate, calcium chloride and started on dopamine drip. Laboratory work-up was sent and cath lab was alerted for possible need for transvenous pacing in light of patient's profound bradycardia. Subsequent labs showed acute renal failure with Cr of 5.38 (baseline ~1.5), K 8.3, Na 114. Cath lab was deactivated and patient was admitted to medical ICU service. Patient was started on CRRT in the ICU and continued on transcutaneous pacing for few more hours after which he only required backup pacing. Even though patient's hyperkalemia resolved within few hours he continued to stay bradycardiac with rates 40–50s, necessitating the use of epinephrine and dopamine to maintain heart rate and blood pressure in good range. Patient was taking propranolol 40mg twice daily at nursing facility, thus due to concern of beta-blocker toxicity and persistent bradycardia, patient was started on glucagon drip. Patient subsequently made good recovery resulting in normal heart rate as well as improvement of renal function to his baseline and was transferred to medicine floor followed by eventual discharge to skilled nursing facility.

Discussion According to the current guidelines of the American College of Cardiology/American Heart Association for pacemaker implantation, clinically significant symptomatic bradycardia is one of the major indications for pacemaker implantation. However, if symptomatic bradycardia is related to extrinsic causes, removal of potentially reversible causes of the bradycardia is always the first approach to management. Thus early identification of these reversible causes is vital to avoid any un-necessary need for cardiac pacing. Severe symptomatic bradycardia has been observed during therapy with beta-blockers and other AV nodal blockers, but their deleterious effects are very pronounced in patients with kidney dysfunction. Hyperkalemia is a common clinical condition that can induce deadly cardiac arrhythmias. Renal failure causes hyperkalemia and also causes the accumulation of some AV nodal blockers. This hyperkalemia then synergizes with AV

Abstract C30 Figure 1

node blockers to cause more profound bradycardia and hypoperfusion. Hypoperfusion, in turn, causes worsening of the renal failure resulting in this cycle to worsen.

Conclusion In patients who develop triad of hyperkalemia, acute kidney injury and AV nodal blocker toxicity resulting in bradycardia and hypotension, the underlying pathophysiology is for hyperkalemia to synergize with AV node blockers to cause profound bradycardia. Thus a high index of suspicion of this clinical entity should be present in patients at risk of renal failure and taking AV nodal blockers who present with severe bradycardia.

C31

USE OF MECHANICAL CIRCULATORY SUPPORT DEVICES IN TAKOTSUBO CARDIOMYOPATHY: CASE SERIES

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10.1136/jim-2018-000745.64

Objective Takotsubo cardiomyopathy (TC), also known as stress induced cardiomyopathy or 'broken heart syndrome', is a well-defined clinical entity in cardiovascular medicine. Supportive treatments with inotropes, vasopressors, mechanical circulatory support devices (MCS) and medications such as angiotensin-converting enzyme inhibitors remain the mainstay management. We present two cases of TC complicated by cardiogenic shock which were supported by the use of two different MCS devices.

Method The first case was of a 64-year-old female status post resection of meningioma that was admitted with cardiogenic shock with findings of profound dyspnea and hypotension. She had a lactic acid of 11, creatinine 1.8, troponin 24.9 and ECG with 1 mm ST elevations in leads V2-V3. Emergent coronary angiography showed normal coronaries and left ventriculogram showed apical ballooning and ejection fraction 35–40%. The second case was of a 42-year-old female with history of multiple cardiac stents in the past presented with severe respiratory distress and cardiac arrest requiring cardiopulmonary resuscitation. Her ECG showed diffuse anterior ST elevations and emergent coronary angiography showed normal coronaries. Left ventriculogram showed diffuse hypokinesis of apical segment with EF 30–35%. Both of these cases

presented with an absence of obstructive coronary artery disease, leading us to diagnose both of these cases with TC.

Results In the former case, we proceeded with the placement of an intra-aortic balloon pump (IABP), which was set at 1:1 to augment the cardiac output along with Norepinephrine, Vasopressin and Phenylephrine for circulatory support. Over the next 12 hours we saw an improvement in her cardiac index from 1.2 to 1.92. Due to an additional septic shock component, the patient was tachycardic and the IABP was not timing well with the diastole and hence we decided to remove the IABP. Repeat echocardiogram in 4 days showed improvement in her ejection fraction to 50–55%, cardiac index improved to 2.1 and cardiac output to 3.8. In the latter case, we placed an Impella CP. During our treatment, the patient suffered a compounding anoxic brain injury and was declared brain dead. Per family request, patient was transferred to hospice and all life sustaining support, including the Impella CP device, was withdrawn. The patient expired in the presence of all of her family members.

Conclusion Management in this form of cardiomyopathy is mainly supportive and the cardiac functions in almost all of the cases recover to the baseline in a few days to a few weeks. Use of vasoactive medications, such as catecholamines and inotropes, and MCS devices provide hemodynamic support and maintain effective circulatory blood volume. The two major modalities of these devices are Left Ventricular Assist Devices, such as Tandem Heart, Impella, and Extra Corporeal Membrane Oxygenator, and IABP. We used IABP and Impella CP devices in our patients to augment the cardiac output and reduce the burden on the already strained myocardium. When we compared the outcome of our case series with the case reports published in literature, we reach the following conclusions:

- We encourage the use of MCS devices in this acute non-ischemic process and we also encourage researchers to undertake trials to assess the efficacy of various modalities.
- The presence of comorbidities in a patient with TC such as concomitant septic shock in case 1 and anoxic brain injury in case 2, can drastically change the outcome of management of TC.
- Early recognition and treatment of comorbidities in such patients is essential in ensuring complete cardiac, as well physical, recovery.

C32 A COMPLICATED CASE OF SIGMOID COLON CARCINOMA

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The majority of colorectal cancers are not due to genetic predisposition, rather the majority are due to old age, lifestyle factors, and comorbidities. Individuals with a family history of colorectal cancer among first-degree relatives have a 3-fold greater risk of disease, however, this only accounts for approximately 20% of all cases (2). The main method of detection of colorectal cancer is through screening colonoscopy. The American Cancer Society recommends that screening begin at the age of 50 and is performed every 10 years. If an individual has a first-degree relative that had colon cancer, it is recommended they begin screening at age 40 or 10 years earlier than the age of diagnosis of the first-degree relative. The current treatment options are surgical resection, chemotherapy, and radiation therapy. There have also been successful monoclonal antibodies recently developed.

Our patient was a 52 year old male with a complicated previous medical history involving morbid obesity, coronary artery bypass graft x4, Type II Diabetes, HTN, HLD, CAD, GERD, OSA, arthritis, and depression. The patient's father had a history of both colorectal and prostate cancer. The patient had not yet received a colonoscopy. We performed a screening colonoscopy on the patient and it revealed a sigmoid colon mass. Multiple biopsies were taken and they were positive for carcinoma features. The patient then underwent further evaluation and was noted to have multiple gallstones. We began planning to perform a sigmoid resection and cholecystectomy due to the risk of postoperative cholecystitis. In the operating room there was difficulty inserting a Foley catheter due to fibrous scar tissue surrounding the penis due to a traumatic event during the patient's childhood. This required dorsal reflection of the foreskin and utilization of an ureteroscope along with a guidewire that was then used to slide the catheter over. We then began with the cholecystectomy and sigmoid resection under the ERAS protocol. Under laparoscopy we mobilized the colon and transected the colon 10 cm proximal to the tumor and 10 cm distal to the tumor. We then opened the abdomen and removed the transected portion. After removal we performed a side-to-side colocolostomy in a stapled fashion. We then closed the patient and sent the specimen to pathology. The pathology report revealed that a low-grade adenocarcinoma and all 13 lymph nodes tested showed no evidence of metastatic carcinoma.

C50 A FATAL CASE OF PINEAL GLAND TUMOR

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10.1136/jim-2018-000745.66

Objective To describe a fatal case of papillary tumor of the pineal gland in a 23 year old male.

Method A 23 year old male was brought to our emergency room in a state of unresponsiveness and intubated by the paramedics in field. The family gave history of progressively worsening gait instability and confusion that began three weeks before presentation. An emergent CT head was

performed which revealed obstructive hydrocephalus with a third ventricular mass and uncus and tentorial herniation. External ventricular drainage (EVD) catheter was placed to reduce intracranial pressure. An endoscopic third ventriculostomy with subtotal resection of the mass was performed and the specimen was sent for pathological evaluation. Pathology was consistent with papillary tumor of the pineal gland.

Results Despite two ventriculostomy drains and sub total resection of the tumor, the hydrocephalus persisted on serial CT scan and MRI with no improvement in clinical condition. Patient was eventually terminally extubated.

Conclusion Pineal gland tumors are rare accounting for less than 1% cases of intracranial tumors. Pineal tumors usually present with signs and symptoms consistent with hydrocephalus. Initial approach is directed towards reducing intracranial pressure. Diagnosis is confirmed by biopsy and treatment consists of surgical resection which is frequently followed by adjuvant radiotherapy. Prognosis depends upon disease extent and histological type. Prompt recognition of signs and symptoms of increased intracranial pressure is important and warrants immediate medical attention.

C51 COAGULOPATHY COMPLICATED BY BLEEDING DISORDER

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10.1136/jim-2018-000745.67

Objective Certain acquired hypercoagulable states cause an increase in tendency to develop blood clots, venous and arterial thrombosis. Thrombosis in turn leads to significant morbidity and mortality. Common risk factors for acquired hypercoagulability are age, immobilization, pregnancy, hormonal supplements and cancer. Hereditary factors leading to thrombosis usually present at a younger age. Causes include mutations of Factor V Leiden and Prothrombin 20210A, and deficiency of Protein C, Protein S and antithrombin. Rarely, bleeding and clotting tendencies can present in the same patient leading to a challenging situation requiring a fine balance between those two conditions.

Method Case report.

Results A 61-year-old Caucasian male presented with neck tightness and burning chest pain in September 2012, found to have pericarditis and non-obstructive CAD. He had a history of radiation exposure in Chernobyl, long-standing well-controlled type 2 diabetes associated with hyperlipidemia, chronic back pain, Vitamin D deficiency and depression. He had a smoking history of 30 pack years. His medications included liraglutide, rosuvastatin, trazodone, Vitamin D3, losartan, gabapentin and oxycodone. Electrocardiogram showed old anterior wall myocardial infarction. Angiogram was normal. Hence, clotting factor work up was done. Blood work showed Homocysteinemia (13 U, reference: <10 U), PAI-1 genotype, heterozygous MTHFR C677T and heterozygous MTHFR A1298C mutations. All these factors contributed to hypercoagulability. He was given methyl folate, Vitamin B6 and Vitamin B12 supplementation for homocysteinemia. He was doing well for 2 years, except occasional anginas which were treated with nitroglycerine. During a routine blood work in October 2014, he was found to have thrombocytopenia (platelet count-51,000, compared to 231,000 in April 2013). Between 2014 and 2016, his platelet counts ranged between 40,000 to

104,000, he was diagnosed with immune thrombocytopenic purpura per Hematologist. In July 2016, he developed severe pain in left leg and was diagnosed with deep vein thrombosis and started on rivaroxaban. In August 2016, he was tested positive for DRVVT lupus anticoagulant, cardiolipin antibody IgM and beta-2 glycoprotein 1 IgG antibodies. One week before the DVT diagnosis his platelet count dropped from 51,000 to 26,000. He was treated with prednisone and IVIG- his platelet count started climbing up but still ranged between 50,000–80,000. In December 2016, his platelet count was 3,000 requiring emergent transfusion, IVIG and increased dose of prednisone followed by recovery to 130,000 over the next few days. He was started on rituximab, but his thrombocyte count did not normalize. At the end of January 2017 patient's rivaroxaban was stopped and about 3 weeks later he developed acute PE. Anticoagulation was restarted, and the patient was started on apixaban. Since August through October 2017, his platelet count has been within normal range. On repeating lupus anticoagulant test, the test turned out positive for platelet neutralization and DRVVT test.

Conclusion Thrombocytopenia in the presence of clotting disorders still can lead to development of deep vein thrombosis and severe drop of platelets should increase suspicion for that. Management of thrombocytopenia and deep vein thrombosis at the same time is very challenging and should be done by hematologist who specializes in both.

C58 ELECTROMAGNETIC FREQUENCY AND ITS HEALTH EFFECTS IN A FEMALE

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10.1136/jim-2018-000745.68

Objective We are surrounded by electromagnetic frequencies every moment every day. National institute for occupational safety and health is actively researching the implications of radio frequencies- usually emitted by cell phones and cell towers, extremely low frequencies- usually from our air conditioners and static magnetic fields – DC current. We present the case of a female showing clinical features that remind us the health hazards of being close to such radiation.

Method Case report.

Results In 2015, a 48-year-old female presented with sensitivity to her Smart Meter-which was installed in April 2013. Within months of installation, she developed the following symptoms: back aches, worsening of her reflex sympathetic dystrophy (which she had since 1993), diaphoresis, peri-menopausal issues, hypoglycemia, weight loss, diarrhea, coughing, insomnia (slept just 1 hour at a time), difficulty walking and stress. She had a history of lead and mercury toxicity for which she underwent chelation therapy. Treatment with hormone replacement therapy for peri-menopausal symptoms made her feel worse. She was a non-smoker on an organic Paleo gluten-free diet (20 years). Lab work showed Vitamin D deficiency and dyslipidemia. Since the Smart Meters were removed in July 2015, her sweating reduced, sleep improved, pain decreased, and coughing stopped. Blood sugars were better. She regained 4 lbs. She relocated to a quiet locality with the least radiation. She has since been doing well. She uses Smart Shield 360 to absorb electromagnetic radiations.

Conclusion We concluded that in patients with non-specific symptoms with or without prior history of sensitivity to radiation, we must rule out electromagnetic frequency sensitivity.

C61 HUMAN IMMUNODEFICIENCY VIRUS INFECTION WITH MYCOBACTERIUM AVIUM COMPLEX PROHIBITING MEDICATION ABSORPTION AND CAUSING ELEVATED VIRAL LOAD

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Introduction HIV is a viral infection causing multiple opportunistic infections including mycobacterium avium complex (MAC). MAC causes diarrheal disease and subsequently decreased absorption of nutritional ingredients.

Case presentation We present a rare case of MAC infection in an HIV infected patient causing him to have chronic elevated viral load despite compliance with antiretroviral medications.

Endocrinology/Metabolism

B05 THE ROLE OF ADIPOSE MECHANISTIC TARGET OF RAPAMYCIN COMPLEX 2 LONGEVITY AND THE RESPONSE TO CALORIE RESTRICTION

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Objective Calorie restriction (CR) is a dietary intervention that robustly and reproducibly extends both healthspan and lifespan in diverse species, including mice. In mammals, a broadly conserved metabolic effect of CR is improved insulin sensitivity, and it has been proposed that improved insulin sensitivity may mediate some of the benefits of CR. The mechanistic target of rapamycin (mTOR), a protein kinase which serves as a central integrator of nutrient signaling, has been shown to be a key mediator of the effects of CR in yeast, worms, and flies, and treatment with rapamycin, a specific acute inhibitor of mTOR complex 1 (mTORC1), extends lifespan in mice. Chronic treatment with rapamycin also inhibits a second mTOR complex, mTORC2, which functions as an important mediator of insulin action in tissues including liver, muscle and adipose tissue. We have shown that genetic depletion of Rictor, which encodes an essential protein component of mTORC2, in the liver or the whole body of mice, impairs glycemic control in both males and females, and specifically inhibits male but not female lifespan. Intriguingly, while rapamycin disrupts mTORC2 signaling in adipose tissue, some genetic mouse models of adipose-specific insulin resistance (e. g. the FIRKO mouse) as well as systemic insulin resistance have actually been shown to promote health and longevity. Thus the purpose of this study is to examine the effect of genetically disrupting mTORC2 specifically in adipose tissue on longevity and in the metabolic response to CR.

Method We generated a mouse model of adipose-specific mTORC2 depletion by crossing mice conditionally expression Rictor with mice expressing Adiponectin-Cre (AQ-RKO). We fed AQ-RKO mice and their wild-type littermates either ad libitum or 40% CR, and longitudinally examined weight, body composition, glucose homeostasis and survival.

Results We observed sex-specific effects of disrupting mTORC2 on weight and body composition, with ad libitum fed AQ-RKO female mice having increased body weight and

lean mass relative to littermate controls, and AQ-RKO male mice having reduced body weight and body fat. Compared to wild-type littermate controls, AQ-RKO mice of both sexes fed ad libitum are insulin resistant, and unlike wild-type mice do not have improved insulin sensitivity when placed on a CR diet. In contrast to the results of Rictor deletion specifically in the liver or in the whole body, which impairs male lifespan, male AQ-RKO mice have a normal lifespan; however, female AQ-RKO mice have reduced longevity. However, both sexes of AQ-RKO mice have increased lifespan when placed on a CR diet, and live as long as wild-type mice on CR.

Conclusion While adipose mTORC2 is required for normal female lifespan and is necessary for CR to improve insulin sensitivity, adipose mTORC2 is dispensable for the effects of CR on longevity. The ability of CR to extend lifespan are therefore independent of the effects of CR on insulin sensitivity.

A10 BRAIN GRAY MATTER VOLUME DIFFERENCES IN OBESE YOUTH WITH TYPE 2 DIABETES: A PILOT STUDY

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Objective Adults with type 2 diabetes (T2D) have significantly lower gray matter volume (GMV) compared to healthy peers. The extent of GMV differences in youth with T2D remains unclear. Our objective was to compare global and regional GMV between obese youth with T2D with age, race, and sex similar healthy controls.

Methods In a cross-sectional study, 20 obese youth with T2D underwent T1-weighted brain magnetic resonance imaging

(MRI). Comparisons were made to 20 age, race, and sex similar controls. Differences in global and regional GMV between groups were identified using voxel-based morphometry.

Results Youth with T2D had a significantly lower global GMV-to-intracranial volume ratio (0.51 ± 0.02 in T2D vs 0.53 ± 0.02 in controls, $p=0.02$, Cohen's d 0.85). There were fourteen regions where GMV was significantly lower in the T2D group, and nine of these were found in either the temporal or occipital lobes (figure-blue). There were six regions with increased GMV in T2D (figure-red). All regional differences were significant at $p<0.05$ after adjusting for multiple comparisons.

Conclusions Results from this pilot study show obese youth with T2D have significantly lower global GMV and regional GMV differences, when compared to their age, race, and sex similar peers. Future work is needed to determine whether these brain findings are a direct result of adolescent-onset T2D.

A11 HYPOTHALAMIC MTORC2 REGULATES METABOLIC HOMEOSTASIS

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The mechanistic Target of Rapamycin (mTOR) is a serine/threonine protein kinase that is inhibited by the FDA-approved immunosuppressant and anti-cancer agent rapamycin. Inhibition of mTOR complex 1 (mTORC1) extends lifespan

Abstract A10 Figure 1

and can prevent or delay age-related diseases in mice. However, chronic administration of rapamycin inhibits mTOR Complex 2 (mTORC2) which causes side-effects such as disrupted glucose homeostasis. It has been shown that hypothalamic activity of mTORC2 plays a critical role in the regulation of metabolic homeostasis. The central nervous system, especially the hypothalamus, largely controls energy expenditure and food intake. Recently, we found that mTORC2 increases with age in the hypothalamus of the murine brain. Furthermore, mice lacking *Rictor*, a key component of mTORC2, in neurons have increased fat mass, adiposity, and glucose intolerance (Kocalis, *et al. Molecular Metabolism*. 2014).

Objective Here, we investigated the effects of hypothalamic mTORC2 with respect to metabolic health and lifespan.

Method We used male and female mice with *Rictor* specifically deleted in the hypothalamus and tracked their glucose metabolism, body composition, and energy expenditure with age.

Results Interestingly, *Rictor* deletion impairs glucose and pyruvate tolerance in males but not in females and this phenotype strengthens with age. We also found that *Rictor* deletion in both males and females results in increased body mass, fat mass and lean mass that persists with age. These phenotypes are associated with elevations in heat production.

Conclusion These results suggest *Rictor* hypothalamic deletion has a greater effect on metabolic homeostasis in males compared to females.

A17

ESTRADIOL IMPEDES FIRST TRIMESTER CYTOTROPHOBLASTS FUNCTION VIA ANTI-ANGIOGENIC AND APOPTOTIC SIGNALING

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Objective Proper regulation of estradiol (E2) plays an important role for normal placental development during the first trimester of pregnancy. Previous studies demonstrated that unusually high levels of E2 during early pregnancy could hamper normal development of the placenta via increased apoptosis of cytotrophoblast cells (CTBs). However, the mechanism of this effect in the CTBs is yet unknown. The aim of this study is to determine whether E2 impedes CTBs migration, invasion, and proliferation.

Method The first trimester human CTBs were treated with 17beta-E2 at concentrations between 0 and 100 nM. Expression of invasion related proteins: urokinase plasminogen activator (uPA) and plasminogen activator inhibitor 1 (PAI-1); migration related proteins: Matrix metalloproteinase 9 (MMP-9) and MMP-2; stress and apoptotic proteins: p38 MAPK phosphorylation, Bax/Bcl-2, Caspase-9 and Caspase-3 were measured by western blot in E2-treated CTBs cell lysates. Levels of vascular endothelial growth factor (VEGF), placental growth factor (PIGF), soluble fms-like tyrosine kinase-1 (sFlt-1), and soluble endoglin (sEng) were measured in culture media using ELISA kits. Statistical comparisons were performed using analysis of variance with Duncan's post-hoc test.

Results The expression of uPA was downregulated in ≥ 25 nM E2-treated CTBs compared to basal ($*p < 0.05$); however, PAI-1 was upregulated in ≥ 25 nM E2-treated CTBs. Both MMP-2 and MMP-9 were downregulated in ≥ 25 nM E2-treated CTBs compared to basal ($*p < 0.05$). The expression of proapoptotic

caspase 3, caspase 9, and BAX/Bcl-2 ratio and p38 MAPK phosphorylation were significantly increased in ≥ 25 nM E2-treated CTBs compared to basal ($*p < 0.05$). Secretion of sFlt-1 and sEng were increased while VEGF and PIGF were decreased in CTBs treated ≥ 25 nM of E2 ($*p < 0.05$ for each).

Conclusion These findings suggest that E2 inhibits migration and invasion of CTBs and induces the anti-angiogenic milieu and apoptosis in the first trimester CTBs. These factors may be associated with pregnancy complications including infertility, and uteroplacental inadequacy.

A18

ABSTRACT WITHDRAWN

A19

TCF19, A NOVEL DIABETES GENE, REGULATES STRESS RESPONSE PATHWAYS IN THE PANCREATIC β -CELL

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Objective Diabetes is a disease of reduced functional pancreatic β -cell mass. β -cells sense glucose and release insulin, the hormone responsible for maintaining glucose homeostasis. Reduced β -cell mass is seen in both type 1 and type 2 diabetes resulting in the inability to maintain normal blood glucose levels. Altered rates of β -cell proliferation and apoptosis both impact β -cell mass. The identification of genes that regulate proliferation and survival of the β -cell can provide new therapeutic strategies for diabetes. Transcription Factor 19 (TCF19) is a putative transcription factor associated with both type 1 and type 2 diabetes in genome wide association studies. TCF19 is expressed in pancreatic β -cells and is upregulated in proliferating islets. We have previously shown that knockdown of TCF19 in a β -cell line resulted in decreased cellular proliferation and increased apoptosis, both at baseline and in response to thapsigargin-induced endoplasmic reticulum stress. Therefore, we hypothesized that TCF19 is a key regulator of β -cell proliferation and survival. The objective of this study was to determine the role of TCF19 in β -cell growth and survival using *in vivo* and *in vitro* models.

Methods We generated a germline whole body knockout of Tcf19 in C57BL/6N mice. We obtained metabolic phenotypes on animals between 4–16 weeks of age. RNA sequencing (RNASeq) was performed on pancreatic islets from Tcf19 knockouts and wild type controls. Some results were verified with quantitative PCR (qPCR). To further understand the role of Tcf19 in the β -cell, we expressed human TCF19 in the INS1 rat β -cell line. We performed ³H-thymidine incorporation assays, qPCR, and RNAseq on cells with TCF19 expression versus empty plasmid control. RNASeq data was analyzed with STRING, DAVID, and a locally developed algorithm to identify transcription factors associated with promoters of differentially regulated genes.

Results In lean, young mice lacking Tcf19 we found no difference in body weight, fasting glucose, or fasting insulin compared to controls. We also found no difference in glucose tolerance or *in vivo* insulin secretion. RNAseq of pancreatic

islet RNA revealed upregulation of several genes involved in DNA damage repair pathways, including Ddx60 ($p=3.7E-05$). qPCR verification confirmed that islet mRNA levels of Ddx60 and two additional genes involved in DNA damage repair pathways, Gadd45 α and Dtx3l, were significantly upregulated ($p=1.02E-07$, $1.2E-03$, $3.6E-04$, respectively). In addition, Ki67, the cellular marker of proliferation, was decreased by 3-fold while expression level of Chop, a marker of cellular apoptosis, was significantly increased. Expressing human TCF19 in the INS1 rat β -cell line resulted in a 2-fold increase in 3H -thymidine incorporation ($p=0.02$). Interestingly, no significant increase in cell cycle gene expression was observed. However, RNAseq identified upregulation of 160 genes, with several from the PARP and Oas1 family, genes that are often involved in stress response pathways and DNA damage repair. STRING analysis on upregulated genes from this data set revealed a tight connection between the genes, and further analysis revealed that STAT1, a transcription factor that plays a role in mediating stress responses to various stimuli, was a key regulator associated with promoters of the upregulated genes ($p=1E-17$).

Conclusion Our data suggest that under non-stressed conditions, Tcf19 is not necessary for normal β -cell development and function. However, Tcf19 may be necessary for DNA damage repair, and the loss of Tcf19 may increase susceptibility to DNA damage stressors and decrease proliferation in the β -cell. Taken together, these results suggest that TCF19 may increase DNA repair pathways via STAT1 signaling, thereby improving survival of the β -cell under stress conditions.

*A20

EVIDENCE OF HEPATOTOXICITY FOLLOWING CHRONIC LOW DOSE EXPOSURE TO MICROCYSTIN-LR IN A MURINE MODEL OF NON-ALCOHOLIC FATTY LIVER DISEASE

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Introduction Microcystins are a class of hepatotoxic cyclic heptapeptides produced by cyanobacteria. These toxins frequently contaminate freshwater sources (including municipal and agricultural sources) and pose a serious and growing global public health risk. While the Lake Erie cyanobacteria bloom in 2014 gained considerable notoriety, these blooms occur frequently not only in every single region of the US, but have been reported with increased frequency in almost every country world-wide. The health based criteria for safe exposure limits to microcystins has been extrapolated to humans from toxicology studies performed only in healthy animal models however the effect of these hepatotoxins in at-risk settings such as pre-existing liver disease is unknown.

Objective We tested the hypothesis that the No Observed Adverse Effect Level (NOAEL) of microcystin, as established in healthy animals, would cause significant hepatic injury in a murine model of Non-alcoholic Fatty Liver Disease (NAFLD).

Methods/results We gavaged male Lepr^{db}/J mice with 50 μ g/kg or 100 μ g/kg microcystin-LR (MC-LR, one of the most common microcystin congeners) or vehicle every 48 hours for 4 weeks ($n=12-16$ mice/group). This treatment strategy yielded MC-LR exposures below the published NOAEL levels reported by Fawell, *et al.* (*Hum Exp Toxicol* 1999 Mar;18(3):162-7.)

During the course of the treatment, we observed a non-statistically significant trend in decreased survival with control group showing 100% survival whereas the 50 μ g/kg and 100 μ g/kg group showed 93% and 85% survival respectively. To determine if MC-LR aggravated the lipid accumulation in the livers of the NAFLD mice, we performed Oil Red O staining on liver tissue sections. Quantitative histopathologic analysis of the stained sections indicated that while macrovesicular steatosis did not increase significantly in the MC-LR treated groups, there was a significant ($p<0.01$) increase in microvesicular steatosis in a dose-dependent manner. Next we investigated the changes in genetic markers of major drug-induced hepatopathology using quantitative PCR (qPCR). Here we observed that treatment with MC-LR (both 50 and 100 μ g/Kg doses) yielded significant increases in genetic markers of cholestasis ($>10-100$ fold increases of superfamily of ATP-binding cassette (ABC) transporters Abcb1a, Abcb4, Abcc2, and Abcc3), steatosis (>15 fold increases in Fatty acid synthase and CD36), phospholipidosis (>10 fold increases in Serpina3n and Mrps18b), non-genotoxic hepatocarcinogenicity (>20 fold increases in Cdkn1a, and Ddx39), necrosis (>30 fold increases in Col4a1 and Mlxip1), and generalized hepatotoxicity (>100 fold increases in Aldoa, Cxcl12, and Cyp1a2). Furthermore, we observed that treatment with MC-LR significantly elevated gene expression levels of hepatic antioxidant enzymes ($>100-1000$ fold increase in Peroxiredoxins such as Prdx1, Prdx2 and Catalase), as well as genes involved in reactive oxygen species metabolism ($>10-1000$ fold increase in Ncf2, Nox4 and Noxa1) and also oxygen transporters (>10 fold increase in Ngb).

Conclusion Our results suggest that the NOAEL of MC-LR, as established in healthy animals, results in significant hepatic injury in a murine model of NAFLD as assessed by increases in microvesicular steatosis and genetic markers of hepatotoxicity and oxidative stress.

A41

CHOLECYSTOKININ PROTECTS INS-1 CELLS AND HUMAN ISLETS FROM CYTOKINE-MEDIATED APOPTOSIS

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Objective Cholecystokinin (CCK) is an incretin-like hormone that is produced in the beta-cell under conditions of stress and obesity. Activation of cholecystokinin receptor (CCKR) can attenuate the onset and progression of several modes of cell death in various mammalian cell types. We have previously shown that mice with beta-cell-specific CCK expression are protected against oxidative stress-induced beta-cell death after streptozotocin injection. Conversely, CCK null obese mice had decreased islet mass and increased beta-cell apoptosis. The next step is to determine which of the two CCK receptors mediate CCK's pro-survival effects and to ensure that similar benefits are seen in human islets.

Methods Using the INS-1E rat insulinoma cell line, we performed a time course of cell viability (measured by Trypan blue exclusion) over 48 hours of exposure to cytokine cocktail with CCK, GLP-1, CCKAR agonist A71623, CCKBR agonist (gastrin-17-II), and CCK in combination with GLP-1. Apoptosis was measured in INS-1E cells treated with cytokines and CCK

concentrations ranging from 10 pM to 100 nM for 24 hours by staining for annexin V and propidium iodide (PI) and quantification using imaging flow cytometry. Finally, to test CCK-8's ability to protect human pancreatic islets exposed to cytokines *ex vivo*, dispersed human islets were pre-treated with 100 nM Glu-Gln-CCK-8 or vehicle for 1 hour before treatment with a cytokine cocktail of 75 U/ml IL-1 beta, 750 U/ml IFN-gamma, and 1,000 U/ml TNF alpha. Caspase 3/7 activity was measured 24 hours later using the Caspase-Glo 3/7 assay system.

Results CCK-8 peptide (100 nM) treatment reduced cytokine-induced cell death ($n=7$, $p < 0.05$) for up to 48 hours *in vitro*. The treatment was most effective during the first 24 hours (40.8% vs. 19.3% death). Similar protection was seen with GLP-1 alone. Combination therapy with CCK and GLP-1 did not provide additive benefit. Additionally, we saw similar protection at 24 hrs when using specific CCKAR or CCKBR agonists, suggesting that both receptors may be able to mediate the pro-survival effect in INS-1 cells. Using image flow cytometry, we find that CCK has concentration-dependent bi-phasic efficacy where its most efficient anti-apoptotic dose is different for the early and late stage of apoptosis. The higher concentration of CCK at 10–100 nM range most efficiently suppressed (~2.5-fold) the onset of early-stage apoptosis. However, only the low level (10–100 pM) of CCK significantly prevented the progression of INS-1 cells into the late-stage apoptosis by ~2.8-fold at 24 hours of cytokine exposure ($n=6$, $p < 0.05$). Finally, treatment of dispersed human islets with CCK reduces apoptosis due to cytokine exposure from 2.3-fold to 1.7-fold, as measured by caspase 3/7 activity ($n=6$, $p=0.04$).

Conclusion From these findings, we hypothesize that CCK has therapeutic potential to reduce the progression of islet cells into late apoptosis and that selective activation of CCKR can be exploited to protect pancreatic islet cells from cell death under diabetogenic stress conditions in humans. Future studies will continue to discern the role of the individual receptor agonists in human islet cells, where the expression pattern of CCKR's differs from the INS-1 cell line.

A42 A CURIOUS CASE OF KANSAS LADY

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Introduction The association of Cushing's Syndrome (CS) with neuroendocrine tumors (NET) such as carcinoid tumor (CS) is well documented. Since first report published in 1928, at least 40 other cases have appeared in the literature but all exclusively linked to bronchopulmonary carcinoid tumor. We define a novel and a very rare case of ACTH-independent Cushing syndrome associated with midgut NE carcinoid tumor.

Case report A middle age Caucasian female without significant past medical or surgical history was brought to ED for sudden onset of altered mental status, right lower limb weakness and painless vision loss in left eye. Family mentioned she had significant weight gain, marked fatigue and abdominal pain for past one month. On arrival, she was found to be in acute renal failure (ARF) requiring admission to ICU and continuous renal replacement therapy (CRRT). Brain imaging revealed extensive intracranial thromboembolic disease involving middle cerebral and ophthalmic artery. A week later her mentation

improved but her clinical picture kept deteriorating, her right lower extremity was now consistent with critical ischemia but intervention was not yet possible due to ARF. Investigating weight gain, we found her to have increased cortisol and ACTH level which were not suppressed by high dose dexamethasone. Inferior Petrosal Sinus Sampling (IPSS) was also not possible given cerebrovascular accident. Belly pain lead to abdominal imaging which revealed concerning lesions in pancreas, spleen and liver. Once stabilized, she underwent biopsy of these lesions which proved to be NET (carcinoid) of midgut. Further complicating the picture, throughout her stay she continued to have evolving arterial and venous clots. Extensive workup revealed increased homocysteine levels as well. She was given a final diagnosis of Intra-Abdominal Carcinoid tumor with paraneoplastic Cushing Syndrome. She was started on Ketoconazole, Pasireotide to which she responded appropriately and was eventually discharged home.

Case discussion In general, carcinoid tumors are considered to be low to moderate grade malignant tumors; however, when associated with Cushing syndrome, they are clinically aggressive and have poor outcome. Ectopic ACTH production accounts for about 15% of all cases of CS and is usually due to small cell lung carcinomas (50%), non-small cell lung carcinomas (5%), lung carcinoid (10%), pancreatic tumors (10%). Carcinoid tumors represent 1.2%-1.5% of all gastrointestinal tract neoplasms. The ideal treatment for abdominal carcinoid is an endoscopic or a radical surgical excision. In cases of liver metastases, a surgical resection and/or cytoreductive techniques, such as radiofrequency ablation and chemoembolization, may improve carcinoid syndrome symptom that are mediated by hormones produced by the tumor, to improve the quality of life and increase survival. Somatostatin analogs may induce symptomatic and biochemical responses that stabilize the disease and reduce the growth of metastases through cytostatic effects like in our patient.

A43 GHRELIN RECEPTOR ANTAGONIST [D-LYS-3] GHRP-6 INHIBITS CHRONIC ALCOHOL INDUCED HEPATIC STEATOSIS

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Purpose Alcoholic fatty liver (steatosis) is the earliest and most common response of the liver to excessive ethanol consumption, and the presence of this rise in fat increases the susceptibility of the liver to develop advanced stages of liver disease. In our laboratory, we consistently observe that chronic alcohol administration significantly decreases plasma insulin levels while significantly increasing plasma ghrelin levels. It is well known that insulin (produced in the pancreas) has profound effects on lipid metabolism in both liver and adipose tissue. Ghrelin, on the other hand, is a hormone secreted mainly from the stomach, and is known to inhibit insulin secretion from pancreatic β -cells. During chronic alcoholic administration, decreased serum insulin levels promote adipocyte lipolysis, resulting in release of free fatty acids into the serum. Subsequently, this increased fatty acid mobilization from adipose to the liver can contribute to hepatic steatosis. In our recent studies, we investigated a role for increased ghrelin in this scenario.

Methods For these studies, we pair-fed male Wistar rats with Lieber-DeCarli liquid diet for 6 weeks. After 6 weeks of feeding, a subset of rats in each group were injected with either saline or ghrelin receptor antagonist ([D-Lys-3] GHRP-6 at a dose of 9 mg/kg BW for 5 days. We then analyzed serum and liver tissue to determine if blocking ghrelin activity by the agonist would result in altered measures of lipid metabolism and storage.

Results Rats injected with receptor antagonist normalized serum insulin, serum free fatty acids and hepatic triglycerides levels to control levels in ethanol fed rats. Receptor antagonist-injected animals also showed decreased expression of hepatic fatty acid transporter CD36, and enzymes related to fatty acid synthesis (FAS, DGAT1 & 2) and increased expression of PPAR- α , a transcription factor that regulates the expression of enzyme involved in fatty acid oxidation.

Conclusions Injection of Ghrelin receptor antagonist to alcohol-fed animals abrogated the ethanol-induced defects by improving insulin secretion from pancreas. Consequently, improved circulating insulin levels inhibited fatty acid mobilization from adipose tissue to liver, thereby inhibiting hepatic steatosis. Our studies provide new insights on the role of ghrelin in modulating the pancreas-adipose-liver axis after alcohol exposure.

A44 MATRIX STIFFNESS PROMOTES ADIPOCYTE THERMOGENESIS

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10.1136/jim-2018-000745.79

Objective Mechanical forces are an oft-overlooked aspect of biology that play an underlying role in every cell system. Pushing and pulling, the forces applied on the cell's architecture can alter signaling pathways, differentiation, motility, and cell survival. Outside of their effects on adipogenesis, little is known about how mechanical forces alter adipocyte biology. White adipose tissue is softer and less thermogenically active than brown fat. Based on this qualitative observation, we set out to determine whether environmental stiffness could increase the ability of white adipocytes to perform thermogenesis.

Method Stromal vascular fraction isolated from murine subcutaneous and visceral fat was differentiated on polyacrylamide gels with various stiffnesses.

Results Differentiating the cells on the stiffest substrates had a pro-thermogenic effect on both subcutaneous and visceral adipocytes, as evidenced by upregulation of thermogenic markers including UCP1, Cox8b, and Cyc1. Hormone sensitive lipase and the GLUT4 transporter, genes respectively involved in triglyceride breakdown and glucose uptake in adipocytes, were similarly upregulated in the adipocytes differentiated on the stiffest substrates, suggesting that matrix stiffness can increase the amount of metabolic substrates available for adipocytes to metabolize for heat production.

Conclusion These experiments provide novel evidence that extracellular matrix stiffness is a regulator of thermogenic capacity in white adipose tissue.

A63

MANAGEMENT AND COMPLICATIONS OF GCK-MODY IN PREGNANCY IN WOMEN ENROLLED IN THE US MONOGENIC DIABETES REGISTRY

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Objective GCK-MODY is an autosomal dominant form of diabetes due to heterozygous mutations in the GCK gene. Clinically, there is stable, mild hyperglycemia without typical long-term complications of diabetes and treatment is not required outside of pregnancy. In pregnancy, fetal abdominal growth on second trimester sonograms is used as a proxy for GCK status. Current recommendations are to treat pregnant women with GCK-MODY with insulin only if fetal ultrasound monitoring shows macrosomia, suggesting the fetus is wildtype for the GCK gene. There is concern that maternal insulin use will result in reduced fetal growth if the fetus has inherited the GCK mutation. However, data on management and outcomes of pregnancies in women with GCK-MODY is lacking and best management is debated. The aim of this study was to retrospectively assess hyperglycemia management during pregnancy, complications, and pregnancy outcomes amongst women with GCK-MODY in the University of Chicago Monogenic Diabetes Registry.

Method A survey was distributed electronically via Redcap to women above the age of 18 with a known genetic diagnosis of GCK-MODY. Of the 94 patients who were invited to complete the survey, 55 women completed all or part of the survey. These women reported a total of 151 pregnancies and survey data was completed for 130 of the pregnancies.

Results Pregnancy outcomes included 79 term births (61%), 15 pre-term births (12%), 24 miscarriages (18%), 10 abortions (8%), and 2 currently pregnant (2%). Average timing of miscarriage was 8.7 weeks (range 4–12 weeks). Regarding treatment of high blood sugar during pregnancy, 50 women were on no treatment, 39 were treated with insulin (including 3 patients on insulin and oral medications), and 5 were treated with oral medications only. Among patients treated with insulin, 8 were on insulin prior to pregnancy and 31 were started on insulin during pregnancy. Twenty-two women on insulin (56%) experienced either occasional or frequent hypoglycemia and 9 women on insulin (23%) reported severe hypoglycemia, including need for glucagon in two respondents.

Genetic testing of offspring was done for 17 of the 39 cases of insulin-treated mothers; 8 were diagnosed with GCK and 9 were wild type. Average birth weight was significantly less for GCK offspring compared to wild type offspring at 2902 grams and 3626 grams, respectively ($p=0.003$). SGA was observed in one GCK offspring (1 of 8, 12.5%) compared to no wild type offspring.

Conclusion In our study, the miscarriage rate of 18.5% was comparable to the background population rate of 15%. Patients treated with insulin had a significant incidence of severe hypoglycemia (23%) and one case of SGA occurred in the insulin-treated, GCK-affected offspring group. These data underscore the importance of additional studies to determine optimal management of GCK-MODY in pregnancy to minimize maternal morbidity (particularly hypoglycemia) and prevent fetal complications.

A64

REDUNDANT EFFECTS OF INSULIN-LIKE GROWTH FACTOR-2 ON HUMAN PROSTATE STEM-PROGENITOR CELLS AMPLIFICATION

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Objective Insulin-like growth factor type-1 receptor (IGF-1R) is activated by both IGF-1 and its related hormone IGF-2. Our previous study showed that prostate stem-progenitor cells express IGF-1R and exhibit proliferative response to IGF-1. The goal of the current study is to investigate whether there is a redundancy of IGF-2 and IGF-1 signaling in prostate stem-progenitor cells amplification.

Method Adult prostate stem-progenitor cells were isolated from disease free primary human prostate epithelial cells (PrEC) using 3D prostasphere (PS) culture. Prostate stem cells self-renewal and progenitor cells amplification were evaluated by PS number/size as well as PS-based BrdU retention assay. Gene expression was quantitated by RNA sequencing followed by confirmation qPCR. Protein expression was measured by immunostaining.

Results In addition to IGF-1R, PS cells also expressed high levels of IGF-2R mRNA and protein. Further RNA-seq analysis revealed enrichment of IGF-2 (16.7 folds ↑) in BrdU-retaining prostate stem cells as compared to non-retaining progenitors, implicating a possible role of IGF-2 signaling in prostate stem cells. Similar to IGF-1 effects, IGF-2 (5 μM) treatment significantly increased both the number and size of PS. Interestingly, combination treatments of IGF-1 and IGF-2 did not showed additive effects on PS number/size, indicating a redundancy of IGF-1 and IGF-2 in prostate stem-progenitor cell amplification.

Conclusion In addition to IGF-1, the present study identified IGF-2 as another cell growth hormone that regulates prostate stem-progenitor cells amplification, and that IGF-1 and IGF-2 effects in prostate stem-progenitor cells are redundant.

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B13

A LOOK INTO COUP-TFII ROLE IN GLUCOSE HOMOEOSTASIS AND BLOOD PRESSURE REGULATION IN DAHL SS RATS

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Environmental factors such as diets rich in salt and/or fat significantly increases the risk for developing cardiovascular disease including hypertension, and metabolic syndrome. Through GWAS studies, a locus with significant association for hypertension was found in human chromosome 15 containing the gene Chicken Ovalbumin Upstream Promotor Transcription Factors II (*COUP-TFII*). To validate this gene, we developed a ZFN based mutant rat in Dahl SS (SS) background. Previously, we have shown that under high salt diet the *Coup-TfII*^{mutant} rat had an improved cardiac and renal function when compared to SS rats. Being a known transcriptional regulator, *Coup-TfII* also plays a role in other physiological events including glucose homeostasis and energy metabolism. However, the molecular mechanism behind glucose homeostasis and energy balance still under investigation.

In our study, we found that *Coup-TfII* expression levels are modulated in response to glucose levels in H4IIE rat hepatoma cells; under high glucose condition *Coup-TfII* expression was significantly decreased ($p \leq 0.05$); whereas in low glucose condition *Coup-TfII* expression was significantly increased ($p \leq 0.05$). Similar to our in-vitro findings, *Coup-TfII* gene expression was up-regulated in SS rat liver during fasting as compared the re-fed condition ($p \leq 0.05$). *Coup-TfII*^{mutant} rat have also showed a significant decrease in fasting blood glucose levels when compared to SS rat ($p \leq 0.05$). Furthermore, the *Coup-TfII*^{mutant} rat demonstrated a superior glucose response, along with an increase in insulin sensitivity measured by glucose and insulin tolerance test ($p \leq 0.05$). Further, mRNA expression analysis in livers of SS and *Coup-TfII*^{mutant} rats revealed that the key enzymes involved in both beta oxidation and gluconeogenesis was down regulated in *Coup-TfII*^{mutant} rats compared to SS rats ($p \leq 0.05$). Previously, we have shown that the SS rat when maintained on a high calorie diet (60% Kcal) significantly increases the BP compared to rats fed with low calorie (10% Kcal) diet. Overall, our preliminary findings suggest that *Coup-TfII* is important for glucose homeostasis and blood pressure regulation in SS rats. Further understanding of *Coup-TfII* function will help to dissect the relationship between metabolic syndrome and blood pressure regulation under the influence of high calorie diet.

B47

ALPHAB-CRYSTALLIN EXPRESSION IN BREAST CANCER CORRELATES WITH POOR CLINICAL OUTCOMES

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Objective Triple Negative Breast Cancers (TNBCs) are a group of breast cancers characterized by the absence of the estrogen receptor (ER), human epidermal growth factor receptor-2 (HER-2), and progesterone receptor (PR). TNBCs have an especially poor prognosis, with a one-year survival rate of less than 20%. The presence of αB-crystallin (ABC), a small heat shock protein involved in apoptosis inhibition, has been shown to be associated with lung and brain metastasis in mouse models and poor survival in patients. We investigated the link between ABC expression in breast cancer patients and clinical outcomes, including metastasis.

Method We conducted a study using breast tissue samples from a cohort of 372 female patients diagnosed with breast cancer. Tissue was subsequently stained using immunohistochemistry staining for ABC, and samples were scored based on the amount of ABC present (0, 1+ or 2+ staining).

Results ABC expression correlated with several clinical and pathological features, including tumor size ($p < 0.0001$), advanced stage ($p = 0.003$), proliferation ($p = 0.0015$) and TNBC status ($p < 0.0001$). In addition, ABC expression was associated with poor clinical outcomes, such as an increased likelihood of requiring treatment with chemotherapy ($p = 0.002$), incidence of metastasis ($p = 0.02$), breast cancer-specific mortality ($p = 0.002$) and overall mortality ($p = 0.002$).

Conclusion Overall, breast tumors expressing ABC exhibited more aggressive phenotypes, suggesting ABC plays a critical role in TNBC progression. Future studies will focus on examining the role of ABC in cancer stem cell survival, and potential therapeutic targets.

B48 THE TAXONOMIC COMPOSITION OF THE GUT MICROBIOME IS ALTERED BY AND AFFECTS THE METABOLIC RESPONSE TO DIETARY BRANCHED-CHAIN AMINO ACIDS

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Background Obesity and type 2 diabetes are a major and growing problems both in the United States and worldwide. Obesity afflicts 39 percent of adults worldwide, and obesity and diabetes increase the risk of numerous diseases, including cardiovascular disease and cancer. As dietary interventions based on caloric reduction have proven unsustainable for most people, new and effective strategies to promote metabolic health are urgently needed. An attractive and potentially more sustainable alternative to simply restricting calories is to limit only certain macronutrients. Recently, we demonstrated that a low protein diet improves metabolic health in both rodents and humans, and that specifically restricting dietary branched-chain amino acids (BCAAs; leucine, isoleucine, valine) can recapitulate the beneficial effects of a low protein diet. The gut microbiome has recently emerged as a potential mediator of host metabolism, and has been implicated in obesity. We analyzed the effect of reducing dietary BCAAs on the taxonomic composition of the gut microbiome using 16S rRNA sequencing. Intriguingly, we observed a significant shift in the taxonomic composition of the gut microbiome, including an altered firmicutes to bacteroidetes ratio, which is known to also be altered in obese and insulin-resistant animals. However, the physiological and molecular mechanisms which mediate these effects are unknown.

Objective To determine if changes in the gut microbiome contributed to the beneficial impacts of low protein or BCAA-reduced diets.

Methods We tested the effect of feeding three diets (Control, Low AA, or Low BCAA) to C57BL/6J mice treated with antibiotics (neomycin, vancomycin, and ampicillin) in order to ablate the gut microbiome.

Results We observed that antibiotic treatment did not prevent the effects of a Low AA or Low BCAA diet on body composition or weight. While a Low AA diet improved glucose tolerance in both antibiotic-treated and vehicle-treated mice, a Low BCAA diet improved glucose tolerance only in vehicle treated mice.

Conclusion Our results suggest that the gut microbiome plays a role in the beneficial effects of a Low BCAA diet on glycemic control.

B49 DECREASED CONSUMPTION OF SPECIFIC MACRONUTRIENTS PROMOTES METABOLIC HEALTH AND LONGEVITY

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10.1136/jim-2018-000745.85

Calorie restriction (CR) is the nutritional ‘gold standard’ in extending lifespan and improving metabolic health in many model organisms. CR has proven challenging to translate to

humans as it is extremely difficult to implement in a population that struggles with obesity and cheap, readily available food. CR limits the intake of all macronutrients, but its unclear which restricted macronutrient drives many of these benefits. Many researchers have in turn investigated the effects of limiting only certain macronutrients while leaving caloric intake unaltered, changing the ratio of macronutrient intake instead. 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 and aging than researchers and physicians previously thought.

Objective Our lab has previously determined 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 can improve the health of a diet-induced obese mouse that is metabolically disadvantaged, even as these mice continue to consume a high-fat, high-sugar, otherwise western diet. We have since expanded our research to explore the effects of BCAA restriction in aged mice and in progeroid models of rapid aging. Our objective was to determine the effects of a reduced BCAA diet as an intervention in aged mice, as well as an intervention in two progeroid mouse models.

Method To investigate the effects of BCAA restriction in aging, we intervened in aged male and female mice with a reduced BCAA diet, and compared physiological effects to a Control diet longitudinally, as well as tracked lifespan. In separate progeroid mouse models, we implemented a Low BCAA diet at an early age and monitored lifespan as well as differences in metabolic health over time, compared to Control fed mice.

Results We find that when BCAAs or total amino acids are restricted in a progeroid mouse, we promote longevity and rescue some aspects of cardiac function. BCAA restriction improves weight and glycemic control of aged, wild-type mice as well as progeroid mice. In addition, BCAA restricted diets maintain a healthier aged mouse that is less frail and performs better in a physical challenge.

Conclusion Overall, our work demonstrates that a reduction in dietary BCAAs promotes metabolic health and may promote longevity. This work may represent a highly translatable option to treat age-related disease. Further research will focus on the molecular mechanisms that may promote longevity in amino acid restricted diets.

B50 A CASE OF DRUG INDUCED PANCREATITIS

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Introduction Acute pancreatitis is most commonly caused by gallstone occlusion of the biliary tree or alcohol ingestion. Drug induced pancreatitis (DIP) is a much more infrequent cause of acute pancreatitis with an incidence of 0.1% to 2%¹. Here we describe a case of acute pancreatitis with no identifiable cause which improved after withdrawal of antimicrobial therapy.

Case report A 34-years-old female presented to our hospital for weakness, fatigue, and altered mental status. She was found to have newly diagnosed diabetes mellitus with diabetic ketoacidosis and idiopathic hemorrhagic chemosis concerning for mucormycosis infection for which she was empirically

started on Amphotericin B on the first day of hospital admission. On day eight, she was started on Trimethoprim-Sulfamethoxazole (TMP-SMX) for *Stenotrophomonas* and *Klebsiella* pneumonia. CT scan on day 13 was performed for evaluation of pneumonia, which incidentally showed peripancreatic fat stranding and fluid collection. Subsequent serum lipase was found to be elevated at 282 U/L. A right upper quadrant abdominal ultrasound was negative for cholelithiasis, cholecystitis, or biliary duct dilatation and patient denied history of alcohol use. Amphotericin B was discontinued on day 16, and TMP-SMX was discontinued on day 18 with initiation of Levofloxacin therapy. Repeat abdominal CT on day 21 showed progression to necrotizing pancreatitis. Peripancreatic fluid was percutaneously drained on day 23 with negative cultures. Our patient was discharged on day 30 after clinical and symptomatic improvement with conservative management and continued cessation of previous anti-infective therapies.

Discussion Acute pancreatitis is caused by premature activation of pancreatic zymogens that results in autodigestion of the pancreatic parenchyma. Biliary ductal occlusion from gallstone pancreatitis causes bile stasis with reflux leading to activation of *Zymogen*. Alcohol is thought to induce overproduction of enzymes, which are prematurely activated due to bile stasis². Drug induced pancreatitis is difficult to diagnose due to the low incidence and the challenge of establishing a causal relationship to the offending agent. Drugs associated with acute pancreatitis are classified as class I, II, III or IV based on the weight of evidence and positive recurrence of pancreatitis after re-challenge. Sulfamethoxazole is a class I drug as there have been several case reports documenting recurrent pancreatitis with repeat exposure to TMP-SMX⁴. Amphotericin B has been reported to cause acute pancreatitis, although evidence is limited⁵. The diagnosis of DIP requires ruling out other identifiable causes of acute pancreatitis. The management of DIP requires prompt cessation of the offending medication and treatment of pancreatitis.

Conclusion Drug induced pancreatitis is a rare cause of acute pancreatitis. Nevertheless, for patients presenting with pancreatitis without the common causes, a thorough review of their recent and current medications should be performed with cessation of all offending agents to reduce morbidity and mortality associated with pancreatitis.

C33 DIARRHEA DISTURBING HORMONES: A CASE REPORT OF MYXEDEMA COMA SECONDARY TO CLOSTRIDIUM DIFFICILE COLITIS.

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Introduction Myxedema coma is a life-threatening form of severe decompensated hypothyroidism with an incidence of 0.22 million per year.¹ Inciting factors include metabolic derangements, hypothermia, certain medications (amiodarone, barbiturates) but overwhelming number of cases are attributed to infection usually pneumonia, influenza or urinary tract infection/urosepsis.² *Clostridium Difficile* colitis has rarely been cited as a precipitating factor for myxedema coma and we describe such a case.

Case report A 92 year old male with a past medical history of ischemic cardiac disease, chronic kidney disease and

hypothyroidism (on 50mcg of levothyroxine supplementation, last TSH of 5.56, fT4 of 1.4, 9 months prior to admission) presented to the ER with altered mental status for 1 day and diarrhea for the past 8–9 days (suspected antibiotic use for an unknown infection a few weeks prior). On admission, he was hypothermic (29.7 C), bradycardic (HR 49), with BP 140/71 mmHg and RR 16. On physical examination, the patient was responsive only to noxious stimuli and had non pitting edema bilaterally. Laboratory workup revealed a blood glucose level of 30 mg/dl, CBC with WBC count 1.82, Hgb 8.1 g/dl and platelet count of 112 (pancytopenia), elevated lactic acid, procalcitonin and a creatinine of 4.07 (baseline Cr 1.8–2.8) suggestive of acute kidney injury. A CT of the head demonstrated a small subdural hematoma of unclear chronicity; CT abdomen and pelvis revealed consolidations in RLL and LLL (concerning for aspiration) and evidence of colitis without perforation. Further workup revealed a TSH level of 98.5 and free T3 of 0.4 and free T4 of 0.73. Stool PCR tested positive for *C. difficile*.

Patient was started on IV levothyroxine, hydrocortisone, piperacillin/tazobactam, IV metronidazole and PO vancomycin due to severity of *C. difficile*. His mental status continued to wax and wane over the next two weeks. Steroids were tapered off and after five days piperacillin/tazobactam was discontinued (as management of possible community acquired pneumonia). Metronidazole and vancomycin were continued. After 12 days of IV therapy, levothyroxine was discontinued in favor of PO which was switched back to IV as the patient's condition worsened. High residuals prompted an AXR for ileus which was normal. Hospital course was further complicated by hematochezia and episodes of atrial fibrillation. Two weeks after admission, patient developed worsening uremia with marked metabolic acidosis, hyperkalemia and hypercapnic respiratory failure and was transferred to the ICU. His medical condition continued to deteriorate and family opted for a comfort care approach and he passed away shortly.

Discussion Myxedema coma is a life threatening emergency with mortality rates of 30–60%,² even with prompt diagnosis and treatment. The homeostasis in a hypothyroid state can be easily disrupted by a pathological process, primarily infection, which may precipitate myxedema coma. We postulate that the diarrhea caused by *C. diff* lead to decreased absorption of thyroid supplementation which lead to the patient's condition. Thyroid hormone supplementation is the mainstay of management; however, there is no consensus on the dosing and frequency of administration. While administering therapy, careful administration is key to achieve physiologically effective hormone levels while preventing adverse effects on the cardiovascular system especially in patients with existing coronary artery disease.

Conclusion Unusual infections, like *Clostridium Difficile* Colitis can precipitate myxedema coma in patients with underlying hypothyroidism. A high index of clinical suspicion is warranted as early recognition is crucial for administration of therapy and prevention of fatal outcomes.

C57 DEVELOPMENT OF CLINICAL TRIAL TO TEST THE IMPACT OF LOW BRANCHED CHAIN AMINO ACID DIET ON OBESITY AND PREDIABETES

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Objective In recent mouse studies, a diet low in the branched-chain amino acids (leucine, isoleucine, and valine) was shown to improve metabolic parameters in diet-induced obese mice. Mice consuming a high-fat, high-sugar diet that induced obesity and glucose intolerance were switched to diets in which the branched-chain amino acids were specifically reduced. The diets were equivalent in calories and fat. After 4 weeks, mice that were fed the branched-chain amino acid reduced diet had returned to their normal weight as a result of decreased fat mass, and had improved glucose tolerance. We aim to determine if a low branched-chain amino acid diet could be a translatable intervention for humans suffering from obesity and pre-diabetes. Our objective is to determine the feasibility of replacing two meals a day with beverages made from a branched-chain amino acid free medical food, and determine if reducing dietary branched-chain amino acids consumption in males with prediabetes and obesity improves metabolic parameters.

Method We are currently recruiting 12 subjects; 6 will be randomized to a control (whey protein powder) arm, and 6 will be randomized to consume beverages made from a branched-chain amino acid free medical food. Subjects are males aged of 35–65 with BMI 28–35 and fasting glucose 101–125 mg/dL who are not planning on starting a new exercise or diet program and have maintained a stable weight within the past 3 months. At a screening visit, we will measure BMI, assess a 4-day food diary to ensure minimum required protein intake and baseline caloric intake, and perform a taste test for palatability of the low branched-chain amino acid and whey protein powders. We will also draw labs that assess metabolic parameters, including Hgb A1c, fasting blood glucose, fasting insulin, ALT, and AST. If they meet screening criteria, they will start with a base visit (visit 2) that includes resting metabolic rate assessment with a calorimeter, an oral glucose tolerance test, DXA for body composition, and jumping mechanography to assess muscle function. Meal replacement powder will be dispensed at this visit. A stool sample will be collected to analyze the microbiome before starting the meal replacement beverages. Approximately 30 days after starting the meal replacement powder, subjects will have a third visit that includes BMI, review of a food diary, and drawing labs to assess metabolic status. Approximately 60 days after the start of the diet, visit 4 will repeat what was done at the base visit 2, fully assessing the effect of the diet on body composition and glucose tolerance. The diet will be stopped at this time. A follow-up visit about 2 weeks after stopping the diet will complete the study. Subjects will be called weekly to assess for adverse events or new medical issues.

Results We are actively recruiting subjects for this trial.

Conclusion All potential subjects so far screened report that both the branched-chain amino acid free beverages and whey protein powder beverages are palatable, and we expect to be able to present preliminary results.

Epidemiology/Health Outcomes/Quality Improvement/Bio-Informatics

A52

INHIBITION OF 14–3–3 PROTEINS PROVIDES A NOVEL ANTIFUNGAL STRATEGY

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10.1136/jim-2018-000745.89

Objective Fungal infections are one of the most common complications in post-operative as well as immuno-compromised patients. Though fungal, bacterial and viral infections are suspected triggers of autoimmune diseases, it is unusual to find an infected patient with active autoimmune disease. To understand and exploit the immunological features of autoimmunity that protect us against fungal infections, we began our investigation with autoantigen, the key player of autoimmunity. We recently reported 14–3–3z as an autoantigen in human aortic aneurysms caused by autoimmune diseases. 14–3–3 proteins are ubiquitously present in eukaryotes, and play essential role in cell survival and proliferation. The 14–3–3 family of proteins is evolutionarily conserved from yeast to mammals. Simulation of yeast 14–3–3 (a.k.a BMH) showed high similarity with human 14–3–3 structures. The BMH protein plays essential role in life cycle of yeast. These observations led us to investigate if human 14–3–3 inhibitors can be repurposed as anti-fungal agents.

Method We used bioinformatic analysis including LoGo analysis, phylogenetic analysis and structure simulations by VMD or Raptor to analyze human and yeast 14–3–3 proteins. We tested effect of 14–3–3 inhibitors (R18 and BV02) on the growth and cellular infection ability of *Candida Albicans* in vitro or in human oral epithelial cells, respectively.

Results Our preliminary results showed effective inhibition of *Candida albicans* growth by human 14–3–3 inhibitors. We performed short-term (1 hour) contact assay and found 20–30% decrease in fungal viability. Importantly, 14–3–3 inhibitors were equally effective on curbing the fungal growth in both proliferation assays as well as cellular infection assays. This effect was diminished in the case of non-pathogenic fungi, e.g. *S. cerevisiae*.

Conclusion Overall, our bioinformatic-based discovery suggesting novel antifungal role of the human 14–3–3 inhibitors indicate that the sequences and structural similarities between the mammalian and fungal proteins may influence the antigenic nature of these proteins, and may be responsible for molecular mimicry in autoimmune responses.

B34

ABSTRACT WITHDRAWN

A32

THE IMPACT OF MATERNAL DEPRESSION ON FUTURE CHILD PROBLEM BEHAVIOR

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10.1136/jim-2018-000745.90

Objective Although children are highly responsive to changes in their environment between infancy and preschool, literature has focused almost exclusively on the impact of prenatal and perinatal maternal depression on child health. Our purpose was to examine the impact of exposure to maternal depression when a child is age 3 on internalizing and externalizing child problem behavior at ages 3, 5, and 9 and to investigate whether race/ethnicity is a moderator of this relationship.

Method We used data from the Fragile Families and Child Well-Being Study. Ordinal logistic regression was used to model problem behavior on maternal depression status at year 3, and adjusted analyses included child, maternal, and household variables.

Results Weighted, adjusted analyses indicated that children whose mother was depressed when the child was age 3 were significantly more likely to have higher externalizing (adjusted odds ratio [AOR]=2.31, 95% confidence interval [CI]: 1.13 to 4.72) problem behavior scores at age 3 compared to those whose mother was not depressed. At age 9, children whose mother was depressed when the child was age 3 were significantly more likely to have higher internalizing (AOR=1.92, 95% CI: 1.42 to 2.61) and externalizing (AOR=1.65, 95% CI: 1.10 to 2.48) problem behavior scores compared to those whose mother was not depressed. Race/ethnicity did not have moderating effects on this relationship.

Conclusion These results indicate that exposure to maternal depression after the prenatal and perinatal periods has a negative impact on children's behavioral development through age 9. Interventions that directly target maternal depression at this critical time should be developed.

C16 PATIENT AND SOCIETAL FACTORS ASSOCIATED WITH ACUTE DECOMPENSATED HEART FAILURE ADMISSION

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Objective Acute decompensated heart failure (ADHF) is a common and serious health condition responsible for about 5% of all emergency hospital admissions in the United States. Patients hospitalized for ADHF have up to 30% risk of readmission within 30–60 days post discharge. Many interventions, medications, and treatment plans have been implemented to reduce these high hospitalization rates and resulting financial burden on the healthcare system. However, for better allocation of resources, much needs to be learned about the root causes leading to hospital admission. We aim to identify factors associated with ADHF and hospital admission at the patient and societal level.

Methods We examined the medical records of 109 congestive heart failure patients who were admitted to the University Hospital, San Antonio, Texas with at least one symptom (dyspnea, orthopnea, or edema) and one sign (rales, peripheral edema, ascites, or radiographic pulmonary edema) of volume overload. These patients were potential participants for a clinical study of high dose aldosterone antagonist for the treatment of loop diuretic resistant ADHF. Other inclusion criteria included: glomerular filtration rate (eGFR) >30 ml/min, and absence of concomitant systemic infection, liver disease, and acute pulmonary emboli. Patient charts were examined for demographics, vitals, co-morbidities, and echocardiogram findings. Additionally, we examined the admission history chart for possible reasons leading to volume overload and hospital admission. Those reasons were multifactorial and categorized into following six groups:

- unable to afford medications;
- noncompliance with medications and/or dosage;
- no regular healthcare/insurance;
- noncompliance with food and/or diet restrictions;
- admission despite compliance with medications and dietary restriction; and
- could not determine.

Results Lack of healthcare/insurance and medication availability in combination was the most common cause (34%) for ADHF admission. Admission despite compliance with medications and dietary restriction was the next common reason (30%), suggestive of either disease progression or inadequate dose of diuretics. No information was available regarding the frequency of encounters with a health professional to allow adjustment in the dose of diuretics. Table 1 shows the study population characteristics by the different categories for potential reasons for admission. On multiple comparison analysis, group C population with no regular health care/insurance, was younger than the rest of the groups. However, other demographics and co-morbidities did not differ between these groups. Moreover, the heart failure severity assessed by ejection fraction and pulmonary arterial systolic pressure was also similar among all the groups.

Abstract C16 Table 1 Demographics, comorbidities, and clinical data according to factors of admission

	Overall (n=109)	A (n=15)	B (n=19)	C (n=22)	D (n=5)	E (n=33)	F (n=15)
Age (years)	56±13	54±9	53±13	52±12	59±20	59±14	66±12
Sex (% Male)	68	73	79	59	80	60	73
Hispanic (%)	63	73	79	68	60	51	53
Non-Hispanic	21	20	15.79	4.55	20	27.27	40
White (%)							
DM (%)	51	53.3	57.9	40.9	25	57.6	53.3
HTN (%)	70	80	84.2	59.1	25	72.7	66.7
CVA (%)	14	20	10.5	9.1	0	15.2	20
PVD (%)	9	20	15.8	4.6	0	6.1	13.1
Current Smoker (%)	28	33.3	15.8	36.4	20	21.2	40
SBP (mmHg)	134±27	145±32	128±28	144±26	113 ±10	127±23	137±19
DBP (mmHg)	82±20	91±25	81±21	91±22	76±18	76±16	77±14
EF (%)	31±18	26±17	33±21	27±15	30±19	36±17	37±22
PASP (mmHg)	45±12	40±10	43	45±11	58±10	48±15	46±12
			±9.51				

DM=diabetes mellitus, HTN=hypertension, CVA=cerebral vascular accident, PVD=peripheral vascular disease, SBP=systolic blood pressure, DBP=diastolic blood pressure, EF=ejection fraction, PASP=pulmonary artery systolic pressure

Conclusions Lack of accessibility to the health care and medications were the most common reasons for ADHF admission in our study population. This group comprised of a younger population. The results of our analysis provide guidance for the local health care policies to reduce ADHF admission and hospital costs.

C17 ASSESSING COST-EFFECTIVENESS AND SOCIAL JUSTICE IN PHARMACOGENOMIC AND PUBLIC HEALTH APPROACHES TO THREE MAJOR CANCER GROUPS

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Objective Define and contrast medical/pharmacogenomic and public health approaches to precision health, comparing the cost-effectiveness of primary and tertiary preventive

approaches to cancer, and their applicability to different racial-ethnic and socio-economic groups.

Background In the emerging culture shift represented by precision medicine, the U.S. Precision Medicine Initiative (PMI) has initially focused on cancer research. The fact that non-small cell lung cancer comprises 85% of all lung cancers yet has a 5-year survival rate of 21%, and that 40–60% of metastatic colorectal cancer patients with wild-type *KRAS* status do not respond to anti-EGFR therapy suggests the need for targeted approaches. The development of diagnostic tests to further the identification of pharmacogenomically responsive patients can heighten success rates, but affordability and cost-effectiveness need consideration. Public health-oriented proposals for early genetic testing combined with later-stage medical-surgical interventions provide a useful alternative for reaching diverse groups. The use of large collections of pooled patient data for a particular cancer type ('big data'), drawn from multiple sources and clinical trials, bears consideration.

Method Lung, breast, and colorectal cancer management represent key examples within the wider body of precision oncology literature. PubMed and Google-based searches with cost-effectiveness, health policy, and disparities as key terms were conducted, yielding 67 pieces of relevant literature. Pharmacogenomic regimens (therapy + companion diagnostics) were evaluated in terms of quality-adjusted life years (QALYs) gained and incremental cost-effectiveness ratio (ICER), then cross-compared with primary prevention strategies leading to early intervention. Current information on health system- and PMI-based precision centers was examined. Articles were assessed for potential to reduce or widen disparities for diverse groups.

Results While assay costs can be minimal (~\$60 Can) for the use of EML4-ALK fusion oncogene testing in the therapy of non-small cell lung cancer, therapeutic costs can run up to \$250,632 per QALY gained. Research is proving useful for recruiting African American PMI cohort participants, and engaging non-smoking Asian populations. In the determination of *HER2* status for Herceptin use in breast cancer, cost-effectiveness is comparable to *BRCA1/2* testing with early-stage cancer patients. The cost-effectiveness of *KRAS* testing for colorectal cancer management varies by country. At \$29,600–63,900 per QALY gained, universal Lynch syndrome genetic testing in recently diagnosed CRC patients is as low as \$29,600–63,900 per QALY gained. Recent drug pricing strategies, e.g., in leukemia immunotherapy, can make regimens more affordable to different racial-ethnic and socio-economic groups. Information on cancer risk scores for early intervention is becoming increasingly available, but can still be costly (> \$3,000).

Conclusion Distinction must be made between the cost-effectiveness of precision oncogenomics in individual patients, and in patient groups. Therapeutic costs may overrun savings from the use of combination diagnostic-therapeutic strategies. Though genetic testing as a form of primary prevention in lung cancer is premature, genetic testing in primary as opposed to later-stage prevention in breast and colorectal cancer is cost-effective. While public health is often considered a guarantor of social justice, balanced recruitment of minorities in PMI research and innovative market pricing approaches can also make precision oncogenomics sensitive to these concerns. Potential benefits of precision health to diverse groups may also accrue when strategies are used on a wider scale.

C18

HIGH RATES AND LOW DOCUMENTATION OF HOSPITAL ACQUIRED ACUTE KIDNEY INJURY

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10.1136/jim-2018-000745.93

Objective Hospital-acquired acute kidney injury (HA-AKI) is a common condition that occurs in 5–20% of hospitalized patients depending on diagnostic criteria and patient characteristics. HA-AKI is associated increased risk for development and progression of chronic kidney disease (CKD). HA-AKI is still often under-recognized and under-documented which may lead to poor continuity of care. We sought to determine HA-AKI rates, documentation and follow-up in general medical inpatients at an urban, academic medical center.

Method Our sample included 1164 unique general medicine inpatients discharged between 1/2011 and 6/2012 without history of transplant or ESRD. Our primary outcome was the incidence and severity (stage) of acute kidney injury (AKI) using the Kidney Disease Improving Global Outcomes (KDIGO) classification of acute kidney injury. A dynamic baseline serum creatinine was defined for each time point as the average of all serum creatinine levels measured within the prior 7 days. In addition, we investigated the AKI documentation rates using ICD-9 codes and proportion with nephrology contact post-AKI. We used logistic regression to analyze likelihood of AKI after adjusting for (1) demographic factors: age, gender, race/ethnicity, and education; (2) prior CKD; (3) diabetes and hypertension; and (4) hospitalization within the previous year and length of stay.

Results Our sample of urban adult hospitalized general medicine patients was 67% African-American and 56% female with an average age was 56.2 years. The incidence of hospital-acquired AKI was 21% (243/1164) with 83.5% Stage I AKI, 6.6% Stage II AKI, and 9.9% Stage III AKI. In multivariable analysis, factors associated with developing HA-AKI include prior CKD Stage 4 or 5 (OR 3.5 and 4.0, respectively), length of stay 4 days or longer (OR 4.3), diabetes (OR 1.5), CHF (OR 1.6), all $p < 0.05$. AKI was coded in discharge ICD-9 codes in only 38% of cases, although the rates increased to 71% for those with Stage III AKI. Only 35% (84/243) of patients with HA-AKI had any nephrology contact (referral, consult or visit within 3 months of discharge).

Conclusion HA-AKI incidence in our general medicine inpatients is 21% which is higher than national estimates. In our high risk patient population, we miss opportunities to document HA-AKI and refer for these individuals for follow-up.

C26

A SINGLE INSTITUTIONS EXPERIENCE WITH GREENLIGHT PHOTOVAPORIZATION OF THE PROSTATE: EVALUATION OF IMMEDIATE POSTOPERATIVE COMPLICATIONS

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10.1136/jim-2018-000745.94

Introduction and objective Treatment of benign prostatic hyperplasia (BPH) using greenlight photovaporization of the prostate (PVP) has emerged as a popular minimally invasive alternative to transurethral resection of the prostate (TURP).

In this study, we aim to review our experience with PVP to determine the immediate postoperative complications.

Methods A retrospective chart review was performed on all consecutive patients who underwent PVP at a single institution from 2010 to 2016. Urodynamic study was only performed on patients who were in urinary retention at the discretion of the physician. All patients who undergo a PVP received 5 days of postoperative antibiotics.

Results A total of 204 consecutive PVP were performed between 2010 and 2016. A void trial was attempted on 171 patients within two days of the procedure. A total of 125 of 171 (73.1%) patients passed a void trial on POD 0/1. 16 patients stayed an extra day for a second void trial, of which 11 (68.7%) passed their second void trial. Of the 46 patients that failed a void trial, 29 (61.7%) had a foley catheter preoperatively. A total of 12 patients (5.9%) developed a febrile episode. Preoperative foley catheter was associated with being discharged home with a foley catheter, $p < 0.001$. Having a preoperative foley catheter was also associated with a longer operative time (68.35 vs 79.64 minutes, $p = 0.002$) and longer length of stay (LOS), 1.51 vs 0.91 days, $p = 0.026$. The average procedure duration in patients that developed a fever postoperatively compared to those that did not was 86 minutes vs 72 minutes, $p = 0.14$. Preoperative foley catheter was not associated with a febrile episode post-operatively, $p = 0.27$.

Conclusion A void trial should be encouraged on POD 0/1. In those that fail, it is reasonable to repeat a void trial the following day as they have an equal chance of passing. Patients with preoperative foley catheters have a higher likelihood of failing their void trial. It may be more cost effective to send these patients home on POD0 with foley catheter in place and defer void trial for a later date.

C34 ABSTRACT WITHDRAWN

C55 BARRIERS AND FACILITATORS TO USING WELL-WOMAN CARE AMONG LOW-INCOME WOMEN OF COLOR PRESENTING FOR ABORTION

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10.1136/jim-2018-000745.95

Objective For women who do not obtain well-woman care, the abortion visit presents a potential link to future care. This study focuses on the abortion visit as an opportunity to identify women who do not regularly obtain well-woman care and explores factors that influence their ability to obtain well-woman care.

Methods We conducted semi-structured interviews with women presenting for abortion who reported not having a regular health care provider. Domains explored included: future goals, barriers/facilitators, and outcome expectancies of using well-woman care. Interviews were transcribed and analyzed using Atlas.ti. Salient themes are presented.

Results This study includes thirty-four participants. Despite past challenges trying to engage in well-woman care, most participants recognized its value and planned to seek well-woman care post-abortion. Barriers to care included: work schedules; family obligations; insurance disruptions; provider

accessibility; and not prioritizing their health. Facilitators to care included: family support; integration of health care with school/workplace; obtaining insurance; and strong patient-provider relationships. While many women expected positive outcomes from obtaining care, several women feared being diagnosed with a new medical problem. Several women indicated that past barriers to obtaining care and lacking a provider with which to obtain well-woman care likely contributed to their experiencing an unintended pregnancy.

Conclusion Although most women in this study desired to seek well-woman care post abortion, women expressed concerns about known barriers to obtaining this care. Therefore, future interventions to link women to care after the abortion must help women develop strategies to overcome potential obstacles and leverage facilitators to care.

Gastroenterology/Clinical Nutrition

A45 EXAMINING SPATIAL ACCESSIBILITY TO SCREENING COLONOSCOPY AND DISPARITIES IN COLORECTAL CANCER SCREENING IN CHICAGO

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In the US for the year 2017, colorectal cancer (CRC) was projected to cause greater than 50,000 deaths, making it the second leading cause of cancer related mortality. Guideline consistent screening is known to reduce death related to CRC. However, black Americans are known to have lower rates of both screening and diagnostic colonoscopy compared to whites. In Illinois, black residents have an approximately 7% greater incidence rate and a 30% higher mortality rate when compared to white residents.

It is not known to what degree racial disparities in CRC screening are related to differences in spatial accessibility to CRC screening related healthcare infrastructure. The University of Chicago Comprehensive Cancer Center supported Chicago Multiethnic Prevention And Surveillance Study (COMPASS) examines factors that impact the risk of developing cancer and why some racial or population sub-groups are at greater risk than others. COMPASS participants completed an interview questionnaire regarding their health history and healthcare behaviors including receipt of CRC screening by colonoscopy, sigmoidoscopy, or barium enema.

Objective Use geographic information systems to explore the association between CRC screening utilization amongst COMPASS participants and spatial accessibility to outpatient screening colonoscopy facilities.

Method 1,212 COMPASS participants age 50 years or older, with public and/or private health insurance, were grouped according to their residential census tract. Seventy healthcare facilities that offer screening colonoscopy procedures were identified through review of Illinois hospital and ambulatory surgery center accreditation listings. Confirmation of on-site screening colonoscopy services and the number of endoscopy procedure rooms per facility were obtained by telephone interview. Spatial accessibility to screening colonoscopy infrastructure was estimated through the enhanced two-step floating catchment area (E2SFCA) method using 6, 12, and 18 mile catchment areas with distance impedance weights of 1, 0.28,

and 0.03, respectively. Mapping and geospatial analysis were performed using Esri ArcMap version 10.4.

Results The total prevalence of CRC screening among COMPASS participants was 59%. The CRC screening rate in black participants was 56%, compared to 65% among non-blacks [$p=0.005$]. On univariate analysis, black race was associated with decreased spatial access to screening colonoscopy [odds ratio (OR)=0.97; confidence interval (CI): 0.97 to 0.98]. On multivariate analysis, COMPASS participants who resided in areas with high spatial accessibility were more likely to report a history of prior CRC screening after controlling for age, sex, insurance type, and black race [OR=1.63; 95% CI: 1.07–2.48].

Conclusion In Chicago, there are significant racial disparities in CRC screening utilization and spatial access to facilities that provide screening services. Among COMPASS participants, black race was associated with a lower odds of CRC screening and decreased spatial accessibility to screening colonoscopy. Small-area variation in screening infrastructure may be an important determinant of CRC related healthcare disparities. Equalizing access to healthcare for all is a key factor in eliminating cancer-related disparities.

B14 SITE-2 PROTEASE AND NON-ALCOHOLIC FATTY LIVER DISEASE

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10.1136/jim-2018-000745.97

Objective Mechanisms of liver injury in non-alcoholic fatty liver disease (NAFLD) are incompletely understood. Recent studies have confirmed that that excessive fatty acid (FA) synthesis contributes to hepatic triglyceride (TG) accumulation. Hepatic cholesterol, FA, and TG synthesis is controlled by sterol regulatory element-binding proteins (SREBPs), a family of membrane-bound transcription factors. In cultured cells, SREBPs are synthesized as inactive precursors in the endoplasmic reticulum (ER) that are transported by Scap, a regulatory protein, to the Golgi apparatus. In Golgi, SREBPs are cleaved by two proteases, Site-1 and Site-2 protease (S1P and S2P), which liberate transcriptionally-active nuclear SREBPs. Obesity and insulin resistance stimulate the major hepatic SREBP isoform, SREBP-1c, to drive excessive hepatic lipogenesis. Elimination of SREBP-1c by knockout of SREBP-1c itself or of Scap reduces hepatic lipogenesis and ameliorates hepatic steatosis in obese, insulin resistant mice, providing direct evidence that the SREBP pathway may be a therapeutic target for NAFLD. However, SREBP-1c and Scap are poor targets for small-molecule inhibitors, and so are not ideal candidates as drug targets. Whether S2P is needed for SREBP activation in the liver is unknown. Also, whether antagonism of S2P, a protease that may be amenable to pharmacological inhibition, has ameliorative effects on hepatic steatosis is unknown. In this study, we assess whether ablation of S2P in vivo blocks SREBP activation and reduces hepatic triglycerides to therefore be a potential therapeutic strategy in NAFLD.

Method Mice with liver-specific deletion of S2P (*L-S2P* mice) were generated by inserting *loxP* sites flanking exon 4 of *Mbtps2* and resultant *floxed* mice were injected via the tail vein with adeno-associated viruses (AAV) expressing Cre recombinase. Control littermates received AAV-GFP. Groups of

L-S2P and control mice were subjected to fasting and refeeding with high-sucrose diet, a condition of maximal SREBP-1c stimulation and insulin-stimulated lipogenesis. Other groups of mice were treated with ezetimibe and lovastatin, a condition of maximal SREBP-2 stimulation. Protein and mRNA levels were measured by immunoblot analysis and qPCR or RNA-Seq, respectively. Plasma and hepatic lipid levels were measured by biochemical assay. Statistical significance between groups was assessed by the student's *t* test.

Results Hepatic S2P deficiency prevented formation of nuclear SREBP-1 and SREBP-2, which reduced mRNA levels of SREBP target genes in sterol biosynthetic ($\downarrow 78\%$ *Acsc2*, $\downarrow 80\%$ *Hmgcs1*, $\downarrow 69\%$ *Hmgcr*, $\downarrow 86\%$ *Fdps*, $p<0.001$) and lipogenic pathways ($\downarrow 74\%$ *Acaca*, $\downarrow 75\%$ *Acy*, $\downarrow 90\%$ *Fasn*, $\downarrow 96\%$ *Scd1*, $p<0.001$). Importantly, mRNA levels of *Pnpla3*, a phospholipase for which a common sequence variant (*I148M*) in humans is associated with NAFLD and its progression to cirrhosis and hepatocellular cancer, was reduced by 95% in S2P-deficient mouse livers. Serum and liver TG levels in *L-S2P* mice were reduced by 47% and 57%, respectively ($p<0.001$). The insulin-induced overactivation of SREBP-1c and its lipogenic target genes provoked by fasting and refeeding was completely abolished in *L-S2P* mice, as was the overactivation of nuclear SREBP-2 and its cholesterologenic target genes provoked by cholesterol deprivation with lovastatin and ezetimibe. Hepatic S2P ablation was overall well-tolerated by mice, which developed no overt signs of toxicity.

Conclusion These results demonstrate an essential role for S2P in regulating SREBP proteolysis and cholesterol, FA, and TG synthesis in the liver. Ablation of S2P resulted in reduced lipogenesis and hepatic TG contents. Furthermore, S2P is required for the hepatic expression of *Pnpla3*, and hepatic S2P ablation was well-tolerated in mice. Therefore, S2P inhibition may potentially be of therapeutic benefit for NAFLD in humans, particularly in individuals bearing *PNPLA3 I148M* alleles. Further studies will be needed to determine if S2P ablation can prevent or reverse NAFLD in dietary and genetic mouse models of obesity. Lastly, further studies will also be required to determine if S2P, which also impacts the unfolded protein response (UPR) through its proteolytic activation of activating transcription factor 6 (ATF6), could have other roles in NAFLD pathogenesis by modulation of the hepatic UPR.

B15 MYC ONCOGENE AMPLIFICATION AND COMMONLY MUTATED GENES IN ADENOSQUAMOUS CARCINOMA OF PANCREAS

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Objective Adenosquamous carcinoma of the pancreas (ASCP) is a rare variant of pancreatic ductal adenocarcinoma (PDA) and has a worse prognosis. Up to date, little has been known in the molecular carcinogenesis of ASCP and no findings have promoted a successful targeted therapy. Our present study has investigated the genetic sequences of ASCP in comparison to conventional PDA and identified the specifically mutated genes in ASCP in order to develop targeted therapy for this aggressive malignancy.

Method A total of 112 surgically resected PDA cases including 14 ASCP cases were analyzed by whole-exome sequencing. Somatic point mutations and insertion/deletion of DNA in the tumor tissues compared with their corresponding normal tissues were identified using the MuTect and VarScan2 algorithms. The significantly mutated genes were defined by the MutSigCV algorithm. A total of 26 ASCP cases were further analyzed for MYC amplification by Fluorescence in situ hybridization (FISH) at the MYC locus using Vysis LSI MYC dual color 'break apart' rearrangement probe.

Results Detected by whole-exome sequencing, MYC oncogene mutation is found in 14% of 112 PDA and 57% of 14 ASCP in our study cohort. FLG1 mutation is also frequent (10%) in the PDA and more frequent (29%) in ASCP in this cohort. In addition, other genes including KRAS, TP53, CDKN2A, and SMAD4 are commonly mutated in both ASCP (figure 1A) and conventional PDA. The amplification of MYC oncogene is uniquely associated with poor outcome (figure 1B). In the recent TCGA data, amplification of MYC is also identified frequently in PDA (14%) and defined poor-outcome (figure 2). MYC application is associated with increased expression of KRT5 and CDKN2A/p63 which are markers of ASCP. FISH study for MYC amplification on 26 ASCP cases, in which 9 cases with precursor lesions pancreatic intraepithelial neoplasia (PanIN), show that 77% (7 of 9 cases) of PanIN and its associated invasive ASCP have copy increase or amplification of MYC. These findings suggest that MYC amplification is a driver in the oncogenesis of ASCP.

Conclusion The identification of MYC amplification and other commonly mutated genes in ASCP provides potential targets for developing new therapeutic approaches for the treatment of ASCP.

B16 RISK OF URINARY STONES IN PATIENTS WITH CELIAC DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Objective Patients with celiac disease are thought to have higher risk of urinary stones due to malabsorption or some other mechanisms. However, the risk of urinary stones in patients with celiac disease according to epidemiologic studies remains unclear. We performed this meta-analysis to assess the risk of urinary stones in patients diagnosed with celiac disease compared to controls.

Method A systematic review was conducted in MEDLINE, EMBASE, Cochrane databases from inception through December 2017 to identify studies that evaluated risk of any types of urinary stones in patients with celiac disease. Effect estimates from the individual study were extracted and combined using random-effect, generic inverse variance method of DerSimonian and Laird.

Results Three observational studies with a total of 43,598 participants were enrolled. Compared with controls, celiac disease was associated with significantly increased risk of urinary stones with a pooled OR of 1.90 (95% CI, 1.14 to 3.17). We found no publication bias as assessed by the funnel plots and Egger's regression asymmetry test with $p = 0.23$. However, the heterogeneity of the included studies was high.

Conclusion Celiac disease is associated with 90% increased risk of urinary stones compared to controls.

B51 EXPRESSION OF THE HEPATOCYTE ASIALOGLYCOPROTEIN RECEPTOR IS DECREASED IN HUMAN CIRRHOTIC LIVERS OF DIFFERENT ETIOLOGIES

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Purpose Liver cirrhosis is a common cause of mortality and the second most frequent reason for liver transplantation. A variety of diseases can progress to liver cirrhosis, including primary biliary disease, auto-immune hepatitis, non-alcoholic fatty liver disease, cholangitis, hepatitis B and C-related injuries, and alcoholic liver disease (ALD). Our laboratory has extensively examined ALD in animal models, and identified abnormal function of the hepatic asialoglycoprotein receptor (ASGPR) in rats and mice fed alcohol. Since expression of the ASGPR has been implicated in maintaining a healthy liver in humans, and its activity is decreased by up to 50% in some diseased livers, we sought to characterize and quantify ASGPR content in livers of human cirrhotics of various etiologies, namely non-alcoholic liver disease (NAFLD), hepatitis C (HPC), and alcoholic liver disease (ALD), and compare the results to normal liver tissue.

Methods Normal human liver tissue and liver tissue from transplant patients with a previous history of ALD, NAFLD, and HPC, and diagnosed with cirrhosis was provided by our collaborators at the University of Kansas Medical Center. All

Abstract B16 Figure 1

tissue was stained for ASGPR using standard immunohistochemistry (IHC) and then analyzed using Definiens Image Analysis Software for quantification of IHC intensity. Guidelines for selection of these areas was based on previous studies conducted using Definiens Software. Entire tissue sections were then analyzed and the amount of each intensity of stain was quantified as a percentage of the overall section. H scores were then calculated using a previously published method: $(\% \text{ low} \times 1) + (\% \text{ medium} \times 2) + (\% \text{ high} \times 3)$.

Results Using Definiens Image Analysis Software, the average ASGPR IHC intensity in human cirrhotic liver tissue was lower compared with normal controls (control H score=266). The average H scores for ALD was 177 (a significant 30% decrease compared to controls), while H scores for the HPC (211) and NAFLD (214) samples were similar to each other, but also significantly less than controls. Additionally, intensity in the ALD sections was significantly less than either the NAFLD or the HPC. There was an N of 5 for each of these unique etiologies.

Conclusions These data suggest that expression of the ASGPR is decreased in the injured, cirrhotic liver of multiple different etiologies in humans, similar to what is identified in the alcohol-injured livers of rats and mice. The data also suggest that the expression of ASGPR in alcoholic liver disease is even lower than that in Hepatitis C or non-alcoholic fatty liver disease.

B52 SELECTED HYDROXYEICOSATETRAENOIC ACIDS IN PATIENTS WITH PANCREATIC CANCER: A PRELIMINARY REPORT

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Objective Previous experimental reports have proved that lipoxygenase (LOX) derivatives of arachidonic acid (AA), such as hydroxyeicosatetraenoic acids (HETEs), may significantly participate in the pathogenesis of pancreatic cancer. However, these observations have not been confirmed in human studies.

Method In this study, we comprehensively evaluated the peripheral concentrations of selected LOX-derived HETEs (5-, 12-, and 15-HETE) in patients with pancreatic adenocarcinoma (n=36), other pancreatic diseases (n=39), as well as in control individuals (n=35).

Results In comparison to the control individuals, patients with pancreatic adenocarcinoma had significantly higher concentrations of 5-, 12-, and 15-HETE (at least $p < 0.05$ in all cases). Similar results were observed in patients with other than cancer types of pancreatic diseases, who had elevated levels of all examined HETE acids compared to healthy individuals (at least $p < 0.003$ for all). However, the concentrations of the examined HETEs were not significantly associated with the TNM stage of pancreatic cancer in our patients. Finally, analyses of receiver operating characteristic – ROC curves demonstrated that all HETEs examined here had relatively low area under the curve (AUC) values for discriminating pancreatic adenocarcinoma from non-cancerous conditions ($p > 0.05$ in each case).

Conclusion This study demonstrates preliminary translational evidence for the significance of the examined HETEs in the clinical pathogenesis of pancreatic cancer and other pancreatic diseases in humans. Moreover, our data show that HETEs examined here do

not present sufficient clinical potential to be used as independent biomarkers for differentiating pancreatic adenocarcinoma from other non-cancerous conditions in humans. Supported by the TANITA Healthy Weight Community Trust.

B53 ALTERATIONS IN THE GASTRIC LANDSCAPE AND THEIR EFFECTS ON HELICOBACTER PYLORI PATHOGENESIS

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10.1136/jim-2018-000745.102

Objective Infection with *Helicobacter pylori* (Hp) remains the most significant risk factor for the development of gastric adenocarcinoma, a leading cause of cancer-related deaths worldwide. The sequence of events leading to gastric neoplasia begins with the gradual loss of acid-secreting parietal cells, followed by the expansion of pre-neoplastic changes in the setting of chronic inflammation. This early mucosal response is characterized by an increased proliferation of gastric progenitor cells and the reprogramming of post-mitotic chief cells at the gastric gland base into a proliferating population of metaplastic cells. While the metaplastic response is normally a transient alteration in the gastric landscape to facilitate subsequent restoration of normal architecture, epithelial repair can be blocked, leading to a progression to gastric dysplasia in the setting of chronic inflammation. It remains unclear how Hp adapts to changes in the gastric landscape that accompany metaplasia. Hp adhesion to gastric epithelium is mediated by the binding of two of its adhesins, BabA and SabA, to host Lewis B and sialylated Lewis X (sLe^x), respectively, antigens terminally expressed on gastric mucins. We hypothesized that Hp interacts differently with metaplastic gastric epithelium and that this could explain Hp's ability to expand its niche within the stomach.

Methods We explored the differential binding of Hp to metaplastic tissue both *in vivo* and *in situ*. Mice were orally gavaged with Hp and chronically infected for 6–8 weeks. We then injected mice intra-peritoneally with three daily doses of high-dose tamoxifen (HD-Tam; 5 mg/20 g body weight), which we have previously shown induces an acute and reversible gastric metaplastic response. Bacteria were harvested from distinct regions of the murine stomach (corpus vs antrum), and the topographic and glandular distribution of Hp was evaluated by bacterial harvesting and immunofluorescent staining of histological sections, respectively. To directly probe binding of Hp to metaplastic gastric epithelium, a novel *in situ* Hp adherence assay was developed, wherein Hp binding to free-floating, thick (100 µm), fixed tissue sections of uninjured and metaplastic gastric epithelium could be qualitatively and quantitatively assessed.

Results Induction of metaplasia following treatment with HD-Tam results in an expansion of sLe^x expression along the length of the gastric unit axis. Consistent with this change in expression pattern, Hp is able to penetrate deep within metaplastic glands *in vivo*, while it is largely restricted to the surface epithelium of uninjured glands. This phenotype could be reproduced *in situ*, demonstrating that Hp binds metaplastic epithelium independent of active acid secretion. In addition, the ability of Hp to penetrate deep within gastric glands *in situ* could be inhibited by cleaving terminal sialic acid residues or by pre-treating sections with glycoconjugates that compete for binding to sLe^x. Following recovery from injury, the sLe^x expression pattern reverts to that of uninjured tissue.

Accordingly, Hp is unable to penetrate deep within recovered glands, suggesting that Hp's binding is mediated in part by reversible changes in sLe^x expression. Finally, consistent with *in situ* findings, Hp is able to expand its topographic distribution *in vivo* by more effectively colonizing the gastric corpus of mouse stomachs undergoing metaplasia compared to uninjured stomachs, implying that Hp has a tropism for metaplastic epithelium.

Conclusion We present a potential mechanism by which Hp can expand its niche and interacts with metaplastic gastric epithelium through its binding to sLe^x, an early host-microbial interaction that likely shapes the pre-neoplastic gastric milieu.

B54 THE EFFECTIVENESS OF NANOFORMULATED COPPER/ZINC SUPEROXIDE DISMUTASE IN AMELIORATING ETHANOL AND/OR FREE FATTY ACID-INDUCED LIVER INJURY

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10.1136/jim-2018-000745.103

Objective Obesity and excess body weight is strongly associated with the severity of alcoholic liver disease (ALD). Although oxidative stress appears to be a common mechanism linking obesity with ALD, the role of oxidative stress initiated by superoxide in modulating the pathogenesis of obesity-linked ALD is unclear. Moreover, the potential role of antioxidants in modulating the progression of ALD in obesity remains largely unknown. Obesity and ethanol feeding is associated with increased free fatty acid (FFA) release from adipose tissue. The objective of this study is to determine the effectiveness of nanoformulated copper/zinc superoxide dismutase (nanoSOD) in attenuating free fatty acid (FFA) and ethanol-induced hepatocyte injury.

Method We used primary hepatocytes and genetically-engineered and ethanol-metabolizing HepG2 hepatoma cells over-expressing either cytochrome P450 2E1 alone (e47 cells) or both cytochrome P450 2E1 and alcohol dehydrogenase (VL17A cells). Cells were treated with linoleic acid (LA, 120μM), a FFA, and/or ethanol (50 mM). In separate experiment, we delivered nanoSOD to ethanol-fed mice.

Results We show that combined treatment with LA and ethanol but not the individual treatments led to a significant increase in DCF fluorescence ($P<0.05$), a marker of oxidative stress in these cells. Next, we show that nanoSOD was more effective in delivering SOD1 protein to primary hepatocytes and e47 hepatoma cells ($P<0.001$) compared to native SOD. Along the lines, pre-treatment with nanoSOD was more effective than native SOD in reducing LA+ethanol-induced DCF fluorescence in all three types of cells tested. Further mechanistic studies showed that primary hepatocytes pre-treated with nanoSOD showed a significant increase in AMPK phosphorylation upon LA+ethanol treatment. Of note, AMPK signaling plays a critical role in attenuating ethanol-induced hepatocyte injury. We next conducted an *in vivo* study delivering nanoSOD to ethanol-fed mice. NanoSOD improved hepatic AMPK signaling and reduced ethanol-induced liver injury in mice.

Conclusion Together, our data suggest that delivery of SOD1 to hepatocytes is effective in ameliorating ethanol-induced oxidative stress and liver injury and this effect is mediated at least in part, via improved AMPK signaling. The findings will

be relevant to determining the therapeutic potential of nano-formulated antioxidant enzymes in treating ALD in the presence or absence of obesity.

C03 CULTURE NEGATIVE NEUTROCYTIC ASCITES FOLLOWING A URINARY TRACT INFECTION: A CASE REPORT

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Bacterial infections are very common, and account for major morbidity and mortality in cirrhosis. These infections account for about 30% to 50% of deaths in patients with cirrhosis. Common types of infections include spontaneous bacterial peritonitis (SBP) (25% to 31%), and its variants, urinary tract infection (UTI) (20% to 25%), pneumonia (15% to 21%), bacteremia (12%), and soft tissue infection (11%). Bacterial infections are common in patients with liver cirrhosis, including the association between the two most common ones, SBP and UTI, as explored in detail in the following case report. A 50 year old, unemployed man. Independent in his daily living activities with history of chronic alcoholism and IV drug use. Medical history of HIV, Hepatitis C, Chronic Kidney Disease and Chronic Liver Disease. He has been not compliant with medical treatment. The patient presented at the emergency room for the first time on February 9, 2017, complaining of abdominal distention and shortness of breath. Abdominal sonogram showed hepatomegaly, severe ascites, no liver masses identified. Urinalysis was positive for Nitrites. Admitted with complicated liver cirrhosis, ascites de novo, and complicated urinary tract infection as principal diagnosis. Child -Turcotte-Pugh was found in 10 points class C. Paracentesis was performed, showing a SAAG of 3.0, WBC 81, RBC 66, total protein 1.0, Albumin 0.2, Cytology: unsatisfactory due to scant cellularity. Blood and peritoneal fluid cultures showed no growth in 5 days. Urine culture showed colony count less than 10,000 cols/ml. He was treated with Rocephin IV, which was changed to Levaquin IV for 5 days. Initial chief complaint resolved and patient was discharged back home with outpatient follow up with Internal Medicine and Gastroenterology. He returned 5 months later, on July 24, 2017, complaining of bloating sensation, diffuse abdominal pain 8 out of 10, pressure like. Also refers subjective fever. At this time he was under medical treatment for HIV with Isentres (Raltegravir) and Descovy (Emtricitabine/Tenefovir), however still not compliant with medical treatment or diet. Jaundice was present on physical exam, along with a fever of 38.1, tachycardia of 112; diffuse abdominal distention and tenderness with present fluid wave. Abdominal sonogram shows severe ascites with no new findings in comparison with prior sonogram. CT ABD & Pelvis shows large amount of ascites, no masses identified. Child -Turcotte-Pugh 13 points class C, alpha-fetoprotein 46.3 ng/ml. 7 liters of yellowish fluid were removed during paracentesis. Peritoneal fluids analysis shows: WBC 960, PMN 78% (748.8 cell), RBC 132, Albumin 0.3, Total Protein 1.0, Albumin blood 1.4, SAAG 1.1. Peritoneal fluid culture shows no growth in 5 days, peritoneal fluid cytology revealed no malignant cell. A diagnosis of culture negative neutrocytic ascites was made and treatment with Rocephin and Albumin were administered with adequate clinical response. After 6 days the patient was discharged home with Norfloxacin oral for secondary prevention

of SBP and follow up with Gastroenterology in an outpatient setting. He returned on 08/08/2017 complaining of intermittent, dull, 4 out of 5 diffuse abdominal pain, associated with chills, subjective fever, and anorexia. At this time, physical exam showed presence of fever of 38.3, tachycardia of 110, fluid wave on abdominal palpation and bilateral lower extremities pitting edema +2. Child -Turcotte- Pugh 13 points, Class C, HIV RNA copies 295/ml, Absolute CD4 388 cells/ul. Abdominal sonogram shows severe ascites, no masses. Paracentesis was performed on 8/29/2017, 6 liters were removed with, WBC 455, PMN 96% (431.5), RBC 1320, Albumin (blood) 2.1, Albumin 0.4, TP 1.3. SAAG 1.7. Blood Culture & Peritoneal Fluid shows no growth in 5 days $\times$ 2. Diagnosis of Culture negative neutrocytic ascites was made. Rocephin and Albumin were administered, successfully. Patient was discharged 7 days after admission on Norfloxacin, with follow up as outpatient with gastroenterology. In the present case, a clear association was established between Urinary Tract Infection and Culture Negative Neutrocytic Ascites on a patient with liver cirrhosis. Preventive measures, extended patient education, early recognition of risk factors, prompt and proper diagnosis and management are necessary to minimize morbidity and mortality in patients with liver cirrhosis and associated infections.

C04 SERUM METABOLIC PROFILES PROVIDE NEW INSIGHT ON THE EFFECT OF ALCOHOL AND METABOLIC PATHWAYS IN HUMANS

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Objective Excessive alcohol consumption can lead to the disruption of several metabolic pathways which may perpetuate the development of alcoholic liver disease (ALD). Several studies have mainly focused on analyzing the differential expression of genes linking to ALD. However, many processes are regulated beyond the gene/transcriptional level as such studies only provide a partial illustration into the specific pathways involved. The present study took a novel and high-throughput approach to assess for the alterations of metabolites in the following well characterized cohorts: controls, heavy drinkers without liver disease (HD), and those with ALD using metabolomics analysis.

Method Comprehensive serum metabolomics analyses using Ultrahigh Performance Liquid Chromatography-Tandem Mass

Spectroscopy (UPLC-MS/MS) were performed on non-drinker controls (CTRL, n=22), heavy drinkers without significant drinking within 10 days of enrollment (HD1, n=57), heavy drinkers with significant drinking within 10 days (HD2, n=90), and subjects with alcoholic liver disease (ALD, n=33). **Results** Using $p \leq 0.05$ as a cutoff, 142, 268, and 420 metabolites were altered in HD1, HD2, and ALD when compared to CTRL, respectively. Alterations in the levels of these metabolites were found in pathways related to carbohydrate, amino acid, fatty acid, and bile acid metabolism. Principal component analyses significantly differentiated the ALD sera from CTRL and HD. Pyruvate levels were slightly increased in ALD sera and lactate levels were significantly elevated in ALD and HD2 sera, relative to CTRL ($p < 0.05$). Serum levels of several long chain fatty acids (i.e palmitate) were significantly elevated in the serum of patients with ALD. Branched-chain amino acids were reduced in the serum of patients with ALD, along with the α -ketoacids produced by branched-chain aminotransferase (BCAT). Many bile acids were also elevated in the HD1 and HD2 sera, relative to CTRL. The bile acid synthesis intermediate, 7 α -hydroxy-3-oxo-4-cholestenoic acid (7-HOCA), was sharply higher in the ALD sera, relative to all other groups. Further analyses also revealed levels of fibroblast growth factor (FGF) family; such as FGF21 were elevated in HD (442 ± 82 pg/ml) and ALD (632 ± 112 pg/ml) compared to CTRL (222 ± 24 pg/ml) ($p = 0.001$).

Conclusion Metabolomic analyses provide a useful means to identify unique metabolites altered by alcohol which has future implications for clinical practice in terms of identifying and quantifying heavy alcohol use. Further studies are needed to explore the mechanism related to such changes and ALD pathogenesis.

C23 RECURRENCE OF RENAL CELL CARCINOMA PRESENTING AS HEMATEMESIS FROM ESOPHAGEAL METASTASIS

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Renal cell carcinoma (RCC) is a relatively uncommon malignancy and accounts for approximately 3% of all adult malignancies. Esophageal metastasis with recurrent RCC is exceedingly unusual. To the best of our knowledge, only six cases of esophageal metastases have been reported in literature. Our patient's upper gastrointestinal (GI) bleeding was successfully controlled with low doses of hemostatic radiation

Abstract C23 Figure 1

Abstract C23 Figure 2

Abstract C23 Figure 3

Abstract C23 Figure 4

therapy (RT) to the gastroesophageal lesion. A 70-year-old Caucasian male with a history of hypertension and renal cell carcinoma status post radical nephrectomy five years ago deemed to be in remission, was admitted with complaint of hematemesis. Esophagogastroduodenoscopy (EGD) showed a 7 cm non-obstructing, fungating mass involving the gastroesophageal junction concerning for malignancy. Biopsies from the mass were consistent with metastatic renal cell carcinoma. Patient's upper GI bleeding was successfully treated with six sessions of directed radiotherapy to the gastroesophageal. In conclusion, RCC is an indolent malignancy that can metastasize to the GI tract after many years of definitive treatment at the time of diagnosis. Involvement of the esophagus and stomach is extremely rare in this metastatic disease process. Patients can present with overt signs of GI bleeding secondary to the hyper-vascular characteristic of the metastatic lesion. If resection is possible, endoscopic or surgical resection is the treatment of choice. Otherwise, multidisciplinary treatment, including directed radiotherapy and molecular-targeting therapy is needed for more palliative targets.

C35 SPLENIC RUPTURE AFTER DIAGNOSTIC UPPER ENDOSCOPY

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Introduction Upper GI endoscopy is considered a safe procedure that has low risk of complications. The adverse event rate has been reported as 1 of every 2,500 to 11,000 diagnostic upper endoscopies and mortality rates range from none to 1 in 2000. These complications typically include bleeding, perforation of upper GI tract, and cardiopulmonary reaction to sedation. We present a unique case of a splenic laceration after an outpatient routine diagnostic EGD.

Case report A 55 year old female with history of pyloric stenosis, peptic ulcer disease, hypothyroidism, and

hyperlipidemia presented to the emergency department with abdominal pain hours after an outpatient routine EGD with pyloric biopsies for evaluation of pyloric stenosis. Patient experienced acute onset, worsening diffuse abdominal pain along with multiple syncopal episodes. Upon presentation, patient was hypotensive (71/41 mmHg) and abdominal exam revealed tenderness to palpation and guarding. Bedside ultrasound in the emergency department revealed large amounts of free fluid in abdomen. Blood work showed a hemoglobin of 7.8, down from normal level few weeks earlier. After resuscitating the patient, she underwent emergent exploratory laparotomy. Intraoperatively, patient was found to have a splenic laceration with 3L of hemoperitoneum along with findings of pyloric stenosis and gastric outlet obstruction. No bowel perforation was found. Splenectomy and retrocolic gastrojejunostomy were performed. Her postoperative course was uncomplicated. Patient recovered well and was discharged on postop day 6.

Conclusion Splenic injury most commonly occurs from blunt trauma, however it can also be caused from hematological, metabolic, infectious, and iatrogenic causes. Iatrogenic traumatic injury to the spleen related to endoscopy is an extremely rare complication with a small number of cases reported in medical literature, mostly following colonoscopy and ERCP. The mechanism of the injury is thought to be due to a capsular tear or laceration from retraction devices or tension of the gastrosplenic ligament and short gastric vessels that result from surgical or endoscopic maneuvers of the colon, stomach, pancreas, kidney, or abdominal aorta. To our knowledge, this is the first reported case of splenic rupture following routine diagnostic EGD without balloon dilatation. It is important to include splenic rupture as an extremely rare, but potential complication with patients undergoing upper endoscopy.

C36

CLOSTRIDIUM PERFRINGES CAUSING SEPTIC ARTHRITIS SECONDARY TO ACUTE CHOLECYSTITIS: A CASE REPORT

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Introduction Both native and prosthetic joints are susceptible to bacterial infections resulting in septic arthritis. Although the spread in native joints is usually from hematogenous spread, prosthetic joint infections from bacteremia are less frequent. The causative agents of joint infections are usually gram-positive aerobes with anaerobes attributing to 1% of the disease. We report a case of prosthetic arthritis by *Clostridium perfringens* secondary to Acute Cholecystitis.

Case report A 77-year-old Caucasian male with a PMH significant for diverticulosis and B cell lymphoma stage IIIa (in remission for 5 years), osteoarthritis with prosthetic knee replacement 2 years ago, chronic systolic heart failure presents to the ED with complaints left knee pain and swelling that started a day back. The patient had presented 3 days prior to the Emergency Department for abdominal pain that radiated into his chest. His symptoms improved and he was discharged home. With the Knee pain the patient reported fever at home as high 102F recorded at home. The left knee is painful with

weight bearing and range of motion. No other joint was involved and there was no previous history of sexually transmitted disease or recent trauma. On evaluation in ED, patient has arthrocentesis with large numbers of WBC of 141 350. No Organism was seen on stain nor was any crystals observed. There was high concern for infection and was evaluated by orthopedic surgery. The patient was started on Vancomycin and Metronidazole. Synovial fluid cultures grew *Clostridium perfringens*. Gastroenterology was consulted given suspicion for Intestinal source but the Colonoscopy performed was negative. The patient underwent Irrigation of the joint and Debridement by surgery. CT abdomen was obtained, given that it is not a typical organism for joint infection. Patient was transitioned to Ertapenem and Moxifloxacin after sensitivities returned. CT abdomen showed abnormality in mesentery, concern for infection vs malignancy. A PET scanned showed distended gallbladder and fat attenuation at mesentery that did NOT have uptake. Surgery consulted who recommended a HIDA scan given gallbladder. Surgery, recommended a cholecystectomy tube and laparoscopic Cholecystectomy. Pathology of the gallbladder grew *Clostridium perfringens*. The patient was discharged on IV Antibiotics that he would have to continue to 6 weeks.

Discussion With increasing prevalence of an aging population and their associated comorbidities there has been a synchronous risk of anaerobic infections. *Clostridium* soft tissues and joint infections although result from exogenous inoculation like trauma and or surgery, can spread hematogenously mostly from a GI source as a part of the flora of the lower intestinal tract. Treating these infections aggressively with concomitant irrigation of the joint would result in treating the infection based on reports that are present in literature.

C43

PREVALENCE OF GASTRIC INTESTINAL METAPLASIA IN A DIVERSE COMMUNITY

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Objective Gastric Intestinal metaplasia is an intermediate precancerous gastric lesion where normal gastric mucosa is replaced by intestinal epithelium. The goal of this study is to determine the prevalence and demographic of this lesion in a diverse community in NYC

Method A single center case control study, at a tertiary care center, performed on all patients who were diagnosed with intestinal metaplasia between January 2015 and October 2015 and compared to a matched control group without intestinal metaplasia.

Results Among 535 patients who underwent esophagogastroduodenoscopy (EGD), 99 patients had intestinal metaplasia (18.5%). There was no significant difference in *h pylori* infection between patients with intestinal metaplasia and control group (n=38 vs 36, p>0.05). Male/Female ratio was 1.0 in patients with intestinal metaplasia. Intestinal metaplasia was more common in patients with Hispanic heritage.

Conclusion Gastric intestinal metaplasia is a common precancerous gastric lesion that is only diagnosed by biopsy. No current guidelines are established for surveillance.

Genetic and Molecular Medicine

B17 ABSTRACT WITHDRAWN

Hematology and Oncology

B06 ONCOGENIC FACTORS REGULATE NAMPT GENE (NICOTINAMIDE PHOSPHORIBOSYLTRANSFERASE) PROMOTING LUNG NON-SMALL CELL CARCINOMA PROGRESSION

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Objective Nicotinamide phosphoribosyltransferase (NAMPT) is a pleiotropic protein, functioning as an enzyme, cytokine, growth factor and adipocytokine. NAMPT is involved in inflammation, cell growth, survival, DNA replication and repair, and energy metabolism and has been reported to increase in more than ten different cancers (carcinogenesis, progression, invasion and metastasis). Meta-analysis of genome-wide expression data identified NAMPT-influenced genes implicated in cancer pathobiology with NAMPT a novel oncogene with a central role in carcinogenesis. We further investigated molecular mechanisms of NAMPT transcriptional regulation by oncogenic factors in lung non-small cell carcinoma (NSCLC).

Method NAMPT CRISPR/Cas9 KO or scramble control plasmids were transfected into the NSCLC A549 cell line. The proliferation and migration of cells were measured by BrdU cell proliferation and migration assay, respectively. The secretion of NAMPT (eNAMPT) from cells were measured by ELISA. The proximal promoter region of NAMPT was cloned from human genomic DNA and fused to luciferase reporter vector, then transfected into lung NSCLC and non-cancer cell lines. The promoter containing genetic variants were generated by site-directed mutagenesis. The promoter activities were measured by dual-luciferase reporter assays following challenge with the oncogenic growth factor, EGF.

Results Cell migration and proliferation of NSCLC A549 were significantly attenuated in cells transfected by NAMPT CRISPR/Cas9 KO, compared to scramble controls ($p < 0.01$). NSCLC cells A549 and H1993 secreted greater amounts of eNAMPT than the non-cancer cell lines HBE and BEAS-2b. Transfection of the NAMPT promoter into lung cancer cells A549 and H1993 revealed significantly greater promoter activity compared to non-cancer cells HBE and BEAS-1b ($p < 0.05$).

EGF 100 ng/ml robustly increased NAMPT promoter activity in A549 cells ($p < 0.01$). Genetic variant rs61330082 (-1535C/T), associated with decreased risks of several different carcinomas and decreased oncogenic transcription factor binding to NAMPT in silico, significantly attenuated EGF-induced increase in NAMPT promoter activities ($p < 0.01$).

Conclusion Our studies demonstrated that NAMPT is transcriptionally regulated by oncogenic factors, influenced by a cancer-related genetic variant, and promotes progress of lung NSCLC. These findings indicate that NAMPT is a potent therapeutic target in the treatment of lung NSCLC.

A01 REDUCED HEMOLYSIS AND RELATED COMPLICATIONS IN FEMALES WITH SICKLE CELL DISEASE

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Objective Sickle cell disease (SCD) is an inherited erythrocyte disorder characterized by chronic hemolysis and vasculopathy. Females have reduced levels of hemolysis compared to males in both the general population (Jordan A, *et al. Vox Sang* 2016) as well as in SCD (Kanas T, *et al. Transfusion* 2016). This phenomenon may be due to the effects of gender on hemoglobin (Hb) F levels (Dover GJ, *et al. Blood* 1992), red blood cell membrane stability (Jordan A, *et al. Vox Sang* 2016), and nitric oxide (NO) bioavailability (Gladwin MT, *et al. Circulation* 2003). We wished to confirm reduced hemolysis in SCD females and whether this would be associated with reduced hemolytic complications, some of which are associated with mortality. Finally, we wished to see if there were suggestions of improved survival in females compared to males with SCD.

Method We investigated differences in laboratory and clinical features by gender in 395 (155 male, 240 female) SCD patients treated at the University of Illinois at Chicago (UIC) and in 668 (304 male, 364 female) SCD patients from the multicenter Walk-PHaSST cohort. Comparisons of linear and categorical variables were performed using ANOVA and logistic regression analysis, respectively adjusting for age, SCD genotype, and Hb F levels. Median values and interquartile range (IQR) are provided.

Results In SCD patients either not on hydroxyurea or with Hb F levels available prior to initiating hydroxyurea, we observed higher Hb F values in females vs. males from both the UIC ($n=329$, $P=0.004$) and Walk-PHaSST ($n=368$, $P=0.002$) cohorts (table 1). Hemolytic markers were lower in females vs. males and these relationships persisted after adjusting for HbF levels, including LDH (UIC: $P=0.0004$, Walk-PHaSST: $P=0.01$); total bilirubin (UIC: $P=0.008$; Walk-

Abstract A01 Table 1 Hemolytic markers by gender in sickle cell disease patients from the university of Illinois at Chicago (UIC) ($n=395$) and walk-PHaSST ($n=668$) cohorts

	UIC			Walk-PHaSST		
	Females	Males	P value*	Females	Males	P value*
Hemoglobin F%	4.0 (1.9 – 8.0)	2.9 (1.3 – 5.7)	0.004	3.0 (1.1 – 7.2)	2.3 (1.0 – 5.5)	0.003
LDH (u/L)	287 (210 – 386)	336 (258 – 489)	0.0004	350 (236 – 492)	394 (276 – 636)	0.01
Total Bilirubin (mg/dL)	1.9 (1.3 – 3.2)	2.4 (1.8 – 4.0)	0.008	3.4 (2.1 – 5.5)	4.4 (2.7 – 6.9)	0.002
AST (u/L)	34 (25 – 47)	39 (30 – 52)	0.08	35 (25 – 49)	41 (30 – 69)	0.0002
Reticulocyte count ($\times 10^3/\mu\text{L}$)	261 (172 – 368)	332 (224 – 442)	0.04	187 (127 – 281)	233 (158 – 322)	0.01
Pulse Pressure (mmHg)	43 (39 – 51)	52 (45 – 61)	< 0.0001	49 (41 – 56)	52 (44 – 60)	0.0003
Leg ulcer history	14/232 (6%)	28/150 (19%)	< 0.0001	65/364 (18%)	61/304 (20%)	0.09
TRJV > 3.0 m/sec	7/153 (5%)	8/99 (8%)	0.2	30/312 (10%)	43/273 (16%)	0.01

* P values adjusted for age, sickle cell disease genotype, and hemoglobin F% in both cohorts along with site in the Walk-PHaSST cohort

Abstract A01 Figure 1

PHaSST: $P=0.002$), AST (UIC: $P=0.08$; Walk-PHaSST: $P=0.0002$), and absolute reticulocyte count (UIC: $P=0.04$, Walk-PHaSST: $P=0.01$) (table 1). Less hemolysis would be expected to decrease the occurrence or severity of a hemolytic vasculopathy and its manifestations. Pulse pressures were lower in females than males in both cohorts (UIC: $P<0.0001$; Walk-PHaSST: $P=0.0002$). Additional manifestations less frequently observed in females than males included leg ulcer history (UIC: $P<0.0001$; Walk-PHaSST: $P=0.09$) and tricuspid regurgitant velocity $>3.0\text{m/s}$ (UIC: $P=0.2$; Walk-PHaSST: $P=0.01$) (table 1). The degree of hemolysis is an independent predictor for early mortality in SCD (Kato GJ, *et al.* Blood 2006, Nouriae M, *et al.* Haematologica 2013). There were progressively higher ratios of females: males with increasing age in SCD patients (Cochran's linear trend; UIC: $P=0.03$, Walk-PHaSST: $P=0.005$) (figure 1). We compared gene expression in peripheral blood mononuclear cells by gender in 180 SCD patients from UIC using the Affymetrix Human Exon 2.0 ST array. Restricting analyses to autosomes with an FDR <0.05 , no statistically significant differences in gene expression were observed. We also determined the X-linked G6PD A- status by PCR in 259 SCD patients from the UIC cohort. G6PD A-deficiency was observed in 4% (6/155) of females and 10% (10/104) of males and was not associated with hemolytic markers.

Conclusion In summary, females had a lower degree of hemolysis, decreased vasculopathy, and represented a progressively higher proportion of SCD patients with increasing age in both the UIC and Walk-PHaSST cohorts. Future investigation of loci on the sex chromosomes for effects on Hb F levels and the degree of hemolysis are warranted. Understanding the mechanisms for reduced hemolysis in women with SCD, such as the potential effects of testosterone and estrogen on erythrocyte membrane stabilization, may also help guide future therapies.

B08

ARSENIC DISTURBS PROSTATE STEM-PROGENITOR HOMEOSTASIS BY ACTIVATION OF NRF2 PATHWAY

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Objective 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 suggested that arsenic blocks autophagic flux in human prostate stem-progenitor cells and drives transformation through sustained NRF2 pathway

activation. The present study sought to determine the impact of the NRF2 pathway on prostate stem-progenitor cells homeostasis.

Method Primary human prostate epithelial cells (PrEC) from disease-free donors were used. Stem-progenitor cells were enriched by 3D prostasphere (PS) culture and their differentiation capability was evaluated by prostate organoid (PO) culture $\pm 1\text{ }\mu\text{M}$ iAs. Illumina HumanHT12 Gene Expression Microarray analysis was applied to identify iAs-dysregulated genes. Stable gene overexpression and knockdown in PS were achieved by lentiviral infection.

Results Gene Set Enrichment Analysis (GSEA) analysis of iAs-dysregulated genes revealed that iAs activated the NRF2 pathway in both PS and PO groups. Interestingly, we found that the NRF2 pathway was enriched in control stem-progenitor cells (PS) and decreased during differentiation (PO). This suggests that NRF2 activation may contribute to iAs modulation of prostate stem-progenitor homeostasis. Indeed, we found that PS formation was increased when NRF2 pathway was activated by Oltipraz (an NRF2 inducer) or NRF2 gene overexpression whereas NRF2 knockdown by shRNA markedly inhibited PS formation suggesting that NRF2 activation increases prostate stem-progenitor cell self-renewal capacity. Furthermore qRT-PCR following NRF2 knockdown in 2D-cultured PrECs induced expression of epithelial differentiation genes (CEACAM6, LCN2, S100P) and led to prostate stem-progenitor depletion.

Conclusion NRF2 activation increased prostate stem-progenitor cell self-renewal while NRF2 inhibition drove cell differentiation and stem-progenitor cell depletion, together indicates that NRF2 plays an essential role in maintaining homeostasis of normal prostate stem-progenitor cells. Since iAs chronically elevates NRF2 expression, we proposed that iAs may transform normal prostate stem-progenitor cells by disturbing their normal homeostasis via NRF2 pathway activation.

A21

STEM CELL LINEAGE HIERARCHY BY KERATIN PROFILING IN NORMAL HUMAN PROSTATE EPITHELIAL CELLS AND PROSTATE CANCER

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Objective Keratins are intermediate filament proteins that perform both mechanical and non-mechanical functions. Several specific keratins have been implicated in stem cells and cancers. Using a sphere-based label retention assay, we recently isolated and characterized prostate stem cells and cancer stem-like cells from mixed progenitor populations (PMID 28651114), identifying keratin 13 (KRT13) as a specific

prostate stem cell marker regulating self-renewal. Herein, we utilize detailed keratin profiles to further clarify the human prostate epithelial lineage hierarchy and identify prostate cancer stem-like cells.

Methods and results Primary prostate epithelial cells were 3D cultured (5 days) to form prostaspheres (PS) with mixed stem and daughter progenitor cells. The stem cells were separated from progenitors using long-term label retention and FACS. In normal prostate tissues from 3 healthy donors, RNA-seq revealed enrichment of KRT13, 23, 80, 78, 86 and 4 in label-retaining prostate stem cells while KRT6, 17, 14, 5, 8, 18 and P63 were enriched in non-retaining progenitors. We next used Fluidigm C1 captured single cell RNA-seq and identified three major clusters in the label-retaining stem cell population; *Cluster I* represents quiescent stem cells (KRT13, 23, 80, 78, 4 enriched), while *Clusters II & III* contain active stem cells and bipotent progenitors, respectively (KRT16, 17, 6 enriched). GSEA analysis found stem cell and cancer related pathways enrichment in *Cluster I*. Three additional clusters were identified in non-retaining progenitor cells, with *Cluster IV* representing unipotent basal progenitor cells (KRT5, 14, 6, 16 enriched) and *Clusters V & VI* as early & late stage unipotent luminal progenitors (KRT8, 18, 10 enriched). Cancer stem-like cells were similarly isolated from three prostate cancer specimens and RNA-seq with MetaCore pathway analysis found enrichment of cytoskeleton remodeling_Keratin filaments. Interestingly, in addition to normal stem cell keratins (KRT13, 23, 80, 78, 4), other keratins (KRT10, 19, 6, 75, 16, 79, 3, 82) were enriched in cancer stem-like cells. Surprisingly, stem-like cells from patient-matched benign regions revealed a similar keratin profile, suggesting a cancer field effect for stem-like cell populations.

Conclusion Taken together, using gene profiling with an emphasis on keratin patterns, we have delineated the lineage hierarchy of human prostate stem cells originating from the activation of quiescent stem cells to bipotent progenitors that give rise to unipotent basal and luminal progenitor cells. We have identified common keratins enriched in stem cells from normal prostate and cancer/benign tissues, as well as keratins unique in stem-like cells from prostate cancer. This clarification of the stem cell lineage hierarchy and keratin profiling of human prostate stem cells and cancer stem-like cells may provide enhanced opportunities for translational studies that target therapeutic-resistant cancer stem-like cells. (CA-172220)

A22

AUTOMATED MAPPING AND ANALYSIS OF STROMAL CELLS IN TUMOR MICROENVIRONMENT IN PANCREATIC ADENOCARCINOMA AND CHOLANGIOCARCINOMA USING DEEP LEARNING

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Objective A characteristic histologic feature of pancreatic adenocarcinoma (PAD) and cholangiocarcinoma (COL) is extensive desmoplasia alongside leukocytes and stromal cells. Advances in mRNA-sequencing have enhanced our understanding of cancer biology in relation to selective changes in expressivity amongst stromal cells. Desmoplastic changes secondary to aberrant expression in stromal cells creates a barrier to absorption and penetration of therapeutic drugs, but few models exist to analyze the spatial and architectural elements composing the complex tumor microenvironment (TME) in association with mRNA levels.

Methods The histopathology images (H&E stain) and mRNA-seq of 178 PAD and 36 COL patients were obtained from the Cancer Genome Atlas (TCGA) of National Cancer Institute and analyzed with the deep learning algorithm, which characterizes histological features in comparison to the corresponding mRNA-seq, allowing for rapid automated analysis of large quantities of data. Ninety genes enriched in leukocytes (CD8+ T cells, B cells, CD4+ regulatory T cells, macrophages, neutrophils, NK cells, and plasmacytoid dendritic cells), 7 genes for cytolytic activities (GZMA, PRF1, GZMH, GZMK, NKG7, CD3E, and CD247), and 5 genes involved with desmoplastic changes (PDFGRA, ACTA2, COL1A1, COL1A2, and PDPN) were analyzed. For each patient, mRNA levels of select genes were analyzed against histologic features, including degree of desmoplastic reaction, number of leukocytes, and degree of leukocyte clustering and isolation from tumor cells.

Results Deep learning analysis demonstrates that the number of fibroblasts and degree of desmoplasia correlates with and predicts the mRNA expression of genes associated with fibroblastic and desmoplastic changes. The mRNA level of CXCL12 correlates with the degree of leukocyte clustering and spatial isolation in PAD and COL. As shown in figure 1, a histology image from a patient having an elevated mRNA level of CXCL12 reveals a higher degree of leukocyte

Abstract A22 Figure 1 Shows histopathology images of patients with pancreatic adenocarcinoma obtained from TCGA. (A) a patient with CXCL 12 mRNA level of 241.26 and (B) that of 5,283.512 gene counts, respectively. Scale bar=300 μm in both (A) and (B)

clustering (figure 1B), compared to that with a low expression of CXCL12 mRNA (figure 1A). The 5 genes associated with desmoplasia and fibrosis do not have a linear relationship with CXCL12 mRNA levels ($R^2 < 0.1$) in COL and ($R^2 = 0.2196$ to 0.6279) in PAD. Cytolytic activity, measured by the mRNA levels from 7 genes, does not correlate with CXCL12 expression ($R^2 < 0.1$) in COL, and ($R^2 = 0.3530$ to 0.6060) in PAD (figure 2).

Conclusion A deep learning model enables automated analysis and mapping of desmoplastic changes within stromal and malignant cells, revealing the spatial and architectural relationship in the TME with varying gene expression. This demonstrates that the degree of leukocyte clustering and isolation from tumor cells correlates with CXCL12 mRNA levels in PAD and COL. CXCL12 expressivity appears to be a contributing factor, limiting access of leukocytes to tumor cells and diminishing an important mechanism combating tumor progression. Varying degrees of desmoplastic reaction and cytolytic activities of immune cells within the TME were also observed in association with CXCL12 expression in PAD and COL. Further biomarker-driven prospective studies in the context of immunotherapy and anti-fibrosis are warranted.

Abstract A22 Figure 2 Is the gene correlation map of 171 genes enriched in the stroma of pancreatic adenocarcinoma. These genes include those associated with cytolytic activities, desmoplastic reaction, stromal and immune cells, and genes associated with stimulatory or inhibitory signals of antigen presenting cells and Tcells. Each box demonstrates a squared correlation coefficient (R^2) of two respective genes

A53

ASCORBIC ACID INDUCES EPIGENETIC MODULATION OF LYMPHOMA CELLS VIA TET (TEN-ELEVEN TRANSLOCATION) ACTIVITY ENHANCEMENT

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Objective The Ten-Eleven Translocation (TET) enzymes have been found to be mutated in both diffuse large B-cell (DLBCL) and peripheral T-cell (PTCL) lymphomas resulting in

DNA hypermethylation. Various important tumor suppressor genes, such as SMAD1 (part of TGF- β signaling), are under-expressed due to aberrantly methylated promoters or enhancers. Recent studies in embryonal stem cells showed that Ascorbic Acid (AA) is a cofactor for TET with a binding site at the catalytic domain, and enhances TET activity. We hypothesized that AA could potentially enhance TET activity in lymphoma cells to cause DNA demethylation, reactivate expression of tumor suppressor genes, and enhance chemosensitivity. We also aimed to determine the frequency of AA deficiency in lymphoma patients.

Method In vitro TET activity was performed on DLBCL cell line LY-1 and PTCL cell line Karpas-299 with pH neutralized AA (L-AA). Genome wide quantitative 5-mc and 5-hmc was evaluated using Liquid Chromatography Electrospray Ionization Tandem Mass Spectrometry (LC-ESI-MS/MS). SMAD1 expression was determined using qRT-PCR. Proliferation assay was performed on LY-1 and Karpas-299 using the Cell Titer Blue assay. Plasma AA levels were measured using fresh samples and standard assay procedures.

Results AA, at doses achieved by the intravenous route, increased TET activity in LY-1 and Karpas 299. Genome wide 5-mc was significantly reduced and 5-hmc was increased, correlating with increase in TET activity. SMAD1 expression was increased with AA treatment. Pre-treatment with AA enhanced chemosensitivity of LY-1 and Karpas-299 to cisplatin and doxorubicin respectively. Since AA leads to the generation of H₂O₂ in-vitro, catalase was used as control. This did not reverse the effect of AA on epigenetic changes. Proliferation inhibition and enhanced chemosensitivity was seen despite catalase control. 29% (10/34) of unselected lymphoma patients had plasma AA levels that were deficient. Patients with high bulk disease were significantly more prone to AA deficiency.

Conclusion AA has the potential to modify TET function in lymphoma and enhance chemosensitivity. AA deficiency seen in some lymphoma patients may further impair TET function and contribute to resistance.

A54

VINCRIStINE INDUCED UNILATERAL VOCAL CORD PARALYSIS

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10.1136/jim-2018-000745.116

Introduction Vincristine is a vinca-alkaloid chemotherapeutic agent that is used in treatment of neoplastic disease. While it has many possible adverse reactions, vocal cord paralysis has rarely been documented. Of the published cases, bilateral vocal cord paralysis of children is most common. We present a case of unilateral vocal cord paralysis of an adult patient leading to stridor, dysphagia, and vocal hoarseness one month after receiving first dose of Vincristine. To our knowledge, this is the first case of an adult experiencing unilateral vocal cord paralysis after administration of single dose of Vincristine therapy.

Patient presentation A 60-year-old woman was diagnosed with B-cell acute lymphoblastic leukemia (ALL), positive for Philadelphia 1 chromosome and p190 mutation. She presented for induction chemotherapy with R-Hyper CVAD (Rituximab, Cyclophosphamide, Vincristine, and Doxorubicin) plus Methotrexate and Cytarabine. One month after receiving her first dose of Vincristine 2mg on day 4 of cycle 1A, she presented

with stridor, hoarseness, dysphagia, and shortness of breath. Urgent laryngoscopy revealed left vocal cord paralysis (figure 1). No other focal neurological deficits were found on physical examination. A Gel-Foam injection of left vocal cord was performed for appropriate medialization and temporary relief of symptoms and Vincristine was held from her chemotherapy regimen. Her presenting symptoms completely resolved 5-months later.

Discussion Vincristine has been shown to cause neuropathies in 19.6% of patients⁶. This is thought to be secondary to binding of alpha-tubulin dimers which disrupts the formation of microtubules causing alteration in size and orientation leading to impaired axonal transport with subsequent axonal degeneration². Sensory fibers are usually affected earlier and more severely than motor fibers⁵. Previous studies have shown that 60% of the patients experiencing neuropathy begin to manifest with a clinically significant sensory or sensorimotor neuropathy at cumulative doses ranging from 30–50 mg⁶. Vocal cord paralysis caused by Vincristine use can be unilateral or bilateral, however bilateral involvement has been more commonly reported in the literature at this time. Bilaterally affected vocal cords can be life-threatening requiring intubation and mechanical ventilation⁴.

Vincristine-induced vocal cord paralysis has no specific treatment, however the use of pyridoxine and pyridostigmine has been associated with a more rapid recovery time in a series of patients who experienced peripheral neuropathy secondary to Vincristine. Most reported cases of Vincristine-induced vocal cord paralysis have shown that it is usually reversible and complete resolution can occur within 6–9 months⁵.

Conclusion We present a rare case of Vincristine induced unilateral vocal cord paralysis successfully managed with conservative therapies. We recommend that this novel approach be considered in future Vincristine induced unilateral vocal cord paralysis without respiratory distress.

Abstract A54 Figure 1 Laryndoscopy showing paralysis of left vocal cord

B18 PRE-CLINICAL EVALUATION OF CINOBUFOTALIN AS A POTENTIAL ANTI-OVARIAN CANCER AGENT

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Objective Cinobufotalin (CINO), a cardiotonic steroid (CTS) or bufadienolide, is extracted from the skin secretions of the traditional Chinese medicine giant toads (Chan su). Recently it has been demonstrated that CINO inhibits lung and ovarian cancer cell function. In this study, we evaluated the molecular mechanism of CINO by which it inhibits ovarian cancer cell function by utilizing three ovarian cancer cells; SK-OV-3, CRL-1978 and CRL-11731. We also performed CRL1978 tumor xenograft model in nude mice and evaluated whether CINO inhibits the tumor growth.

Method 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 and mitochondrial membrane potential (MMP) has also been measured using MMP kit utilizing FACS analysis. Male nu/nu mice were injected with CRL-1978 cells. When tumor volumes are measured at approximately 200–300 mm³, treatment with CINO was initiated. Upon completion of treatment mice were monitored for up to a week before euthanasia, xenografts were excised, then measured, weighed, and preserved. The sections were observed by microscopic examination.

Results Concentration of CINO at 0.5 μ M inhibit SK-OV-3, CRL-1978, and CRL-11731 cells proliferation, migration and invasion without cell death and loss of cell viability. 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. A statistically significant decrease ($p < 0.05$) in tumor size was observed after treatment with both 1 and 5 mg/kg concentrations of CINO when compared to vehicle.

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. Treatment with Cinobufotalin inhibits the growth of Clear cell ovarian cancer cell line CRL-1978. This model is a valid testing platform for additional tumor cell cultures.

B35 WHEN YOUR GUARDIAN ANGEL TURNS AGAINST YOU (EXTRANODAL NATURAL KILLER CELL/T-CELL LYMPHOMA)

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Objective Extranodal natural killer/T-cell lymphoma, nasal type (ENKTCL-N) is an extremely rare form of Non-Hodgkin Lymphoma. It occurs in strong association with Epstein Barr Virus infection. It is most prevalent in Asian and Native American population with a male predominance. Our aim is to increase awareness about this rare condition and to encourage clinicians to broaden their differential diagnosis in cases

of non-resolving pneumonia. We present a case of ENKTCL-N in a young male masquerading as non-resolving pneumonia.

Method N/A

Results A 37-year-old Native American man presented with shortness of breath, fever, productive cough and weight loss of one-month duration. He had treatment failure with oral antibiotics for suspected community-acquired pneumonia. He had stable vital signs upon admission. Physical exam was mostly unremarkable except for a small ulcer on right anterior shin. Laboratory findings were within normal limits. Chest X-ray showed diffuse patchy consolidation. Chest CT Angiogram ruled out pulmonary embolism. He failed to improve on broad-spectrum intravenous antibiotics initiated for possible drug-resistant pneumonia. Eventually, biopsy of the right shin lesion was performed which came back positive for ENKTCL-N. PET scan revealed hypermetabolic activity involving lungs, pancreas, bilateral lower extremities, pelvis and sternum. Biopsy of the right upper lobe of lung revealed tumor cells positive for CD3 and CD56. In situ hybridization was positive for Epstein Barr virus-encoded ribonucleic acid. Bone marrow biopsy was negative for malignancy. A final diagnosis of extranodal natural killer cell/T-cell lymphoma, nasal type was made. He had a prolonged hospital course during which he received multiple rounds of chemotherapy and radiation treatment, complicated by neutropenic fever and liver failure. He passed away 12 months after initial diagnosis.

Conclusion ENKTCL-N is a rare, aggressive lymphoma with poor prognosis. Non-resolving pulmonary infections despite appropriate medical management should prompt a clinician to consider alternative differential diagnoses. Median survival time is usually less than 12 months but this patient lived for 1 year. All reported cases had 100% mortality. This holds true for our patient as well.

B36

PROTEIN KINASE D1-CD36 SIGNALING IN ARTERIOLAR DIFFERENTIATION OF MICROVASCULAR ENDOTHELIAL CELLS: A LINK BETWEEN ENDOTHELIAL CELLS AND SKIN CANCER STEM CELLS FOR TUMOR PROGRESSION?

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Cancer stem cell (CSC) subpopulation in tumors plays a pivotal role in cancer development, growth and metastasis, and drug resistance. CSCs promote tumor angiogenesis by generation of higher levels of proangiogenic factors, such as VEGF and SDF-1, and recruitment of more endothelial cells (ECs). In turn, perivascular ECs activated Notch signaling in tumor microenvironment (TME) influences dynamic changes in CSC populations and may contribute to phenotypic and functional plasticity and diversity of CSCs.

Objective To determine whether PKD-1-CD36 signaling axis mediates crosstalk between endothelial cells and skin cancer stem cells for tumor progression.

Methods To determine the impact of arteriolar differentiation of microvascular ECs in TME as the CSC niche for skin cancer progression, we have developed a human microvascular endothelial cell line (HMVEC-D). To further study interactions of CSCs with differentiated arteriolar EC from MVECs in tumor progression, we have identified a subpopulation of skin CSCs (SCSCs) that expressed specific surface markers

CD44 and ALDH1A and established a skin cancer model in the control and transgenic mice.

Results HMVEC-D formed tube-like structure in two dimensional Matrigel assay. When exposed to VEGF or transduced with constitutively active PKD-1, HMVEC-D increased expression of delta-like ligand 4 and neuropilin 1. We observed that these cells formed spheres in three dimensional agarose gel assays. We then implanted SCSCs (500 to 20000 cells/per injection) into control and transgenic mice: Tie2-CreER; *pkd-1^{loxP/loxP}* that allow inducible endothelial lineage-specific deletion of PKD-1 in response to tamoxifen. When inoculated into mice, we observed that primary tumors grew significantly after 13–15 days, and that tumor not only invaded locally but also generated liver and lung metastasis. We also observed that a subset of metastatic CSCs expressed both CD44 and CD36 in the skin cancer tissues. Intriguingly, injection of tamoxifen to induce PKD-1 deletion in the tumor endothelium did not inhibit the malignant progression of skin cancer. Some of the mice started to die at day 27 and later.

Conclusion Our studies suggest that the PKD-1-CD36 signaling axis plays a pivotal role in arteriolar differentiation of TAECs and tumor angiogenesis and may regulate interactions between TAECs and SCSCs. Targeting the PKD-1-CD36 signaling axis might act synergistically on tumor associated arterioles and CD36⁺ metastatic CSCs. It could be a promising therapeutic strategy when combined with conventional anticancer treatment.

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C05

METASTATIC SARCOMATOID CARCINOMA TO THE HEART, PANCREAS, AND UPPER EXTREMITY

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Introduction Sarcomatoid carcinomas (SC) are uncommon, poorly differentiated, and aggressive lung malignancies. We present a case of metastatic SC with cardiac involvement, initially presenting as pancreatitis in a 58 year-old man.

Patient presentation A 58-year-old man with hypertension and 30 pack-year smoking history was admitted to an outside hospital (OSH) with acute pancreatitis. Abdominal OSH CT imaging revealed a 3x3x3-cm pancreatic mass. An incidental left ventricular (LV) mass was also found on transthoracic echocardiogram (TTE), an incidental left ventricular (LV) mass was found. Therapeutic lovenox was initiated for presumed LV thrombus.

He was transferred to our center for further workup and management of LV mass and possible malignancy. Repeat TTE revealed a 1.3 × 2 × 2-cm fixed homogenous mass attached to LV apical septum with irregular borders. Cardiac MRI displayed 3 masses suggestive of metastatic disease in the LV apical septum, left lateral wall, and inferolateral LV wall (figure 1). CT scan revealed a large necrotic mass in the right lung apex with enlarged necrotic mediastinal, right supraclavicular, and right hilar lymph nodes as well as numerous subcentimeter pulmonary nodules (figure 2). A gluteal muscle lesion was also noted. A tissue sample of a right upper extremity mass demonstrated sarcomatoid carcinoma.

He was discharged with planned oncology follow-up but was re-admitted 3 days later for acute hypoxic respiratory failure in the setting of post-obstructive necrotizing pneumonia. In light of his poor prognosis, he elected to transition to hospice care.

Discussion SCs are a heterogeneous group of non-small cell lung carcinomas (NSCLC) that contain sarcoma-like elements (malignant spindle or giant cells) in addition to malignant epithelial components.¹ This rare disease comprises less than 1% of all lung cancers.² The prognosis is dismal and overall 5-year PSC survival of ranges from 16 to 33%.³

SC exhibits a 4: 1 preference for males and prevalence in smokers, with an average age of presentation of 60³. SCs typically metastasize via lymph nodes and blood vessel routes typically to the brain, bone, adrenal gland and liver. The heart and pancreas, while unusual, have been previously reported sites of metastasis.³

While surgery remains a mainstay of treatment for localized SC, effective systemic chemotherapy regimens have not been well defined for metastatic SCs. Treatment for SC typically follows first-line chemotherapy regimens commonly used for NSCLC. However, both platinum-containing and platinum-free regimens exhibited high rate of resistance and minimal efficacy for disease stabilization.⁴ Epidermal growth factor receptor (EGFR) overexpression and K-ras mutations has been reported in SC, offering possibilities for targeted therapy.^{3,5,6} A recent case of 7-month disease stability with gefitinib, an EGFR tyrosine kinase inhibitor, highlights the potential benefit of targeted immunotherapy with accurate characterization of this disease.³

In contrast to primary cardiac tumors, cardiac metastases are relatively common. The reported incidences range from 2.3–18.3%.³ Endocardial metastases are typically due to hematologic invasion through the heart chambers with intracavitary lodging. Myocardial or epicardial involvement almost exclusively involves retrograde lymphatic spread⁷. The most common primary tumors with cardiac metastasis are mesothelioma (48.4%), melanoma (27.8%) and lung adenocarcinoma (21%). Of lung carcinomas, undifferentiated carcinoma has a 21.2% rate of cardiac metastasis. Across all lung cancer histotypes, the pericardium is most typically involved.⁷

Conclusion SC is a rare disease with dismal prognosis and little data exists for successful treatment options. We present a case of metastatic SC characterized by pulmonary, cardiac, pancreatic, and muscular metastases.

Abstract C05 Figure 1 Cardiac MRI displaying masses within LV apical septum (1), left lateral wall (2), and inferolateral wall (3). LV: Left Ventricle

Abstract C05 Figure 2 CT scan of chest with large necrotic mass in right lung apex

C47

COMPARISON OF 3,4',7-O-TRIMETHYLQUERCETIN INDUCED APOPTOTIC SIGNALING IN THREE OVARIAN CANCER CELL LINES

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Objective Ovarian cancer is the fourth leading cause of cancer mortalities. The survival rate is approximately 90% if the tumor is detected earlier stages. Significant progress in the field of translational research has been geared towards determining if a therapeutic natural compound can be formulated to induce apoptotic signals in the cancer cells. Quercetin is a class of flavonoids which is a component of several different plants. 3,4',7-O-trimethylquercetin (34'7TMQ), a derivative of quercetin, has shown to inhibit melanoma B16 cell metastatic activity *in vitro*. Our study evaluated the effect of 34'7TMQ on three types of ovarian cancer cells (SK-OV-3, CRL11731 and CRL1978) and we previously found that it inhibited ovarian cancer cell migration and invasion without effecting proliferation. This phase of the study was directed to elucidate if 34'7TMQ induced apoptotic signaling in the cancer cells. The expression of pro-apoptotic proteins such as BAX/Bcl-2, p38 MAPK, and Caspase-9 were measured by Western Blot analysis. The induction of apoptotic signaling was detected by immunofluorescence using Annexin V and DAPI stains.

Method Western Blot Assay Cells were cultured in 6-well plates and treated with 0, 3.125, 6.25 and 12.5 μ M 34'7TMQ for 24 hours. Cells were scraped and lysed using a protein inhibitor cocktail followed by protein determination by bicinchoninic acid (BCA) protein assay kit (#23227; Thermo). Protein samples were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) on Invitrogen™ Novex™ NuPAGE™ 4–12% Bis-Tris gel (Fisher Scientific, Waltham, MA). Proteins were subsequently transferred onto a nitrocellulose membrane (Bio Rad, Hercules, CA, USA). Protein density was visualized using enhanced chemiluminescence detection system (LAS-4000; Fujifilm, Tokyo, Japan) and quantified by Image J Software® (<https://imagej.nih.gov/ij/>). Immunofluorescence CRL-1978 cells were seeded on coverslips in a 6-well plate and allowed to adhere

overnight. The cells were then stimulated with 0, 3.125, 6.25 and 12.5 μM 34'7TMQ 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).

Results In CRL-1978 cell line, the expression of BAX/Bcl-2 and Caspase-9 increases whereas the expression of p38 MAPK is decreased. Expression of all three pro-apoptotic proteins are upregulated in the SK-OV-3 cell line. Lastly, in the CRL-11731 cell line, it appears that p38 MAPK and Caspase-9 are upregulated whereas BAX/Bcl-2 is downregulated. This shows that 34'7TMQ has a differential mechanism of action in each of the cancer cells. The Annexin V staining displayed the expression of Pro-Apoptotic signaling in CRL-1978 cell line. In the control sample (0 μM 34'7TMQ), nuclei that are stained DAPI and Annexin V staining are observed to be intact. On the contrary, in 6.25 μM 34'7TMQ, the nuclei are distorted and there is significant overlapping of DAPI and Annexin V and more green patches (referring to apoptotic signaling). This demonstrates that 3,4',7-O-trimethylquercetin induces apoptotic signaling in CRL-1978 ovarian cancer cell line.

Conclusion Our data from the western blot analysis demonstrates that 34'7TMQ is capable of inducing apoptosis in CRL-1978, SK-OV-3, and CRL-11731 cell lines but it affects each cell line differentially. The data from immunofluorescence confirms that 34'7TMQ is inducing apoptosis on CRL-1978 cell lines.

C48

MULTIPLE CANCERS AFTER CHEMOTHERAPY, RADIOTHERAPY AND HORMONAL THERAPY AT UNIVERSITY OF FLORIDA: A PILOT STUDY

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Objective We aim to characterize the occurrence of multiple primary cancers in patients diagnosed with one cancer and explore risk factors for this. Individuals with cancer are at increased risk for subsequent tumours. This risk is multi-factorial and include genetic predisposition, environmental exposure, exposure to carcinogenic cancer therapies, and life-style factors. Use of chemotherapy and radiotherapy has improved survival. Unfortunately, it comes at a price due to therapy-related malignancies. In some reports occurrence of a second cancer is highest 5–10 years after diagnosis of the first. We aim to further understand whether prior exposure to chemotherapy, radiotherapy and hormonal therapy has a role in the development of another different primary cancer.

Method The University of Florida, Jacksonville cancer database was used to identify patients with a diagnosis of cancer in 2011. A total of 1487 patients were included. We observed the number cancers diagnosed in 2011. Additionally, the number of different primary cancers occurring before and after 2011 were also recorded for this study population. Exposure to chemotherapy, radiotherapy and hormonal therapy were also recorded.

Results A total of (74 patients, 5. 10%) had more than one cancer, with lung cancer being the most common second

cancer, followed by renal and prostate cancer. One patient had a third cancer. Most second cancers occurred within 3 years after diagnosis of the first. 29 (9%) of the 341 who had chemotherapy for the first cancer compared to 46 (4%) of the 1146 with no chemotherapy had a second cancer ($p=0.0009$). There was no significant difference in the rate of a 2nd cancer between patients with and without radiotherapy (6% versus 4%, $p=0.151$), nor between patients on both chemo/radiotherapy and without the combo (13% versus 5%, $p=0.191$). Patient on hormonal therapy had higher rate of a 2nd cancer (9%) compared to patients without hormonal therapy ($p=0.017$).

Conclusion Second cancers can occur after treatment of one cancer. Exposure to chemotherapy and hormonal therapy may further increase this risk. There should be heightened awareness among physicians in the detection of new cancers, especially within five years after diagnosis and treatment of the initial one. Further research is needed in developing systems for screening patients for another cancer after having one. This may be critical in reducing the national burden of cancer.

C56

PILOT STUDY: HIGH DOSE FISH OIL IN COLORECTAL CANCER (CRC) PREVENTION IN PATIENTS WITH LYNCH SYNDROME

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Lynch syndrome is the most common inherited CRC. It is an autosomal dominant disorder responsible for about 3% of newly diagnosed CRC. It is caused by germline mutation in one of DNA mismatch repair (MMR) genes (MLH1, MSH2, MSH6, PMS2) or loss of expression of MSH2 due to deletion in the EPCAM gene. These derangements result in a Micro-Satellite Instability (MSI) which is associated with a 70% lifetime risk of CRC in these patients.

Effective interventions to reduce the risk of development of colorectal cancer are limited to surveillance and surgical prophylaxis. While patients with hereditary colorectal cancer syndromes have the highest risk of developing colorectal cancer, majority of chemoprevention trials are focused on sporadic CRC.

Prostaglandin E2 (PGE2) is associated with a higher risk of colon cancer. Eicosapentaenoic Acid (EPA) is an omega-3 fatty acid linked to reduction of PGE2 in colon tissue. EPA at 2 gram daily for 6 months given to patients with Familial Adenomatous Polyposis (FAP) resulted in 22.4% reduction in adenoma number and 29.8% reduction in adenoma size. The efficacy of EPA as a chemopreventive agent in FAP has prompted the currently ongoing seAFOod Polyp Prevention Trial, a large placebo-controlled, randomized trial of EPA in patients with a history of colorectal adenoma within the English Bowel Cancer Screening Program.

Experimental studies have demonstrated that inflammation inactivates MMR function and increases mutation rates. PGE2 has been shown to silence DNA repair genes by enhancing DNA methylation to promote colonic tumor growth. A large retrospective analysis by Song et al showed that high marine ω -3 PUFA intake is associated with lower risk of MSI-high CRC, suggesting a potential role of ω -3 PUFAs in protection against CRC through DNA MMR. Based on these findings

and prior data showing a stronger inverse association of ω -3 PUFA with proximal colon cancer, we hypothesize that marine ω -3 PUFAs will more likely to inhibit inflammatory pathways associated with the development of tumors that arise from defective MMR.

To the best of our knowledge, there is no published prospective trials that looked into the potential chemopreventive role of ω -3 PUFA in lynch or MSI high colorectal cancer survivors. Finding an effective way to reduce the burden of CRC in this high risk population beyond screening colonoscopies and prophylactic surgery is an area of great unmet need.

Supported by published EPA chemo-preventive properties, we are proposing a prospective randomized placebo controlled pilot trial evaluating safety and feasibility of high dose fish oil in patients with lynch syndrome.

We will investigate whether 12 months of EPA 2G po daily would result in bio-molecular, metabolomics and intestinal microbiota changes consistent with chemopreventive efficacy. This will include biomarkers of carcinogenesis, proliferation, apoptosis, and angiogenesis in blood, stool, and colonic tissue in this patient population. This trial is supported by a Kansas University Cancer Center grant and is planned to open for enrollment around April 2018.

C59

RARE MYXOID LIPOSARCOMA WITH BRAIN METASTASIS

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Introduction Of the various soft tissue sarcoma (STS) subtypes, leiomyosarcoma, liposarcoma, and malignant fibrous histiocytoma are most likely to metastasize to the brain.¹ Only 1–3% of patients with STS have subsequent brain metastases (BM).² Liposarcoma is the second most common STS which comprises 10–20% of all soft tissue malignancies in adults.³ Based on literature review, the mean interval for detection of brain metastasis of STS is between 20–30 months, however, BM of liposarcoma has been detected up to 36-months after initial treatment with overall survival ranging from 7–16 months.⁴ This case reviews a 65-year-old male with liposarcoma in the left lower extremity, who presented six months later with BM to the left frontal lobe.

Patient presentation A 65-year-old male with past medical history of myxoid liposarcoma of left lower extremity status post-surgical resection and radiation therapy presented to our hospital for increasing numbness and weakness of bilateral lower extremities, urinary retention and saddle anesthesia six-months after initial diagnosis. Magnetic Resonance Imaging (MRI) revealed retroperitoneal metastasis along with multiple spinal lesions from the 8th–10th thoracic vertebrae and 1st–2nd lumbar vertebrae. Laminectomy with excisional biopsies were found to be metastatic myxoid liposarcoma. His spine was stabilized and he was discharged to rehabilitation with palliative chemotherapy. Three weeks later, he again presented to our hospital with new onset altered mental status. Brain MRI revealed a 3 × 3.5 centimeter heterogeneously enhancing hemorrhagic mass within the left frontal lobe causing an 11-millimeter left-to-right mid-line shift. Due to the location and rapid growth of metastatic lesion, surgical intervention was not a treatment option. Our patient declined palliative

radiation and returned home with hospice care where he soon passed away.

Discussion Myxoid Liposarcoma (MLS) is composed of uniform round shaped primitive non-lipogenic mesenchymal cells with small signet ring lipoblasts in a prominent myxoid stroma. MLS accounts for about 10% of all adult soft tissue sarcomas, comprising more than one-third of all liposarcomas. MLS occurs mostly in the deep soft tissues of the extremities as a large painless mass. The karyotypic hallmark of myxoid liposarcoma is (t12: 16) (q13: P11) which leads to the fusion of the DDIT3 and FUS genes at 12q13 and 16p11 and is present in 90% of cases.⁵

The origin of the liposarcoma helps to dictate the extent of the relapse.^{1,3} In STS of the extremity or trunk, the first sight of distant metastasis is usually the lung with rare local recurrence. In contrast, patients with retroperitoneal and visceral STS tend to have local recurrence of the tumor rather than metastasize to different sites.¹ MLS, specifically, metastasizes to the bone, like the spine, and other soft tissues.

Despite available treatment options, prognosis is grim. The extent of the systemic disease along with the Karnofsky Performance Scale (KPS) are important prognostic variables in patient outcomes.³ Current literature offers very few survival markers. In one cohort study of 40 patients presenting with STS BM, the overall 1-year and 2-year disease specific survival was 55% and 25%, respectively, with a median survival of 15-months. The 1-year and 2-year post-metastasis survival was 34% and 20%, respectively, with a median survival of 7-months.¹

Treatment for BM consist of resection of the tumor, whole brain radiation therapy, or stereotactic radiosurgery (SRS). The standard treatment consists of early surgical intervention of isolated intracranial metastases to prolong disease free and overall survival.⁸ In recent years, more patients have been treated with SRS, which is delivered as a single dose of radiation. SRS is only considered for tumors less than 3-cm in diameter, without mass effect,⁷ and does not provide increased survival.⁸

Conclusion We present a case of a rapidly progressive MLS which progressed to BM and death after approximately 6 months. We recommend that patients with MLS receive early and regular brain MRI to diagnose early brain metastasis.

C62

CHRONIC MYELOID LEUKEMIA WITH EOSINOPHILIA LEADING TO STROKE, NSTEMI AND PNEUMONIA

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Introduction Chronic myeloid leukemia (CML) with eosinophilic differentiation is not just an uncommon disease but even a rare cause of hyper-eosinophilia syndrome. It can have multifarious presentation ranging from asymptomatic eosinophilia to multiple end organ damage. We report a case of newly diagnosed CML with significant hypereosinophilia which evoked not just hyper-viscosity syndrome but leukostasis lead to ischemic stroke, myocarditis and eosinophilic pneumonitis.

Case report A 57 year old male with history of newly diagnosed chronic myeloproliferative disorder with eosinophilia, gout, mitral valve leaflet perforation, severe mitral

regurgitation presented to emergency with one day history of right sided hemiplegia, expressive aphasia and gait instability. On arrival patient was disoriented, lethargic, afebrile and tachypnea. Laboratory results were concerning with leukocytosis – white blood cells 658 k/dl with eosinophilia 400 k/dl cells. Troponin-I levels were elevated but without dynamic electrocardiographic changes, later coronary angiography showed non-obstructive coronary arteries as well. MRI brain did show multiple acute infarcts in left cerebral hemisphere. Patient underwent leukapheresis and later on started on high dose corticosteroids and hydroxyurea as a treatment of eosinophilic CML. Late on, there was concern of health care acquired pneumonia as well since patient spiked fever during his clinical course. Bronchoscopy with lavage was consistent with eosinophilic pneumonitis. As the counts returned within normal limits and results of his bone marrow biopsy and flow cytometry were back, which confirmed the diagnosis of CML, he was started on imatinib.

Discussion Hypereosinophilia syndrome secondary to myeloproliferative disorder requires prompt diagnosis, especially when it presents with end organ damage especially to vital organs such as brain and heart. Early institution of steroid therapy has both morbidity and mortality benefit.

Infectious Disease

B09

BLOOD GROUP A PREDICTS ENTEROTOXIGENIC *ESCHERICHIA COLI* SEVERITY

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Objectives Enterotoxigenic *Escherichia coli* (ETEC) are a predominant diarrheagenic *E. coli* pathovar responsible a substantial burden of acute diarrheal illness, deaths, and post-diarrheal sequelae including malnutrition, growth delays, and impaired cognitive development. Clinically, ETEC diarrheal illness ranges from mild to severe cholera-like disease. ETEC express heat-stable toxin (ST) or heat-labile toxin (LT), or both. LT is an AB₅ toxin closely related to cholera toxin. While epidemiological surveys have highlighted an association between individuals with blood group O and severe cholera, there is no apparent increase in ETEC disease severity linked to blood group O. Interestingly, our recent studies of ETEC pathogenesis led to the finding that a secreted adhesin specific to ETEC, EtpA, binds preferentially to blood group A (BgA) glycans. These interactions govern the effective delivery of both LT and ST to target epithelial receptors thereby contributing to disease severity. The study goal is to advance our understanding of the relationship between EtpA, disease severity, and blood type.

Methods A variety of molecular methods were using to confirm an interaction between EtpA and BgA sugars. We screened against an array of more than 400 glycans, and confirmed the interactions with biolayer interferometry and hemagglutination. Next we generated a CRISPR-derived mutant of BgA expressing HT-29 carcinoma cells to produce only blood group O sugars which were again used to confirm the BgA-EtpA interaction. To advance our findings, were propagated intestinal stem cell derived enteroids as polarized

monolayers from individuals with Blood Group A, B, or O. Finally, we obtained a convenience sample of 106 volunteers in controlled human infection model (CHIM) studies of ETEC diarrhea who served as vaccine placebo controls in prior studies. Blood type was determined in a blinded fashion and a meta-analysis was performed to determine the association between blood type and diarrheal severity.

Results Our glycan array containing more than 400 human glycans demonstrated that EtpA binds specifically to BgA sugars which were confirmed using biolayer interferometry whereby EtpA bound to BgA but not group B or O sugars. Only BgA red blood cells agglutinated in the presence of EtpA. Using the CRISPR-derived mutant of HT29 cells, EtpA binding was disrupted in the mutant line (blood group O) as was adhesion of the EtpA-expressing H10407 ETEC strain. Moreover these *in vitro* studies demonstrated that both EtpA and blood group A expression were essential for effective delivery of both toxins. We next confirmed these findings in polarized enteroid monolayers derived from human intestinal stem cells. Using enteroid lines from individuals with blood groups A, B, or O we demonstrated preferential binding of EtpA, as well as enhanced EtpA dependent bacterial adhesion and toxin delivery to blood group A cells. These findings prompted an examination of the relationship of blood group and disease severity using samples obtained from four prior ETEC CHIM studies in which 106 volunteers were challenged with the EtpA-expressing H10407 strain. A meta-analysis demonstrated that blood group A or AB volunteers were more likely to develop moderate or severe diarrhea (MSD) relative to blood group O and B volunteers (odds ratio=1.44, 95% CI: 1.10 to 1.90). Overall, 81% (95% CI: 66 to 97%, N=24) of BgA patients developed MSD while for group O, 56% (44–69%, n=64) and B, 53% (25–82%, n=15) developed MSD. Age and race were not associated with MSD.

Conclusions Collectively our results provide additional insight into the molecular pathogenesis of these common pathogens. EtpA appears to be the sole BgA binding lectin expressed by ETEC and is likely to be responsible for the increased disease severity in BgA volunteers. These findings have significant implications for design and interpretation of future ETEC CHIM studies and can inform the rational design of vaccines to protect individuals at risk for the most severe cholera-like presentation of these infections.

B19

PRIMARY HUMAN TYPE I ALVEOLAR EPITHELIAL CELLS PRODUCE BIOLOGICALLY-ACTIVE NEUTROPHIL AND MONOCYTE CHEMOKINES IN RESPONSE TO *BACILLUS ANTHRACIS* SPORE EXPOSURE

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Objective The lung is the entry site for *Bacillus anthracis* in inhalation anthrax, the deadliest form of the disease. Spores escape through the alveolar epithelial cell (AEC) barrier and migrate to regional lymph nodes, germinate and disseminate to cause disease. Although several proposed mechanisms involve a carrier cell in alveolar escape, all require that the AEC barrier is overcome.

Method We incorporated our primary human type I AEC model, microarrays, qRT-PCR, multiplex ELISA, and neutrophil and monocyte chemotaxis assays to study the response of AEC I to 1 MOI of *B. anthracis*, (Sterne) spores.

Results Spore exposure altered gene expression in AEC after 4 and 24 hours and differentially expressed genes (± 1.3 fold, $p \leq 0.05$) included CCL4/MIP-1 β (4 hours), CXCL8/IL-8 (4 and 24 hours) and CXCL5/ENA-78 (24 hours). Gene enrichment analysis revealed that pathways involving cytokine or chemokine activity, receptor binding, and innate immune responses to infection were prominent. qRT-PCR and multiplex ELISA assays confirmed that the AEC I response to spores included induction of neutrophil and monocyte chemokines. Specifically, at 24 hours of spore exposure, there was significant induction of the neutrophil chemokines CXCL8/IL-8 (35 fold, $P < 0.0001$) and CXCL5/ENA-78 (9.5 fold, $P < 0.01$). There was also induction of the neutrophil chemokines CXCL3/GRO β (2 Fold) and CCL20/MIP-3 α (12 fold) though induction did not reach statistical significance. The monocyte chemokines CXCL10/IP-10, CCL3/MIP-1 α , and CCL4/MIP-1 β were only produced by spore-exposed cells but induction did not reach statistical significance. Chemotaxis assays demonstrated spore induction of biologically active neutrophil and monocyte chemotactic activity. CXCL8/IL-8 was the major neutrophil chemokine induced, and CXCL5/ENA-78 also directly contributed to the neutrophil chemotactic activity present. As naïve media spiked with equivalent amounts of CXCL3/GRO β and CCL20/MIP-3 α did not induce neutrophil chemotaxis, but addition of corresponding blocking antibodies to spore-exposed supernatants inhibited chemotaxis, these chemokines may contribute to neutrophil chemotaxis by priming. None of the monocyte chemokines directly induced chemotaxis at the levels present in spore-exposed AEC I supernatants.

Conclusion These data provide the first whole transcriptomic description of the human AEC I initial response to *B. anthracis* spores. A major part of that response is induction of neutrophil and monocyte chemotactic activity release from AEC I. This role of this response in the pathogenesis of inhalational anthrax is likely to attract inflammatory cells that either aid in destruction of *B. anthracis*, or that may facilitate escape of the pathogen from the alveolar space.

B20 ABSTRACT WITHDRAWN

B21 UPREGULATION OF INTERFERON-REGULATED SIGNATURES IS ASSOCIATED WITH ERYTHROPOIETIC SUPPRESSION IN UGANDAN CHILDREN WITH CEREBRAL MALARIA AS COMPARED TO SEVERE MALARIAL ANEMIA

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Objective Among the severe malaria syndromes, severe malarial anemia (SMA) is the most common, whereas cerebral malaria (CM) is the most lethal. However, the mechanisms that differentiate these syndromes are unclear. We combined whole-blood transcriptomics with analysis of hematological indices and plasma cytokine profiles to gain a better understanding of the molecular and cellular mechanisms that differentiate CM and SMA.

Method We performed genome-wide transcription profiling by Illumina BeadChip microarray using peripheral whole blood obtained from Ugandan children with acute CM (n=17) or SMA (n=17) on hospital admission and healthy community children without *P. falciparum* infection (controls, n=12). We determined differential expression of genes and functional transcription modules between groups using linear models. Plasma erythropoietin levels were tested by high-sensitivity radioimmunoassay. We measured plasma cytokines by Bio-Plex multiplex immunoassays. Multiple linear regression models were used to determine the relationships between the expression of specific transcription modules, clinical indices, and plasma cytokines.

Results Principal components analysis and unsupervised hierarchical clustering analysis of whole-blood expression data revealed clustering by disease state with sub-clustering of SMA children with sickle-cell disease (SMA HbSS, n=6). Thus, all subsequent analyses included adjustment for the HbSS genotype. Modest increases in the expression of neurological-related gene modules were observed in children with CM when compared with controls or with SMA. Compared to controls, TLR and inflammatory signaling, neutrophil, and monocyte modules were differentially upregulated in both CM and SMA. Differential expression of Th1 CD4 T cell modules were observed in CM, but not in SMA, relative to controls. Unexpectedly, erythrocyte differentiation and heme biosynthesis modules were markedly decreased in CM relative to SMA despite significantly higher hemoglobin levels in CM and appropriate increases in plasma erythropoietin in response to anemia. Consistent with this finding, both red blood cell distribution width and expression of reticulocyte-specific genes were significantly lower in CM than SMA even after controlling for erythropoietin levels. In univariate analyses, transcription modules related to viral sensing and immunity/interferon regulatory factor 2 (IRF2) targets network (M111.0 and M111.1), T-cell activation, and cytokine/chemokine receptor signaling were found to negatively predict reticulocyte signatures. Multiplex analysis of plasma cytokines and chemokines revealed interferon gamma-induced protein 10 (IP-10 or CXCL10) to correlate positively with M111.0 and negatively with reticulocyte signatures. M111.0 module expression remained a significant negative predictor of reticulocyte-specific gene expression after adjusting for hemoglobin, parasite density, IP-10 levels, and malaria syndrome. Notably, both expression of M111.0 and IP-10 levels were significantly increased in CM relative to SMA irrespective of HbSS status, suggesting a potential pathway relevant to erythropoietic suppression and/or syndrome-specific pathogenesis during CM.

Conclusion During severe malaria syndromes, upregulation of interferon-regulated pathways is associated with increased IP-10 levels and T-cell activation signatures, which may contribute to ineffective erythropoiesis and/or CM-specific pathogenesis. Further studies are needed to confirm these findings and examine the role of components within this pathway during CM.

B22

LIPOXINS AND THEIR ROLE IN KAPOSI'S SARCOMA-ASSOCIATED HERPESVIRUS (KSHV) INFECTION AND PATHOGENESIS

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Objective Lipoxins are host anti-inflammatory molecules, which play a vital role in restoring tissue homeostasis. The efficacy of lipoxins, their analog epilipoxins, and aspirin triggered analogs in treating inflammation and related diseases have 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.

Method Most of the experiments were performed in human microvascular dermal endothelial cells (HMVEC-d) and PEL cells (KSHV positive [KSHV⁺]/EBV negative [EBV⁻]; BCBL-1, BC-3 cells). Various tissue sections from diverse populations, including both healthy subjects and subjects with Kaposi's sarcoma, were obtained from the AIDS and Cancer Specimen Resource (ACSR, San Francisco, CA), and used for lipoxin receptor ALX staining by immunohistochemistry. Lipoxin [5(S), 6(R), 15(R)-trihydroxy-7E, 9E, 11Z, 13E- eicosatetraenoic acid], Lipoxin A4 methyl ester [5(S), 6(R), 15(R)-TriHETE methyl ester] were purchased from Cayman Chemical (Ann Arbor, MI), and ethanol was used as solvent control for all experiments involving treatments with inhibitors. Lipoxin A4 in the conditioned medium was determined by ELISA. Taq-Man gene expression analysis was done for host 15- lipoxygenase and 12- lipoxygenase genes. Activation of cellular signal transduction molecules was determined by checking their total and phosphorylated forms by Western blotting. CRISPR/CAS9 technology mediated ALX/FPR gene editing was done to study the role of lipoxin receptor.

Results Our study demonstrates how KSHV manipulates and downregulates the secretion of the anti-inflammatory lipoxin A4 in host cells and the viral factors involved in this process using *in vitro* KS and PEL cells as models. Presence of lipoxin receptor [ALX/Formyl peptidyl receptor (FPR)] in human KS patient tissue sections and *in vitro* KS and PEL cell models offers a novel possibility for treating KS and PEL with lipoxins. Treating *de novo* KSHV infected endothelial cells with lipoxin and epilipoxin creates an anti-inflammatory environment by decreasing levels of NFκB, AKT, ERK1/2, COX-2, and 5-lipoxygenase. Lipoxin treatment on CRISPR/CAS9 technology mediated ALX/FPR gene deleted Human Osteosarcoma cells (U2OS) cells revealed the importance of the lipoxin receptor ALX for effective lipoxin signaling. A viral miRNA cluster was identified as the primary factor contributing to the down regulation of lipoxin A4 secretion in host cells. The KSHV miRNA cluster probably targets enzyme 15-lipoxygenase, which is involved in lipoxin A4 synthesis.

Conclusion Lipoxin treatment in KSHV infected cells have shown to reduce cell proliferation and cell survival. Latency factor LANA-1 levels were found to decrease on lipoxin and epilipoxin treatment. Several Pro-apoptotic gene levels were up regulated on lipoxin treatment. Several host transcription factors were found to play an important role in regulating KSHV life cycle. This study provides a new insight into the treatment of KS and PEL using nature's own anti-inflammatory molecule, lipoxin.

C06

RISK FACTORS FOR CLOSTRIDIUM DIFFICILE INFECTION AMONG PEDIATRIC INPATIENTS: A META-ANALYSIS

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Objective *Clostridium difficile* infection (CDI) is one of the most frequent causes of healthcare associated infections in both adult and pediatric patients. Studies in adult populations have identified several important risk factors, but it remains unclear whether these risk factors apply to the pediatric populations. The objective of this study was to determine the risk factors for CDI in hospitalized pediatric patients in order to inform strategies for recognition and prevention.

Method MEDLINE and three other databases were systematically searched for subject headings and text words related to CDI and pediatrics from 1975 to 2017. All studies evaluating risk factors for primary CDI in pediatric inpatients in multivariate and univariate analyses were eligible. Data from included studies were combined using a random effects model and summary odds ratio (OR) estimates with 95% confidence interval (CIs) were calculated. The Newcastle-Ottawa scale was used to assess the methodologic quality of included studies. Any risk factors that were reported by at least 3 studies were then meta-analyzed to evaluate the association by calculating the summary estimate.

Results Of the 2032 studies identified in the search, 12 studies, together reporting 10,531,861 children met our inclusion criteria. Among these, 22,353 patients developed CDI. Antibiotic exposure increased the risk for CDI (OR, 2.09, 95% CI: 1.28 to 3.43). There was significant heterogeneity among the studies, with an *I*² value of 63%. Also, there were insufficient studies to determine the association between most antibiotic classes and the risk of CDI. We noted no effect of carbapenem antibiotics (OR, 1.68, 95% CI: 0.5 to 5.6) or acid suppressive therapy (OR, 1.13, 95% CI: 0.81 to 1.57) on CDI risk.

Conclusion Antibiotic exposure continues to be the important risk factor for CDI in pediatric inpatients. However the risk was not greater with carbapenem antibiotics. Gastric acid suppression was not significantly associated with an increased risk for CDI. Judicious use of antibiotics may help reduce the burden and incidence of CDI in this population.

C37

THE TRANSCRIPTION FACTOR IRF-7 DIRECTLY REGULATES THE FIRST PHASE OF INTERFERON INDUCTION TO MODULATE RIG-I EXPRESSION DURING INFLUENZA A INFECTION OF HUMAN AIRWAY EPITHELIA

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Objective Influenza A (IAV) infection is a major cause of morbidity and mortality. In 2009, a pandemic caused by the novel H1N1 IAV infected over 300,000 individuals with at least 16,000 confirmed deaths worldwide. To combat a viral infection, the host's immune system must recognize the invader's foreign material, and develop an effective antiviral response. Retinoic acid-inducible protein I (RIG-I) plays an important role in the recognition of IAV in most cell types, and leads to

induction of interferon (IFN), a critical component of the response to influenza infection. In turn, type I IFN induction by RIG-I depends on the transcription factor interferon regulatory factor (IRF-7). There is also positive feedback by IFN on RIG-I mediated IFN induction, though this process is poorly understood.

Method We investigated RIG-I and IFN induction by IAV in Bci-NS1, an immortalized human airway basal cell line. Bci-NS1 cells were infected with A/Puerto Rico/8/1934 (PR8) H1N1 IAV at an MOI =1. Virus diluents (mock) were used as negative controls. After 24 h of infection, cells and supernatants were collected for qRT-PCR and western blot to determine RIG-I and IFN mRNA and protein expression levels. Next, we used siRNA against IRF-7 to specifically block IRF-7 expression in these cells in order to determine the role of IRF-7 in the induction of IFN.

Results As expected, we found that the basal expression level of RIG-I was very low in Bci-NS1 cells, and that IAV infection induced robust RIG-I and IFN expression. siRNA against IRF-7 inhibited RIG-I mRNA expression and IFN induction by IAV infection. Most importantly, even without virus infection, IFN-beta alone induced RIG-I, and siRNA against IRF-7 failed to inhibit RIG-I mRNA induction by IFN-beta.

Conclusion Our results suggest that RIG-I expression is highly inducible and greatly amplified by the first phase of IFN production, and that IRF-7 controls RIG-I expression by directly regulating the first phase of IFN induction during influenza infection in human lung airway epithelial cells. IRF-7 is not, however, involved in the portion of the IFN feedback loop whereby IFN stimulates RIG-I. This discovery will be important in designing strategies for the development of novel treatments for influenza infections.

C38 ABSTRACT WITHDRAWN

C52 'I CANNOT WALK BECAUSE OF THE FLU': A CASE OF CEREBELLITIS POST VIRAL UPPER RESPIRATORY TRACT INFECTION

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Introduction Cerebellitis also known as acute cerebellar ataxia, is an inflammatory process that involves cerebellar dysfunction, caused by infectious, post infectious, or post vaccination disorders. Among the infectious causes, viruses have been the most common reported cause, with Epstein Bar virus (EBV) and Varicella Zoster Virus (VZV) being most common. Parainfluenza type 4 is a rare cause of post viral cerebellitis after a respiratory infection.

Case We present the case of a 40-years-old woman from Cameroon with past medical history of Type I Diabetes Mellitus and HIV. Patient presented with complaints of nausea, weakness, anorexia, and moderate dizziness noted only with sudden head movement and standing. She also reported difficulty walking for 3 weeks and a flu-like illness with lethargy for the past three weeks. She came to the ED after an episode of dizziness resulting in a fall. On physical exam, pertinent findings included intact finger to nose exam and

alternating hand movements. However, patient had ataxia, an abnormal Romberg's test, and a positive heel-to-shin test. Initial laboratory workup was within normal limits except for a low sodium of 132. Absolute CD4 count was 154 on admission. LP was suspicious for viral etiology with CSF analysis showing elevated WBC with lymphocytic predominance, elevated protein, and normal glucose. Respiratory viral PCR 20 (via a nasopharyngeal swab) was positive for parainfluenza type 4 and CSF PCR was negative for HSV1/2, VZV, CMV, JC virus, VDRL, and Toxoplasmosis. MRI brain showed bilateral cerebellar enhancement concerning for cerebellitis. Differential diagnosis included possible infectious cause or Immune Reconstitution Inflammatory Syndrome (IRIS) (figures 1 and

Abstract C52 Figure 1

Abstract C52 Figure 2

2). She was diagnosed with acute cerebellar dysfunction consistent with post-infectious cerebellitis secondary to parainfluenza 4 infection. Her symptoms improved with supportive management and she was discharged home on anti-retroviral therapy and Acyclovir, as well as prophylaxis for HSV/VZV.

Discussion Cerebellitis is an uncommon disease in the general population. All though common viral infections can result in cerebellitis as part of the post-infectious sequelae, Parainfluenza 4 virus is a rare cause of post-viral cerebellitis and needs to be considered in patients presenting with signs and symptoms of cerebellar disease with acute onset.

C53

A CASE OF SEVERE MALARIA

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Introduction Malaria is a mosquito-borne parasitic infection caused by *Plasmodium* protozoans. Typically endemic to sub-Saharan Africa, Southeast Asia and parts of South America, malaria infections may be complicated by both severity and level of resistance of the particular species as well as potential side effects of therapy. Severe malaria is determined by a set of criteria developed by the World Health Organization¹ and is associated with increased overall mortality.² Here we describe a case of severe malaria originating from an area of high resistance.

Case presentation A 56-year-old male patient who returned from Liberia 18 days prior to admission presented to our hospital with cyclic fevers, headache, vomiting, and diarrhea. He endorsed non-compliance with prophylactic Doxycycline due to side effects experienced during previous trips to the country. Peripheral blood smear showed *P. falciparum* malaria with associated parasitemia load of 18.4% (figure 1). Laboratory work up revealed hyperbilirubinemia of 5.5 mg/mL thus meeting criteria for severe malaria (table 1). Our patient was admitted to the medical intensive care unit for treatment with intravenous (IV) Quinidine and oral Clindamycin. On electrocardiogram, his baseline QTc-interval was 422 milliseconds prior to treatment with maximum QTc-interval of 530 milliseconds during treatment. Malarial smear on day 2 of treatment showed a parasitemia load of 0.07% and the patient was transitioned to oral Quinine and Clindamycin. He completed one week of anti-malarial treatment and made a full recovery.

Discussion Severe malaria generally occurs in children in endemic areas as adolescents and adults develop immunity after repeated exposures. However, non-immunized adults who visit endemic areas are at high risk. Age is both a risk and prognostic factor in non-immunized adults. There is a significantly increased probability of developing severe malaria and thus higher mortality in patients greater than 40 years of age.³ IV therapy with Artemisinin derivatives or Cinchona alkaloids is recommended for severe malaria as they are more effective at preventing mortality. When compared to IV Quinidine, IV Artesunate has been shown to significantly reduce mortality by 34.7%,⁴ however, IV Artesunate is not currently available in the United States as it has not been approved by the CDC. Quinidine, a class Ia antiarrhythmic agent, is a derivative of Quinine with anti-malarial activity. Quinidine blocks potassium channels and functions as an insulin

secretagogue, which can cause life threatening QTc prolongation and severe hypoglycemia. Close cardiac monitoring is required to prevent potentially fatal ventricular arrhythmias and hypoglycemia.

Conclusion Severe malaria is associated with a high risk of mortality. Early recognition and treatment is critical both for appropriate therapeutic intervention as well as preventing end-organ damage. Currently, readily available therapy in the United States is intravenous Quinidine in conjunction with either Doxycycline, Tetracycline, or Clindamycin. Routine electrocardiograms with daily blood glucose monitoring is paramount to monitor for QTc prolongation and hypoglycemia.

Abstract C53 Table 1 WHO criteria for severe malaria⁵

For epidemiological and research purposes, severe malaria is defined as one or more of the following, occurring in the absence of an identified alternative cause, and in the presence of *P. falciparum* asexual parasitaemia:

Impaired consciousness:	A Glasgow Coma Score <11 in adults or a Blantyre coma score <3 in children
Acidosis:	A base deficit of >8 meq/l or, if unavailable, a plasma bicarbonate of <15 mmol or venous plasma lactate >5 mmol. Severe acidosis manifests clinically as respiratory distress - rapid, deep and laboured breathing
Hypoglycaemia:	Blood or plasma glucose <2.2 mmol (<40 mg/dl)
Severe malarial anaemia:	A haemoglobin concentration <5 g/dl or a haematocrit of <15% in children <12 years of age (<7 g/dl and <20%, respectively, in adults) together with a parasite count >10 000/µl
Renal impairment (acute kidney injury):	Plasma or serum creatinine >265 µmol (3 mg/dl) or blood urea >20 mmol
Jaundice:	Plasma or serum bilirubin >50 µmol (3 mg/dl) together with a parasite count >100 000/µl
Pulmonary oedema:	Radiologically confirmed, or oxygen saturation <92% on room air with a respiratory rate >30/min, often with chest indrawing and crepitations on auscultation
Significant bleeding:	Including recurrent or prolonged bleeding from nose gums or venepuncture sites; haematemesis or melena
Shock:	Compensated shock is defined as capillary refill ≥3 s or temperature gradient on leg (mid to proximal limb), but no hypotension. Decompensated shock is defined as systolic blood pressure <70 mm Hg in children or <80 mm Hg in adults with evidence of impaired perfusion (cool peripheries or prolonged capillary refill)
Hyperparasitaemia:	<i>P. falciparum</i> parasitaemia >10%

Abstract C53 Figure 1 Peripheral blood smear with multiply infected RBC's with *plasmodium falciparum*

C60

STENOTROPHOMONAS MALTOPHILIA INFECTION
MASQUERADING AS SEEMINGLY BENIGN NASAL ULCER

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Objective *Stenotrophomonas maltophilia* (*S. maltophilia*) is one of the opportunistic, multidrug-resistant gram-negative bacteria. Common presentations include bacteremia, pneumonia, endocarditis and meningitis with rare skin involvement. Important risk factors include health care settings, immunocompromised status, and presence of infected indwelling intravascular devices. We present a case of *S. maltophilia* infection in a neutropenic patient.

Methods N/A

Results A 52-year-old man with newly diagnosed acute myeloid leukemia (AML) was admitted to the hospital for induction chemotherapy. He developed pancytopenia after the treatment. The absolute neutrophil count (ANC) dropped

below 500 and he remained neutropenic for several weeks. He was placed on appropriate antimicrobial prophylaxis. He developed intermittent febrile episodes. Therefore, pan-cultures were obtained and anti-microbial coverage was broadened. Multiple sets of cultures and rest of the infectious workup remained unrevealing. Meanwhile, a small superficial ulcer was noted on the left nasal wall that had failed to heal with topical bacitracin and neomycin. Punch biopsy of the nasal lesion was performed in the setting of non-resolving fevers. The tissue culture came back positive for *S. maltophilia* with concomitant positive blood cultures as well. He was started on Trimethoprim-Sulfamethoxazole. Repeat blood cultures were negative. The fevers resolved and he was discharged home. The nasal ulcer had almost resolved upon discharge. He also underwent clinical remission of AML based on repeat bone marrow biopsy results.

Conclusion *S. maltophilia* infections are rare but prevalence has increased over last few decades. It causes significant mortality and morbidity, particularly in immunocompromised hosts. Evidence from retrospective studies prompts a clinician to consider *S. maltophilia* infection in the differential diagnosis in severely neutropenic, febrile cancer patients. *S. maltophilia* rarely infects intact skin but a high index of suspicion in the relevant patient population with appropriate diagnostic approach can facilitate timely management. It is important to know that these bacteria are resistant to Carbapenems. Trimethoprim-Sulfamethoxazole is the drug of choice.

Nephrology

B07

RADIATION IMPAIRS AFFERENT ARTERIOLAR ENDOTHELIAL FUNCTIONS IN MALE AND FEMALE RATS

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Chronic kidney disease occurs in 15% of hematopoietic stem cell transplant patients, and also in patients who receive radio-nuclide therapy for cancer. There is a 6–8 week latent period after irradiation that leads to the development of proteinuria, azotemia, and hypertension in rats. The current study tested the hypothesis that impaired endothelial-signaling contributes to reduced afferent arteriolar acetylcholine responses in male and female rats exposed to total body irradiation (TBI). Male and female WAG/RijCmc rats were subjected to TBI (6 Gy) and afferent arteriolar responses to acetylcholine using the juxtamedullary nephron technique were determined at 6 weeks post irradiation. Renal functional parameters (blood urea nitrogen and urinary protein excretion) were similar between control and TBI groups in both male and female rats. Afferent arteriolar diameters averaged 23.2 ± 0.9 and 21.7 ± 1.5 μ m in male and female control groups (n=11/group), respectively. In TBI groups, the afferent arteriolar diameters averaged 23.1 ± 1.4 and 22.0 ± 1.0 μ m in male and female groups (n=5–6/group), respectively. In male rats the afferent arteriolar response to acetylcholine (0.01, 0.1, 1, and 10 μ mol/L) was impaired in TBI compared to non-irradiated control rats. Afferent arteriolar responses to 10 μ mol/L acetylcholine were

reduced by 50% in the male TBI rats compared to controls ($P < 0.05$, n=5–6). Similar to the male rats, the TBI female rats demonstrated impaired afferent arteriolar response to acetylcholine compared to controls ($P < 0.05$, n=5–6). TBI male rats demonstrated lower CYP2C11 and higher CYP4A1 renal microvascular protein expression compared to controls ($P < 0.05$). In male rats, the renal microvascular expression of CYP2C23, COX1, COX2 and eNOS were similar between TBI and control groups. In female rats, the CYP2C11 expression in renal microvessel was lower in TBI group ($P < 0.05$) and CYP2C23 expression was not different between groups. Unlike male rats, the female TBI group demonstrated lower eNOS ($P < 0.05$) and higher COX enzymes ($P < 0.05$), and unchanged CYP4A1 expression in the renal microvessels compared to non-irradiated controls. Overall, we demonstrate that radiation impaired afferent arteriolar endothelial-dependent acetylcholine responses in male and female rats. We further demonstrate that the contribution of endothelial signaling pathways to the impaired afferent arteriolar response to acetylcholine caused by radiation is different between male and female rats.

B10

OBESITY AND HYPERTENSION MODULATE MITOCHONDRIAL DYNAMICS, CONTRIBUTING TO RENAL INJURY IN SWINE

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Objective The kidney possesses high numbers of mitochondria, which constantly undergo fusion and fission. Under physiological conditions, the rate of fusion and fission in the kidney is finely tuned to maintain mitochondrial homeostasis, but whether cardiovascular risk factors alter this balance remains unknown. We hypothesized that coexisting obesity and hypertension interfere with renal mitochondrial dynamics, contributing to mitochondrial damage and consequent renal injury in swine.

Method Twenty-eight domestic pigs were studied after 16 weeks of a high-cholesterol/carbohydrate diet or standard chow with or without hypertension (HTN) induced by renal artery stenosis (n=7 each). Renal expression of the mitochondrial fusion marker mitofusin (MFN)-2 and the fission marker phosphorylated dynamin-related protein (pDRP)-1 was measured by Western blot. Mitochondrial ATP generation was measured by colorimetric methods and renal fibrosis by trichrome staining.

Results Blood pressure was similarly higher in Obese, HTN, and Obese+HTN compared to Lean (table). Both HTN and Obese+HTN pigs achieved similar hemodynamically significant stenoses. Renal expression of MFN-2 was higher in Obese compared to Lean, but lower in HTN, whereas expression of pDRP-1 decreased only in Obese+HTN pigs (figure 1). ATP/ADP ratio similarly decreased in Obese and HTN compared to Lean, and further decreased in Obese+HTN, whereas renal fibrosis that increased in HTN, further increased in Obese+HTN. Furthermore, changes in DRP-1 expression, ATP/ADP ratio, and renal fibrosis were attributed to the effects of Obesity, HTN, and their interaction ($p=0.02$, $p=0.03$, and $p<0.001$, respectively; 2-way ANOVA).

Abstract B10 Figure 1 A: body weight, degree of stenosis, and Mean Arterial Pressure (MAP) of study group. B: renal protein expression of MFN-2 and DRP1. C: Mitochondrial ATP production. D: renal fibrosis assessed by trichrome staining. MAP, mean arterial pressure. * $p < 0.05$ vs lean, † $p < 0.05$ vs obese, ‡ $p < 0.05$ vs HTN

Conclusion Obesity, HTN, and their coexistence modulate renal mitochondrial fusion and fission, associated with impaired mitochondrial energy production and renal fibrosis. Obesity and HTN-induced changes in renal mitochondrial dynamics may constitute important mechanisms and potential therapeutic targets to ameliorate renal structural damage.

A12 POLYCYSTIC KIDNEY DISEASE (PKD) IS ASSOCIATED WITH INCREASED NOX4 ACTIVITY AND FUMARATE LEVELS

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Objective Autosomal Dominant Polycystic Kidney Disease (PKD) is the most frequent hereditary renal disease and the fourth leading cause of end-stage renal disease. However, the exact mechanisms of cystogenesis and disease progression remain to be elucidated. Deficiency in fumarate hydratase (FH) is known to be accompanied by increased levels of fumarate and is associated with the development of kidney

cysts, hereditary leiomyomatosis and renal cell cancer. Previous studies in diabetic nephropathy (DN) have shown that NADPH oxidase (NOX)-4 (Nox4) can inhibit FH leading to accumulation of fumarate. No studies to date have explored the role of Nox4 in PKD.

Method ^1H -NMR-based metabolomic analysis of cell extracts (3 PKD lines), urine, plasma and kidney of PCK (n=32) and wildtype (WT; n=24) rats, and human samples (ADPKD n=10; ctrl n=10) was performed on a Bruker 600 MHz spectrometer and the results were confirmed by MS. Abdominal MR imaging was performed on an Avance DRX 700WB at days 10, 21 and 35 ± 1 in PCK and WT rats, and total kidney volumes (TKVs) were measured using Analyze software. Immunoreactivity and protein expression of FH and Nox4 were assessed by staining and western blotting, and FH activity by a colorimetric method (biovision). Mitochondrial structure was assessed by electron microscopy in proximal tubules (PT), medullary thick ascending limbs (mTAL), distal tubules (DT), and collecting ducts (CD) of PCK and WT rats.

Results Metabolomic analysis revealed that fumarate was consistently increased in PKD-deficient cells, PCK rats and human samples (figure 1 A-D). Mitochondrial FH activity was consistently and significantly lower in PCK compared to WT rats

(figure 2A), although protein expression and immunoreactivity did not differ (figure 2B, C). FH activity highly correlated with tissue fumarate levels in PCK and WT rats (figure 2D). Consistent with previous work in DN, decreased FH activity was associated with significantly increased protein expression and immunoreactivity of Nox4 in kidneys from PCK compared to WT rats (figure 3). Furthermore, these findings were associated with disruption of mitochondria cristae, swelling, and decreased matrix density exclusively in tubular cells from CD lining microcysts in PCK rats (figure 4). Mitochondrial area and matrix density were preserved in PT, mTAL, and DT of PCK rats (not shown).

Conclusion Comprehensive multilevel metabolomic analysis identified fumarate as a potential mediator of cystogenesis in PKD. Accumulation of fumarate in PKD may be due to FH inhibition through upregulation of Nox4. Mechanistic and longitudinal studies are ongoing to investigate the role of Nox4, FH and fumarate in PKD.

Abstract A12 Figure 1 (A) miMCD cell extracts; (B) HRC TE cell extracts; (C) rat urine; (D) patient urine

Abstract A12 Figure 2

Abstract A12 Figure 3

Abstract A12 Figure 4

A23

EFFECTS OF IRON SUCROSE ON FGF23 LEVELS IN IRON-DEFICIENT PATIENTS WITH CHRONIC KIDNEY DISEASE

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Objective Elevated levels of fibroblast growth factor 23 (FGF23), an osteocyte-derived phosphate-regulating hormone, are associated with increased risks of adverse clinical outcomes. Fgf23 transcription and FGF23 cleavage determine circulating FGF23 levels. Iron deficiency is a recently identified stimulus of Fgf23 transcription. In health, iron deficiency induced increased Fgf23 transcription is accompanied by parallel increases in FGF23 cleavage. This results in normal levels of the bioactive intact FGF23 (iFGF23) and increased total FGF23 (tFGF23) levels that measure both the intact hormone and C-terminal fragments. Because FGF23 cleavage is impaired in chronic kidney disease (CKD), unlike in health where only tFGF23 is increased, iron deficiency will increase both tFGF23 and iFGF23 levels. Effects of intravenous iron therapy on tFGF23 and iFGF23 levels in iron-deficient CKD patients are not well-known. We investigated the effects of intravenous iron repletion with iron sucrose on both tFGF23 and iFGF23 levels in iron-deficient patients with CKD.

Methods We recruited 22 individuals with iron deficiency anemia and CKD into a detailed physiologic study to study the effects of 5 weekly doses of iron sucrose on tFGF23 and iFGF23 levels over time. Iron deficiency anemia was defined as a hemoglobin <12 g/dl, ferritin <300 mg/dl and transferrin saturation <20%, or a hemoglobin <12 g/dl with a ferritin <100 mg/dl and transferrin saturation <30%. Laboratory measurements were performed at screening, prior to each dose of iron sucrose, one week after completion of the last dose, and at a 3 month follow-up visit.

Abstracts

Abstract A23 Table 1 Characteristics before and after iron sucrose infusion

N=22	Pre-iron sucrose	Post-iron sucrose
Age, yrs	56±13.4	-
Female, %	73	-
Ferritin (ng/mL)	47 (30, 74)	252 (205, 386)
Transferrin Saturation (%)	19±6	25±6
Hemoglobin (g/dL)	10.5±1.0	11.0±1.2
eGFR ml/min/1.73m ²	32.8±18.4	31.9±17.8
Phosphorus (mg/dL)	3.7±0.7	3.6±0.9
tFGF23 (RU/ml)	367 (164, 535)	176 (92, 566)
iFGF23 (pg/ml)	162 (81, 473)	134 (97, 536)

Abstract A23 Figure 1 tFGF23 levels with iron sucrose treatment **Abstract A23 Figure 2** iFGF23 levels with iron sucrose treatment

Results Baseline characteristics before and after iron sucrose therapy are detailed in table 1. Mean estimated glomerular filtration rate (eGFR) was 32.8±18.4 ml/min/1.73m², median ferritin was 47 mg/dl (interquartile range [IQR] 30–74), mean transferrin saturation 19±6%, median tFGF23 367 RU/ml (IQR 164–535), and median iFGF23 162 pg/dl (IQR 81–473). As iron deficiency was treated and ferritin rose to >100 ng/ml, tFGF23 and iFGF23 levels fell (figures 1 and 2). Mean %

change from baseline to tFGF23 nadir was 36%, SD of 27%. Mean % change from baseline to iFGF23 nadir was 21%, SD of 27%. Serum phosphate did not change with iron sucrose therapy.

Conclusion Iron deficiency treatment with iron sucrose lowered tFGF23 values without significant changes in serum phosphate. Iron sucrose therapy lowered iFGF23 values, however there was some variability in the response. Some patients had large falls in iFGF23 (maximum reduction: 349 pg/ml, eGFR 17), and in others we saw no effect. Given that proportionally more intact hormone exists as eGFR declines due to progressive impairment of FGF23 cleavage, we propose that the magnitude of iFGF23 reduction with iron sucrose may be dependent on factors such as eGFR. We hypothesize that the magnitude of iFGF23 reduction may be the greatest in individuals with lowest eGFR because the effects of iron deficiency-induced Fgf23 transcription are magnified when FGF23 cleavage is most impaired. Further research is needed to identify if iron repletion is a therapeutic approach to lower iFGF23 levels in subpopulations of patients with varying stages of CKD.

A24 EFFICIENT CLEARANCE OF FREE LIGHT CHAINS USING HEMOFILTRATION

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Objective Monoclonal gammopathy is relatively common and prevalence is as high as 9% in African American men. High free light chains (FLCs) burden can be toxic to multiple organs. Heart or Kidney involvement manifesting as heart failure or acute kidney injury is associated with significant morbidity and mortality. Very high levels of FLCs usually occur in multiple myeloma and specific chemo or biological therapy can take long time to reduce levels of FLCs. During this time, organs are exposed to light chain toxicity which sometimes can be irreversible. FLCs can cause significant renal failure requiring dialysis or heart failure which can preclude the patient's suitability for stem cell transplant. Removal of FLCs using plasma exchange sometimes not very successful due to high volume of distribution of FLCs. Moreover plasma exchange has to be done in hospital setting, costly, and carries serious complications. We describe a method of clearing free light chains using hemofiltration and we show successful clearance of both kappa and to a lesser extent Lambda free light chains using FDA approved and commercially available hemofiltration system.

Method We used NxStage system-one cyler in combination with matching dialysis filters to measure clearance kinetics of free light chains in an invitro closed system. We also measured Pre and Post hemofiltration free light chains levels in patients with multiple myeloma and are anuric.

Human free light chains were purified in the lab and examined by protein assay, gel electrophoresis, and western blot analysis. These FLCs were used to spike human plasma obtained from blood center of Wisconsin. It was crucial to use plasma as it provides similar concentration polarization of the dialysis membrane that mimics blood and thus provide relevant data. Also, we adjusted the replacement fluid rate to circuit volume to accommodate the difference between circuit and extracellular fluid volume.

Interval aliquots from dialysis circuit were removed during the hemofiltration and analyzed for free light chains levels using immune-assay.

Results

- Western blot analysis of non-reducing gels agreed with previously published data that Majority of the Kappa light chains exist as a monomer while the majority of Lambda exists as a dimer.
- Sieving coefficient for FLCs was 0.7 when mixed in plasma and higher for buffer suspended FLCs.
- After 18 h of hemofiltration approximately 90% of kappa light chains were removed from the closed circuit.
- In an anuric patient, after overnight hemofiltration, the serum concentration of free Kappa light chains was reduced by 77%. The difference in clearance rate between patients and closed system is accounted for by the rate of ongoing addition of free light chains (production minus metabolism).

Conclusion The convective property of hemofiltration combined with sieving coefficient of NxStage filters makes it an effective modality for clearing FLCs in patient with multiple myeloma. This can be important in patients who are suffering from FLCs-related end organ damage. Rapid reduction of FLCs burden can provide organ protection until chemotherapeutic response is achieved. Clinical trials are needed to evaluate the impact of this therapy. Successful use of this technique will be invaluable for patients who have significant AKI due to light chain damage and this might reduce their time on dialysis or improve recovery. Also multiple myeloma patients who are not eligible for bone marrow transplant because heart failure might benefit by improving cardiac function with reduction of FLCs burden. Although dialysis trials have been done in multiple myeloma patients without significant success, all these trials were conducted using diffusive modality and used filters with different characteristics. The availability of the system for home users will make it convenient and cost effective.

*A25

CARDIOTONIC STEROID SIGNALING THROUGH NA/K-ATPASE-A-1 AND SRC KINASE ENHANCE FUNCTIONAL INTERACTIONS BETWEEN IMMUNE CELLS AND ENDO/EPITHELIAL CELLS

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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 renal diseases, such as chronic kidney disease. We have found that CTS mediate pro-inflammatory responses in both renal proximal tubular cells and macrophages upon binding and signaling through the NKA α -1. Inflammation and oxidative stress play a central role in the onset and progression of renal injury associated with CKD. Immune cell adhesion is a critical step in the inflammatory response, however it is unknown whether CTS play a role in driving this important process.

Objective We tested the hypothesis that CTS signaling through NKA α -1 and Src kinase enhances immune cell recruitment and adhesion to endo/epithelium that ultimately advance inflammation.

Methods/results First, we examined the effect of CTS on the expression of the biological markers that are associated with adhesion in both immune and endo/epithelial cells. We found that in THP-1 monocytes the CTS telocinobufagin (TCB, 10 nM, 24 hours) enhanced the expression of the β 2 integrin family members CD11b/CD18 ($p < 0.05$) which are important in cellular adhesion and cell-cell interactions. Additionally, TCB (10 nM, 24 hours) induced the expression of intercellular adhesion molecules I-CAM and V-CAM (both $p < 0.05$) in a human endothelial cell line. Next, we used a functional monocyte adhesion assay to investigate the effect of CTS on immune cell adhesion to endothelial and epithelial cells under physiologically relevant conditions. We found that TCB (10 nM, 24 hrs) induced increases in the adhesion of monocytes to endothelial cells compared to vehicle control ($p < 0.05$). Next, we tested the effect of TCB on macrophage adhesion in 2 stable cell lines derived from LLC-PK1 renal proximal tubular cells which had either normal levels of NKA α -1 (wild type) or 90% NKA α -1 knock-down. In these experiments TCB induced macrophage adhesion was diminished $> 80\%$ in NKA α -1 knock-down cells ($p < 0.01$). Further, pretreatment of wild type cells with a specific peptide inhibitor of the NKA α -1-Src kinase pathway (pNaKtide, 1 μ M) yielded a 75% reduction in macrophage adhesion ($p < 0.01$). Finally, we used a series of in vivo models to study the effect of CTS on inflammatory cells. Here we found that rats injected with TCB (100 μ g/Kg/day i.p. for 4 weeks) showed a significant increase in the accumulation of immune cells in the peritoneal cavity compared to vehicle treated animals ($p < 0.05$). Finally, we infused TCB (100 μ g/Kg/day i.p.) or vehicle into mice expressing wild type NKA- α -1 (WT), as well as mice with either knock-down of NKA- α -1 (NKA-Het) or those expressing a transgenic human NKA- α -1 (NKA-Tg), which renders them more sensitive to CTS. Peritoneal macrophages collected from TCB infused mice expressed increased adhesion markers such as CD11b/CD18 compared to the control group ($p < 0.05$). We also found that these adhesion markers induced by TCB were decreased in NKA-Het mice while they were increased in NKA-Tg vs WT ($p < 0.05$).

Conclusion These findings suggest that CTS potentiate immune cell activation and adhesion to endo/epithelium through an Na/K-ATPase-a-1/Src dependent mechanism.

A26

EARLY AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD) PRESENTS WITH ENDOTHELIAL DYSFUNCTION THAT PRECEDES HEMODYNAMIC CHANGES AND CORRELATE WITH DISEASE SEVERITY

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Objective Vascular manifestations are the most important non-cystic complications and the main cause of death in patients with autosomal dominant polycystic kidney disease (ADPKD). Endothelial dysfunction and vascular remodeling are detectable early in ADPKD, and a decrease in magnetic resonance imaging (MRI)-derive renal blood flow (RBF) has been proposed as a marker of disease severity. Homocysteine (Hcy), a precursor of hydrogen sulfide, is an established biomarker for endothelial dysfunction and vascular disease and linked to increased oxidative stress. However, whether increased circulating Hcy levels correlate with disease

Abstract A26 Table 1

Abstract A26 Figure 1

severity and precede hemodynamic changes in early ADPKD has not been reported.

Method We prospectively measured circulating levels of Hcy (LC/MS/MS) and 8-isoprostane (ELISA) in early (18–30 years old, eGFR > 90 mL/min/1.73 m²) normotensive (<140/90 mmHg without BP medication) ADPKD patients, and in age-matched healthy volunteers (HV) (n=10, 6F/4M each). Total kidney volume (TKV) and RBF were evaluated with MRI.

Results Mean age was 23 years old, but TKV twofold higher in ADPKD vs. HV (table 1). BP tended to be elevated in ADPKD, but eGFR, RBF, and height adjusted RBF (HtRBF) were similar between the groups (table 1). Circulating levels of Hcy and 8-isoprostanes were elevated in ADPKD vs. HV (table 1, figure 1, p<0.05). Furthermore, Hcy and isoprostane (but not RBF) levels directly correlated with TKV and HtTKV (figure 1).

Conclusion Early ADPKD is associated with elevation in circulating Hcy and isoprostane levels, which correlate with disease severity. These findings imply that oxidative stress and endothelial dysfunction might be present before overt hemodynamic changes, and possibly contribute to disease progression. Further experiments are needed to investigate the sources of oxidative stress in patients with ADPKD.

A46

DETERMINANTS OF OUTCOMES AFTER PERCUTANEOUS ANGIOPLASTY OF HEMODIALYSIS FISTULAS AND GRAFTS

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Objective Hemodialysis patients depend upon arteriovenous fistulas (AVF) and grafts (AVG), which often require percutaneous transluminal angioplasty (PTA) to maintain patency. We chose to prospectively evaluate several clinical characteristics of patients having PTA and obtained formal anatomic measurements before and after procedures. We correlated these factors with one month outcomes after PTA to evaluate potential predictors of post-procedure patency.

Method All persons referred for PTA of a patent AVF or AVG from 11/2016–10/2017 who consented were included in the study. Demographic and clinical data were obtained from records; indication for PTA and the type and location of each lesion were collected. Each stenosis was evaluated in two orthogonal planes so percentage of stenosis could be calculated, compared to a reference vessel, before and after PTA. Clinical outcomes were ascertained directly from dialysis unit staff, one month after PTA. Success was defined as being able to maintain dialyzer blood flows of 450 mL/min during dialysis, without other complications, such as: prolonged bleeding, cannulation pain, high venous pressure, low arterial pressure, pulling clots, infiltrations, poor clearance, infections, or swelling of the arm, neck, or head.

Results We observed 115 stenoses in 80 participants, of whom 52.5% were female, 98.8% were African American, reflecting our core hemodialysis population. Mean age was 58.4 years and mean BMI 28.8 kg/m². Success at one month after intervention was seen in 56 patients who had 80 stenoses. The strongest association with success was due to use of aspirin (P=0.007). In addition, referral for high venous pressures as opposed to any other indication, was also associated with procedural success (P=0.01). There was no association with history of hypertension (P=0.9), history of tobacco use (P=0.9), use of renin-angiotensin aldosterone inhibitors (P=0.8), or

statins ($P=0.6$). Interestingly, there were also no anatomic associations with procedural success, although these have been suggested in small studies in the past. Clinical characteristics are presented according to outcome in the table 1 below.

Abstract A46 Table 1 Clinical characteristics by outcome

	All (n=80)	Failure (n=24)	Success (n=56)	p-value
Diabetes, %	61.2	50.0	66.1	0.2
Aspirin, %	56.2	33.3	66.1	0.007
Indication for procedure, %	55.0	33.3	64.3	0.01
Multiple stenoses, %	42.5	41.7	42.9	0.4
Cephalic arch stenosis, %	17.5	12.5	19.6	0.4
Pre-PTA stenosis	59.6 (17.1)	60.8 (18.9)	59.1 (16.3)	0.6
POst-PTA stenosis	19.8 (14.2)	16.9 (12.3)	21.0 (14.8)	0.15
Change in stenosis after PTA	39.8 (19.1)	43.9 (20.5)	38.1 (18.3)	0.13

Conclusion Success after PTA of a hemodialysis AVF or AVG was strongly associated with aspirin use, and also with referral for high venous pressures, as opposed to any other indication. We could not demonstrate any significant associations between procedural success and any anatomic features or measurements.

The usefulness of a platelet inhibitor such as aspirin in this setting is intuitively plausible, and is also an intervention that could be feasibly applied in the outpatient dialysis unit setting. Future work is needed to determine if there are beneficial effects of platelet inhibition or other mechanisms of aspirin on longer term outcomes, validate the current findings in other populations, and investigate the potential biologic mechanisms by which aspirin use may be beneficial for patients with hemodialysis vascular access.

B23 METABOLIC SYNDROME INDUCES POST-STENOTIC KIDNEY MITOCHONDRIAL DAMAGE, MAGNIFYING RENAL INJURY AND DYSFUNCTION IN PIGS WITH RENOVASCULAR DISEASE

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Objective Subjects with renovascular disease (RVD) often manifest the metabolic syndrome (MetS) as well. MetS is associated with nutrient surplus and kidney hyperfiltration, which might exacerbate mitochondrial injury. We hypothesized that

Abstract B23 Figure 1 A. single kidney RBF and GFR were higher in MetS compared to lean, but decreased in MetS+RVD. B. electron microscopic images showing mitochondria with loss of cristae membrane and decreased matrix density in MetS+RVD. C. renal mitochondrial COX-IV activity that decreased in MetS versus lean, further decreased in MetS+RVD. Tubular injury score was higher in MetS vs lean, and further increased in MetS+RVD. * $p<0.05$ vs lean; † $p<0.05$ vs MetS

coexistence of MetS and RVD induces in the post-stenotic kidney mitochondrial damage, aggravating tubular injury and dysfunction in swine RVD.

Method Domestic pigs were studied after 16 weeks of a high-fat/high-fructose diet with or without renal artery stenosis, and Lean animals served as controls (n=7 each). Single-kidney hemodynamics and function were measured in-vivo with multi-detector-CT. Renal mitochondrial morphology was assessed by transmission electron microscopy. Renal mitochondria were isolated (MITO-ISO kit) and their cytochrome-c oxidase (COX)-IV activity measured by colorimetric/fluorimetric methods. Tubular injury was scored in renal sections stained with Periodic acid-Schiff.

Results MetS+RVD pigs achieved significant stenosis (77.5 ±4.9%). Blood pressure was elevated in MetS and MetS+RVD compared to Lean. Renal blood flow (RBF) and glomerular filtration rate (GFR) were elevated in MetS (figure 1), but decreased in MetS+RVD. Renal mitochondrial density was preserved in MetS, but decreased in MetS+RVD, associated with significant mitochondrial structural abnormalities (e.g. loss of cristae membranes and decreased mitochondrial matrix density). Renal mitochondrial COX-IV activity that decreased in MetS versus Lean, further decreased in MetS+RVD, associated with tubular injury (figure 1).

Conclusion Coexistence of MetS and RVD induces mitochondrial structural abnormalities and decreases energy production, associated with post-stenotic kidney injury and dysfunction. MetS+RVD-induced mitochondrial damage may thus contribute to structural injury and dysfunction in the post-stenotic kidney.

B24

VANCOMYCIN VS CEFAZOLIN AS AN INITIAL TREATMENT OF DIALYSIS-ASSOCIATED PERITONITIS

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10.1136/jim-2018-000745.144

Background Peritonitis is a common and serious complication of peritoneal dialysis (PD). Although less than 5% of peritonitis episodes result in death, peritonitis is the direct or major contributing cause of death in around 16% of PD patients. In addition, severe or prolonged peritonitis leads to structural and functional alterations of the peritoneal membrane, eventually leading to membrane failure. Peritonitis is a major cause of PD technique failure and conversion to long-term hemodialysis

ISPD recommends initial empiric treatment for gram positive organisms may include either vancomycin or a first generation cephalosporin, such as cefazolin.

No significant difference in clinical response rates between vancomycin and cefazolin have been found in single center trials.

ISPD recommends center-specific empiric therapy based on local sensitivities of PD-causing organisms.

Objective To determine whether initial, empiric treatment with vancomycin or cefazolin in PD patients with peritonitis has an effect on the rate of repeat, recurrent, relapsing, and refractory peritonitis caused by gram positive organisms.

Secondary objective To assess whether patients who were treated in the hospital had less rates of repeat, recurrent, relapsing, and refractory peritonitis. To assess rate of Culture negative peritonitis

Hypothesis Vancomycin is superior to Cefazolin as an initial empiric therapy for catheter related peritonitis caused by gram positive organisms

Method Retrospective chart review of all patients on peritoneal dialysis who were treated for peritonitis between January 1, 2010 and July 30, 2016

This evaluation has been exempt from review by the Institutional Review Board due to its scope as a quality assurance assessment.

Inclusion criteria Age >18 years, Patients who were diagnosed with catheter related peritonitis. Received at least one dose of either vancomycin or cefazolin. Peritonitis as defined by having 2 or more of the following: abdominal pain or cloudy peritoneal dialysis effluent, white blood cell count >100/mL in peritoneal dialysis effluent, and positive gram stain or culture from peritoneal dialysis effluent

Recurrent: An episode that occurs within 4 weeks of completion of therapy of a prior episode but with a different organism. **Relapsing:** An episode that occurs within 4 weeks of completion of therapy of a prior episode with the same organism or one sterile episode.

Repeat: An episode that occurs more than 4 weeks after completion of therapy of a prior episode with the same organism.

Abstract B24 Table 1 Demographics

Age range	30–96
Mean Age	67
Gender Distribution	Male – 21 Female – 17

Abstract B24 Table 2 Comparison of drug treatment

	Vancomycin group (n=18)	Cefazolin group (n=20)
Repeat	3	3
Recurrent	-	1
Relapse	2	-

Abstract B24 Table 3 In vs out patient

	In (n=22)	Out (n=16)
Repeat	4	2
Recurrent	1	-
Relapse	1	1

Abstract B24 Table 4 Vancomycin treatment in vs out patient

	Vancomycin in (n=15)	Vancomycin out (n=3)
Repeat	2	1
Recurrent	-	-
Relapse	1	1

Abstract B24 Table 5 Cefazolin treatment in vs out patient

	Cefazolin in (n=7)	Cefazolin out (n=13)
Repeat	2	1
Recurrent	1	-
Relapse	-	-

Results Vancomycin was associated with the same number of repeat but higher number of relapse episodes of peritonitis. This difference was not statistically significant. About 68% of the peritonitis episodes that were treated in the hospital received vancomycin as an initial therapy. About 62% of all peritonitis episodes were caused by Gram positive organisms. Culture negative peritonitis accounts for about 18% of all peritonitis episodes

Conclusion Vancomycin is not superior to cefazolin as an initial therapy for gram positive peritonitis. Patient who were treated in the hospital were more likely to receive vancomycin as an initial therapy. The results of this review will be shared with the nephrology department. Limitations: Limited population size

B25 AGING MAY ALTER URINE PH BUT NOT GI ANION ABSORPTION IN WOMEN VS MEN

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Objective When eating identical diets in a CRC setting normal women produce a more alkaline urine pH than corresponding male subjects, due to an increased GI absorption of food anions. This increased alkaline load in women may have beneficial effects to protect bone mineral, particularly in peak reproductive years. We set out to determine whether the pH difference between the sexes was present in 24 hour urine data from an outpatient cohort, if the relationship between sex and pH was influenced by age, and if the relationship between GI anion and urine pH was replicated in this larger cohort.

Method We analyzed pretreatment 24 hour urine data, 3 collections per subject, from 439 male and 284 female calcium stone formers aged 18 to 72 years old and eating free choice diets. A simple plot of urine pH and urine GI anion vs. age revealed higher values in women (F) vs. men (M), up to age 45 – 50. We therefore dichotomized the data into younger (<50, Y) and older (≥50, O) and performed simple ANOVA for each (urine pH and GI anion excretion) by younger vs. older and sex. We also modeled Urine pH using a general linear model (GLM) with age, sex, GI anion excretion, urine sulfate, and urine volume as covariates. All statistical analyses were performed in SYSTAT 13.

Results Among Y women pH exceeded that of Y men (6.18 ± 0.02 vs. 6.03 ± 0.02 , F vs. M, $p < 0.001$) while amongst older people the sex differences were not present (pH, 5.95 ± 0.03 vs. 5.90 ± 0.02 , female vs. male, p, NS). In both cases, the older subjects' urine pH are significantly lower than that of their younger counterparts ($p < .001$). In a GLM modeling urine pH the most significant covariate was GI anion ($f=978$). The other named factors were significant, but had less effect in the model. However when returning to ANOVA analysis for GI Anion, we did not find a marked sex difference in

young patients (31 ± 1 vs. 31 ± 1 , F vs. M, mEq/D, p, NS) while in older patients there was a significant sex difference, but the opposite of the expected trend (GI Anion, 27 ± 1 vs. 36 ± 1 , female vs. male, $p < .001$).

Conclusion Our prior finding of more alkaline urine pH in women as compared to men was replicated in younger women, but not in subjects aged over 50. This suggests that sex hormones may play a regulatory role in urine pH. However hormonal control of the role of gut alkali absorption may not be the primary mechanism by which this urine pH effect is mediated. Our primary hypothesis that young women have significantly higher urine pH than all other groups is supported, and the role of GI anion absorption will be investigated further.

C07 CHARACTERIZATION OF A LONG NON-CODING RNA, THE ANTISENSE RNA OF NA/K-ATPASE ALPHA 1

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Objective While nearly 85% of the human genome is transcribed, only about 2% is translated into proteins. Non-coding RNAs have been suggested to be important regulators of protein-coding genes. The objective of study is to investigate the expression pattern and function of a non-coding antisense RNA, ATP1A1-AS in human kidney cells.

Method Human kidney cell lines (HK2 and HEK cells) were used for ATP1A1-AS analysis. Overexpression and siRNA knockdown of ATP1A1-AS were performed in these cells to test the physiological role of this antisense gene.

Results We have characterized an antisense long non-coding RNA (ATP1A1-AS) that is located on the opposite strand of the sense gene of the Na/K-ATPase alpha1, which is an important membrane transporter for renal salt handling. Our results show that at least 4 splicing variants of ATP1A1-AS gene are transcribed in human embryonic kidney cells (HEK cells) and in adult kidney cells (HK2 cells). Overexpression of the ATP1A1-AS transcript reduced the expression of Na/K-ATPase alpha1 (ATP1A1) by about 20% as assessed by RT-qPCR and Western blot. However, siRNA against the ATP1A1-AS gene had very limited effect on ATP1A1-AS expression as well as Na/K-ATPase gene expression. In addition, overexpression of the ATP1A1-AS transcript causes slower cell growth and more sensitivity to ouabain-induced cell toxicity.

Conclusion These results demonstrate that the antisense ATP1A1-AS gene might serve as a moderate negative regulator of the Na/K-ATPase and suggest that the physiological role of ATP1A1-AS in human cells is in need of further investigation.

C08 INTERACTIONS OF CALCIUM, VITAMIN D, AND KIDNEY FUNCTION WITH PARATHYROID HORMONE LEVELS

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Objective To characterize the in vivo interactions between calcium, eGFR, and vitamin D, and their effects on PTH.

Method Laboratory results performed at Laboratory Corporation of America Holdings (LabCorp) between November 2011

Abstracts

and February 2014 were assessed, if simultaneous PTH, calcium, vitamin D and eGFR were available. Calcium and vitamin D were categorized, and analyses were stratified for National Kidney Foundation stage of chronic kidney disease (CKD). The functional forms of the relationships of PTH with calcium, GFR, and vitamin D were assessed, and each were plotted as mean PTH with 95% confidence intervals. Based on the functional forms of these variables, estimated GFR was log-transformed, and a quadratic term was added to account for the U-shaped relationship between calcium and PTH, with calcium centered at the mean value (9.6 mg/dL). Logistic models were constructed for the outcome of PTH>65. Models were adjusted for age and sex, and the impacts of two-way and three-way interactions between variables were assessed for each model. Percentages of tests in which a PTH>65 was observed were calculated and plotted for each combination of calcium, vitamin D, and eGFR.

Results Among 126,615 patients, 38% were male and mean age was 65.6 years. Compared to those with eGFR>90, PTH levels were more likely to be abnormal in CKD stages 2 and 3A. Higher vitamin D levels were associated with lower PTH in all patients, and this effect became more prominent with decreasing eGFR. The normal U-shaped relationships between calcium and PTH were distorted in CKD stages 4 and 5.

Abstract C08 Table 1

Characteristic	Median (Interquartile range)
Age, years	67 (57, 76)
PTH	42 (29, 65)
Vit D	30 (22, 39)
Calcium	9.5 (9.2, 10.0)
eGFR, ml/min/1.73m ²	53 (36, 79)
Female sex (%)	61.9

Abstract C08 Table 2 Distribution of cGFR and Vit D Categories (N=123,615)

CKD → Stage Vit D ↓	1	2	3A	3B	4	5
<20	4730	5413	4344	5646	4235	751
20-29.9	6313	9587	7323	8763	5377	646
30-39.9	5067	9096	7357	8446	4585	457
≥ 40	4318	8461	5778	6208	3394	318

Abstract C08 Table 3 Logistic model for Probability of PTH>65†

Covariate	Odds Ratio (95% CI)	P
Vit D, per 5 ng/mL	0.83 (0.82, 0.84)	<0.0001
ln(eGFR), per 0.1	0.84 (0.83, 0.85)	<0.0001
Calcium	1.04 (1.01, 1.06)	0.002
(Calcium) ²	1.38 (1.35, 1.40)	<0.0001
Age, per 10 years	1.01 (1.00, 1.03)	0.02
Female sex	1.30 (1.26, 1.34)	<0.0001

† Main effects shown.

Significant interactions: ln(eGFR)*Ca, ln(eGFR)*Ca², ln(eGFR)*VitD, VitD*Ca.

Conclusion 1. Elevated PTH is common in all levels of CKD, even patients with eGFR 60–90 ml/min/1.73m².

2. The normal U-shaped relationship between calcium and PTH becomes distorted at eGFR<30, and chaotic at eGFR<15 ml/min/1.73m².

Abstract C08 Figure 1

3. eGFR and Vitamin D have strong inverse associations with abnormal elevation of PTH, and interact with the relationship of calcium and PTH.

4. Compared to any degree of Vit D deficiency, Vit D >40 ng/mL was associated with significantly lower PTH levels in patients with CKD stages 1–4. Further work is needed to determine if interventions to replete Vit D >40 might reduce hyperparathyroidism and its vascular complications in early CKD.

C39 DANGEROUSLY LOW SODIUM LEVEL: A CASE REPORT ON HYPONATREMIA

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Hyponatremia is a common presentation in an inpatient setting. It has many inciting causes and treatment focuses on volume restriction. However, abnormally low sodium values (<100 mEq/L) are rarely seen and need an extensive treatment plan for cautious correction of sodium levels. We present the case of a 58 years old Caucasian gentleman with a past medical history significant for hypertension, COPD and alcoholism (without cirrhosis) who came to the Emergency Department with altered mental status reported for less than 1 day resulting in fall. A CT scan of the head was negative for any bleeding and laboratory values were significant for a sodium level of 97 mEq/L. Patient was found to have hypo-osmolar hyponatremia and treatment was initiated with normal saline and DDAVP to achieve the goal of 6–8 mEq/L correction per 24 hours with normalization of sodium level achieved in 9 days to a final level of 130 mEq/L. Patient recovered completely without evidence of neurologic dysfunction. Patient's euvolemic hyponatremia was postulated to be secondary to the use of HCTZ and herbal supplements. This case highlights the importance of controlled correction of severe hyponatremia as sudden electrolyte changes can be harmful, even fatal, in such cases.

Abstract C39 Figure 1

C40 PARAOXONASE REGULATION OF CARDIOTONIC STEROIDS IN CHRONIC KIDNEY DISEASE

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Introduction Cardiotonic steroids (CTS) are steroid hormones which are elevated in volume expanded states such as chronic kidney disease (CKD). The 2-pyrone ring structure of CTS is critical for their binding to the Na⁺/K⁺-ATPase and subsequent initiation of pro-inflammatory and pro-fibrotic signaling which can promote cardiac and renal disease. Paraoxonases (PONs) are a family of hydrolytic enzymes which are capable of hydrolyzing chemical structures similar to the 2-pyrone rings found in CTS, however the native physiologic substrate (s) of PON's are unknown.

Objective We hypothesized that 2-pyrone containing CTS are substrates for PON hydrolytic activity (2-pyronease-like activity) and that this specific activity is decreased in the setting of CKD.

Methods/results We first examined the ability of the CTS to compete with a chemically similar specific fluorogenic substrate of PON's (7-hydroxycoumarin). PON-1 purified from human plasma (both RR and QQ genotype of the PON-1 Q192R polymorphism) was reacted with 7-hydroxycoumarin in the presence and absence of equimolar amounts of the CTS telocinobufagin (TCB). PON-1 hydrolytic activity toward 7-hydroxycoumarin was reduced 90% in the presence of TCB (p<0.01 for both PON-1 QQ and RR variants). In order to confirm that this reduction was related to hydrolysis of the TCB, we developed a specific LC-MS assay to measure the 2-pyrone active form of TCB. Incubation of TCB with PON-1 overexpressing HEPG2 cells led to a >65% decrease in the 2-pyrone form of TCB at 24 hours (p=0.0054). Next, we measured circulating PON-1 protein (ELISA) and 2-pyronease-like activity in diabetic nephropathy CKD patients (n= 39; consisting of n=14 Stage 3 CKD, n=15 Stage 4 CKD, n= 10 Stage 5 CKD) vs non-CKD controls (n=15). Interestingly, we found that while circulating PON-1 protein levels were increased slightly, but not significantly, across CKD stages, circulating PON-1 2-pyronease-like activity was decreased significantly (p<0.001) across all CKD stages vs non-CKD controls (32% decrease in Stage 3 CKD, 34% decrease in Stage 4 CKD, and 41% decrease in Stage 5 CKD).

Conclusion These findings suggest that CTS may be physiologic substrates for PON's and participate in a novel regulatory mechanism via hydrolysis of the CTS 2-pyrone ring. Furthermore, circulating PON-1 appears to have diminished 2-pyronease-like activity in the setting of CKD.

Neurology/Neurodegeneration

B12 MYELIN DENSITY IN THE PRIMARY MOTOR CORTEX IS RELATED TO THE DENSITY OF ASSOCIATED LOWER MOTOR NEURONS IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS

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Objective Amyotrophic lateral sclerosis (ALS/Lou Gehrig's Disease) is a neurodegenerative disease that causes progressive loss of voluntary motor function and death within 2–5 years in most patients. Loss of motor neurons is the hallmark pathology and its mechanism is incompletely understood; however, results from a mouse model of ALS have suggested that dysfunction of oligodendrocytes (cells that make the myelin that is essential for efficient nerve conduction) may be an initiating

Abstract B12 Figure 1 PMC myelin density is related to the density of associated lower motor neurons in patients with ALS. PLP immunostaining of an ALS and age-matched subject with multiple sclerosis (MS). (B) shows cortical demyelination that is typical in MS. The age-matched ALS patient in (A) does not exhibit demyelination. (C) a positive linear correlation between the myelin density in the IMC layers 5 and 6 (containing the motor neurons and their projecting axons) and the neuronal density of the associated lower motor neurons in the hypoglossal nucleus

factor. In tissues from ALS patients, myelin density has been shown to be decreased, which could support primary dysfunction of oligodendrocytes, but could also be a secondary effect of loss of motor neurons. There have been no studies to date that have examined ALS tissues for evidence of primary oligodendrocyte dysfunction by measuring both myelin density and motor neuron density. The objective of this study is to determine if there is evidence of primary oligodendrocyte dysfunction in the primary motor cortex (PMC) of ALS patients

Method We removed the brain, brainstem and spinal cord from consented ALS patients soon after death. The PMC was excised from the right hemisphere and cut into 5–6 sections covering superior, middle, and inferior motor cortex (IMC); alternating sections were either short-fixed in 4% paraformaldehyde for 2.5 days or snap-frozen. Short-fixed PMC sections and brainstem were sliced 30- μ m-thick and immunostained for neurons (using the HuR antibody in PMC and SMI-32 in brainstem) and myelin (using the proteolipid protein, PLP, antibody). Immunoblotting was performed on cortex dissected from frozen PMC to quantify myelin-associated proteins (PLP and cyclic-nucleotide 3'-phosphodiesterase, CNP). In PMC, upper motor neuron and myelin density were measured from immunostained tissues using automated algorithms. In the brainstem, the density of lower motor neurons in the hypoglossal nucleus, which receives input from projecting upper motor neurons in the IMC, was quantified on immunostained tissues by manually rating by an observer blinded to other immunostaining data.

Results Immunostaining for PLP in PMC from 11 ALS patients and immunoblotting for PLP (in N=7) and CNP (in N=10) did not reveal demyelination (figure 1A) or decreased myelin proteins, providing no evidence for primary oligodendrocyte dysfunction in ALS PMC. The IMC was found to have significantly lower myelin density detected by immunostaining compared to the other PMC regions (-4% – -19%, $p=0.010$ – 0.046 , N=10). In the IMC, myelin density was not associated with upper motor neuron density, but was significantly linearly correlated with the density of associated lower motor neurons in the hypoglossal nucleus ($r=0.7$, $p=0.02$, N=9, figure 1C).

Conclusion The absence of demyelination in ALS PMC suggests that the oligodendrocytes are not dysfunctional. Further investigation of the PMC region with the lowest myelin density revealed that myelin density in IMC layer 5 (containing the upper motor neurons) and layer 6 (containing their axons projecting to the lower motor neurons in the brainstem) was not correlated with the density of upper motor neurons, but

was correlated with the density of associated lower motor neurons (in the hypoglossal nucleus). Our results do not support primary oligodendrocyte dysfunction initiating upper motor neuron death in ALS. Decreases in myelin density in ALS PMC may be secondary to loss of connection with associated lower motor neurons.

C09

GREY MATTER INJURY AFTER MODERATE CLOSED-SKULL TRAUMATIC BRAIN INJURY

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Objective Traumatic brain injury (TBI) is a highly-prevalent cause of morbidity and mortality worldwide with no effective therapy. The majority of TBI cases are mild or 'concussive.' These patients overwhelmingly recover well. Patients with complicated-mild or moderate TBI, however, suffer a dramatically higher burden of long-lasting deficits. These patients are therefore an attractive target for investigation. Though significant work has been made to understand white matter injury after TBI, efforts to understand grey matter injury have not been as numerous. Moreover, techniques and tools to easily understand diffuse grey matter injury are not readily available which makes developing new techniques ever more important.

Method We developed a non-surgical, tunable, monitored model of mouse TBI based off of the closed-head impact model of engineered rotational acceleration (CHIMERA) platform, called modCHIMERA, that targets this TBI severity group. modCHIMERA is characterized by both impact and inertial loading (linear and rotational), with acceleration exceeding scaled human injury thresholds, and righting times consistent with a moderate injury.

Results modCHIMERA induces diffuse damage characterized by multifocal white matter injury, cell death, neuroinflammation, and multidomain neurobehavioral deficits. Importantly, modCHIMERA does not generate a dominant focal, cavitary lesion as results from most moderate-severe TBI models. This approximates the diffuse injuries commonly observed in patients with complicated-mild and moderate TBI, and facilitates investigation of grey matter cellular and subcellular damage. Such grey matter injury pathways may drive lasting neurological impairment separate from the white matter pathology that has been the primary focus of most studies on post-TBI neuronal damage. Consistent

with this, modifications to modCHIMERA to limit axonal injury did not eliminate long-term neurobehavioral deficits. To characterize pathways leading to grey matter injury after TBI, cortical regions were assessed after modCHIMERA for neuronal cell death, dendrite length and arbor complexity, dendritic spine density, and synaptic density. Functional connectivity optic intrinsic signal imaging was used to evaluate local circuits vs. those dependent on projection axons, and demonstrates greater impact on ipsilateral node degree consistent with functionally-significant synaptic or dendritic injury.

Conclusion These studies will lead to a greater understanding of traumatic circuit disruption and form the basis for therapeutic studies aimed at preventing circuit injury after TBI.

C10 VARIATIONS IN MICROVASCULAR INSULIN-DEGRADING ENZYME LEVELS IN BV-2 MICROGLIAL CELLS IN RESPONSE TO CYTOKINE AND INSULIN TREATMENT

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Objective Insulin-degrading Enzyme (IDE) is a zinc metalloprotease that degrades amyloid beta, insulin and other amyloidogenic peptides. Low levels of IDE have been linked to the development of both Alzheimer's disease (AD) and diabetes. This common mechanism may explain the increased risk of developing AD that is seen in type 2 diabetic patients. IDE has been identified in microvesicles secreted from microglial cells but the factors controlling their release are not well defined. Our objective was to determine if microvesicular IDE levels could be altered following treatment with different cytokines and insulin. This will give us a greater understanding of the underlying mechanisms controlling IDE secretion and could give us a better understanding of the development of AD.

Methods BV-2 microglial cells were cultured in DMEM-F12 with 10% FBS, 1% Penn/Strep, and 1% Glutamax. The cells were divided into the following groups. 1) Control; 2) Control + insulin (10 nM/mL); 3) LPS (100 ng/mL); 4) LPS (100 ng/mL) + insulin (10 nM/mL); 5) TNF- α (10 ng/mL); 6) TNF- α (10 ng/mL) + insulin (10 nM/mL); 7) TGF β -1 (10 ng/mL); 8) TGF β -1 (10 ng/mL) + insulin (10 nM/mL); 9) IL-4 (10 ng/mL); 10) IL-4 (10 ng/mL) + insulin (10 nM/mL). Insulin treatment was concurrent with cytokine treatment. Conditioned medium was collected at 8, 24 and 48 hours from individual flasks. Microvesicles were isolated by ultracentrifugation at 100,000xg and frozen at -80° C. IDE activity was determined by trichloroacetic acid precipitation assay with ¹²⁵I insulin with 2-hours of incubation. A one-way ANOVA was used to analyze the data with a P<0.05 being significant.

Results All IDE activity at 8 and 24-hours was confined to the microvesicular fraction of the cultured medium P<0.001. At 48-hours there was a small amount of free IDE present in the cultured medium but was significantly less than the amount in the 48-hour microvesicular fraction P<0.001. The maximal effect of the cytokine treatment was observed at 24-hours P<0.0444. At 8-hours the level of IDE activity was low, and the different treatments had no effect. By 48 hours the differences between the treatment groups was no longer present. TGF β 1 and IL-4 treatment showed a strong trend of decreased IDE activity. TGF β 1 showed this at both 24 and

48-hours, while IL-4 only showed this trend only at 24-hours. LPS had no effect on IDE levels at 8, 24 or 48 hours. TNF- α showed a strong trend towards increased IDE activity compared to control. When the 24-hour TNF- α group was co-treated with insulin, the insulin caused a significant decrease in IDE activity P<0.01.

Conclusion IDE is confined to the microvesicular fraction of cultured medium. This may have important implications on the kinetics of *in vivo* extracellular A β clearance. TNF- α treatment appeared to increase IDE activity, while the anti-inflammatory cytokines IL-4 and TGF β 1 appeared to decrease IDE levels. Co-treatment of TNF- α and insulin reversed the effects of TNF- α treatment. This effect might be explained by the anti-inflammatory properties of insulin causing suppression of the activated microglial cells. A low level of immune system activation may be beneficial in increasing levels of IDE and possibly preventing the deposition of A β . Immunosuppression is therefore a possible risk factor for the development AD. This has important implications as many therapies for auto-immune diseases rely on iatrogenic immunosuppression. Immune system activation plays an important role in regulating microvesicular levels of IDE and immunosuppression maybe a risk factor in the development of AD.

C41 COGNITIVE ERRORS IN THE DIAGNOSIS OF MYASTHENIA GRAVIS

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Background Myasthenia gravis (MG) is a neuromuscular disorder requiring chronic immunosuppression. We defined misdiagnosis of MG as either diagnosing patients with MG (and treating them) when they didn't have it or when diagnosing patients with a different condition when they had MG. The objective was to identify the types of cognitive error that resulted in misdiagnosis and clinical factors which led to the cognitive error.

Method Retrospective study of 269 patient charts (from 2011–2017) with ICD-9 code of 358.00/358.01. Those patients who met our definition of 'misdiagnosis' were included and chart reviewed for the cause of misdiagnosis.

Results 20 patients, mean age 60 (SD=±17), 13 women and 7 men were included. 17 were misdiagnosed as MG (different eventual diagnosis). 20% of those had no clear diagnosis. 25% neuropathy and rest were somatoform disorder, stroke, ALS, nutritional deficiencies. 9 were due to framing effect (relying solely on subtle exam clues despite extensive negative testing); 5 blind obedience (relying on incorrectly reported repetitive nerve stimulation from an expert); 4 were anchoring heuristic (relying only on patient reported response to pyridostigmine) and 2 availability heuristics. 3 cases were diagnosed with MG after a different initial diagnosis (2 stroke and 1 GBS) and were due to availability heuristic (stroke and GBS commonly seen as acute presentation).

Conclusion Relying on subtle exam findings, incorrectly interpreted repetitive nerve stimulation and patient reported benefit with pyridostigmine are causes of MG misdiagnosis. Failure to consider MG as a differential in the acute setting can also lead to misdiagnosis.

Pathophysiology

C44 RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS IN SYSTEMIC LUPUS ERYTHEMATOSUS, A CASE PRESENTATION

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Introduction Systemic lupus erythematosus (SLE) is an autoimmune disease known to produce antibodies against several cellular components including the glomerular capillary wall causing renal function compromise. As recent guidelines for lupus nephritis screening and treatment, up to half of SLE patients exhibit renal pathology most commonly diffuse proliferative nephritis (DPGN). On the contrary, rapid progressive glomerulonephritis (RPGN) specifically Pauci Immune p-ANCA/MPO positive nephritis consists of no specific Ig or C3 deposition. These negative immunofluorescence findings help distinguish Pauci immune RPGN from Lupus nephritis where subendothelial and intramembranous IgG-based immunocomplements are abundant. Although SLE usually presents as DPGN, MPGN, or even focal segmental glomerulonephritis (FSGN), there seems to be correlation between SLE and RPGN. Here we present a case of RPGN that shows an overlapping etiology with the patient's SLE diagnosis.

Case presentation 47 year old female with no PMH presented with fatigue, decreased appetite and occasional nausea for 4 weeks. She noticed that her urine had a pink tinge for the 3 weeks. She had lost about 9 pounds over the course of a month and had a significantly decreased appetite. Physical exam was benign and patient's labs showed elevated WBC, increased BUN, creatinine, and ALP with RBCs and protein in urine. Upon further investigation, patient's Hepatitis and HIV serology were negative, urine culture was negative, anti GBM negative, ANA and AntiDNA antibody positive, pANCA positive, Myeloperoxidase antibody positive, Proteinase 2 AB negative and cANCA negative. C3 and C4 levels were normal. Renal biopsy results revealed Pauci immune necrotizing and crescentic glomerulonephritis (ANCA associated) with correlated mesangial proliferative lupus nephritis ISN/RPS class II. The biopsy also showed moderate interstitial fibrosis and tubular atrophy and secondary acute tubule interstitial nephritis. Light microscopy showed crescentic deposits in 29/31 glomeruli, immunofluorescence microscopy stained mesangium for IgG (1–2+), IgM (2+), C3(2+) and trace C1q with no significant IgA staining and Electron microscopy showed no subendothelial or subepithelial deposits, and severe podocyte effacement. Here we described an interesting case of RPGN superimposed on LN like morphology. Steroid and Rituximab therapy led to a good initial clinical response and patient will now be continually followed up outpatient.

Discussion Although 20% of patients with SLE have ANCA positivity by immunofluorescence, there are conflicting reports on the significance of these findings. A study looking at 10 patients with Lupus nephritis showed renal biopsy findings of cellular crescents and basement membrane scarring and necrosis. The biopsy findings in these patients showed very trace subendothelial deposits instead mainly crescentic morphology concluding overlapping LN and ANCA associated GN. Nine out of ten patients were pANCA positive and MPO. Our patient as well as the study presented support the

pathogenic role of ANCA positivity in LN patients with superimposed crescentic findings. Our case of RPGN with LN presentation suggests more than just coincidental findings for correlation between these two diseases. Further studies on pathogenesis of ANCA positivity and its role in SLE can benefit understanding the wide array of nephritis and nephrotic syndromes in SLE patients. It is possible that the widespread inflammatory response seen in SLE patients increases expression of surface antigens such as Myeloperoxidase, PR3, lactoferrin, cathepsin G, lysozyme, and elastase yielding ANCA positivity. Immunotherapy with steroids and Cyclophosphamide or Rituximab show a beneficial clinical outcome in ANCA positive RPGN superimposed on LN.

C45 SIMPLE THROMBUS OR SOMETHING MORE SINISTER: INTRACARDIAC FUNGAL BALL SECONDARY TO TOTAL PARENTERAL NUTRITION; THE ONLY REPORTED CASE

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Background It is extremely rare for *Candida* to cause intracardiac masses or fungus balls with very rare cases reported in neonates. To our knowledge, only one case has been reported so far in the literature of *Candida Albicans* causing Left atrial mass. We report the first case of massive intracardiac candida fungal mass in an adult with native valve endocarditis in a patient on long-term total parenteral nutrition (TPN).

Case A 51-year-old man with acquired short bowel syndrome after colectomy on chronic total parenteral nutrition (TPN) was admitted with sepsis. At presentation he was alert and oriented, afebrile, hemodynamically stable with Mean Arterial Pressure (MAP) of 65., saturating well at room air with the benign physical examination. Admission labs revealed a white count of 12000/mm³ (range 4–11 k/mm³), ESR was 99 and CRP was 139 mg/L. EKG showed normal sinus rhythm without any conduction abnormalities. Patient was started on broad-spectrum antibiotics as well as micafungin and fluconazole. Blood cultures done at the time of admission grew *Candida dubliniensis* and *Candida glabrata*. On day 3 of hospitalization, the patient went into undifferentiated shock. Urgent Transthoracic Echocardiogram (TTE) showed echogenic large right atrial (RA) mass (4x6x2.5cm) extending from the superior vena cava into the right atrium and prolapsing into the right ventricle and right ventricle outflow tract without evidence of outflow obstruction, findings were worrisome for fungal ball versus Intracardiac thrombus.

Abstract C45 Figure 1 Intracardiac fungal mass on echocardiography

Transesophageal echocardiogram (TEE) revealed aortic valve vegetation (1x0.5 cm) in addition to confirming the mass seen on TTE (figure 1). CT chest showed diffuse nodular opacities bilaterally concerning for multiple septic emboli. Cardiothoracic surgery was consulted for surgical intervention of the intracardiac fungal mass, however, the patient was deemed high-risk surgical candidate given his comorbidities and size as well as the extent of the mass. The patient was treated with amphotericin B for 2 weeks followed by micafungin for 8 weeks and fluconazole for the lifetime. TEE was done 3 months after the initial echocardiography showed complete resolution of intracardiac mass without any evidence of persistent vegetations confirming the mass to be fungal in origin as opposed to a thrombus.

Conclusion This case highlights the importance of keeping in mind the rare but dreaded complication of invasive fungal infection in patients on long-term TPN. The case also emphasizes that fungal masses should be considered in the differential whenever atrial or ventricular masses are seen on echocardiogram, especially in septic patients.

C54 PERICARDITIS AS THE PRESENTING SYMPTOM OF GRAVE'S DISEASE, A RARE CASE REPORT

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Introduction Acute pericarditis is the most common pericardial disease and can be caused by viruses, bacteria, tuberculosis, myocardial infarction, malignancy, trauma and autoimmune diseases. Graves' disease is an autoimmune disorder that leads to over activity of the thyroid gland (hyperthyroidism). Well-known cardiovascular complications of Grave's disease are atrial fibrillation, atrial enlargement and congestive heart failure. Moreover, it is linked with autoimmune complications, such as cardiac valve involvement and pulmonary arterial hypertension. However, acute pericarditis has been infrequently reported as a complication of Grave's disease and the exact pathophysiological mechanisms and associations between them still need further investigation.

Case presentation We report the case of a 29 year-old male patient with no past medical history who presented to our hospital with chest pain. Patient reported that his pain started suddenly and described it as sharp, high in intensity, radiating up to bilateral shoulders and back aggravated by deep breaths and movement. His pain was also associated with nausea, shortness of breath, and palpitations. On review of systems, patient admitted to having diarrhea, 50 lbs weight loss and bilateral hand tremor for more than a year. He admitted also to smoking marijuana daily for the past 15 years. On physical examination, the patient was febrile to 101 F, tachycardic to 135, tachypneic to 25, and hypertensive to 150/65 (equal blood pressure measured bilaterally) with no other positive findings. Lab findings included a benign blood count, elevated C-reactive protein to 49 mg/dl, negative D-dimer, normal partial thromboplastin time, negative troponin, negative drug screen, negative acetaminophen, salicylate, and alcohol screen, negative HIV serology, stable electrolytes and benign renal findings. EKG showed sinus tachycardia with diffuse ST elevation in leads II, III, AVF, v2-v6. Chest x-ray is unremarkable.

Transthoracic echocardiogram revealed normal left and right systolic function with an ejection fraction of 65%. Upon further investigation, Thyroid stimulating hormone (TSH) was undetectable, free T4 elevated to 5 ng/dl and TSH stimulating antibodies positive. The patient was diagnosed with acute pericarditis and thyrotoxicosis associated with Grave's disease. He was treated with Ibuprofen and colchicine for his acute pericarditis, and with Propranolol and Methimazole for his thyrotoxicosis.

Discussion The etiology of acute pericarditis is often thought to be autoimmune. Graves' disease, a well-known multisystem autoimmune disease, has been associated with acute pericarditis in a few case reports. It is difficult to tell whether the mutual presence of these two entities represents coincident existence or there is an underlying etiologic pathophysiology linking them. However, our case report, among other published reports, serves as growing evidence that an etiologic association is likely be present, and it may very well be explained by the underlying autoimmune process accounting for both of them.

Pulmonary/Critical Care

OYI FIBROBLAST GROWTH FACTOR 2 DECREASES BLEOMYCIN-INDUCED PULMONARY FIBROSIS THROUGH INHIBITION OF FIBROBLAST COLLAGEN PRODUCTION

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Objective Recently approved treatments for IPF target Fibroblast Growth Factor (FGF) signaling; however the mechanism through which FGFs contribute to pulmonary fibrosis remains unclear. FGF2 promotes recovery from injury in a variety of tissues, including heart, skin, bone, retina, and intestine. We previously reported that mice lacking FGF2 have increased mortality and impaired epithelial recovery following bleomycin treatment, suggesting that FGF2 may be a protective or reparative growth factor following bleomycin-induced lung injury. We therefore hypothesized that overexpression of FGF2 would decrease bleomycin-induced lung injury and subsequent pulmonary fibrosis.

Method We developed an inducible genetic system to express FGF2 in type II pneumocytes. Double transgenic (DTG) mice with doxycycline-inducible overexpression of FGF2 (SPC-rtTA; TRE-hFGF2) or single-transgenic controls were administered intratracheal bleomycin and fed doxycycline chow starting at either day zero or seven. Additionally, wild type mice were administered intratracheal recombinant FGF2 (5 µg in 20 µL PBS) at the time of bleomycin treatment. To test the effect of FGF2 *in vitro*, primary mouse and human lung fibroblasts (HLFs) were treated with recombinant FGF2 (2 nM) with or without TGFβ1 (2 ng/ml).

Results Overexpression of FGF2 in mouse lungs for up to 5 months did not result in histologic abnormalities. Compared to controls, doxycycline-induced DTG mice had decreased Collagen 1 (*Col1a1*), Collagen 3 (*Col3a1*), and connective tissue growth factor (*Ctgf*) expression, decreased number of alpha smooth muscle actin (αSMA) positive fibroblasts, and decreased pulmonary fibrosis 21 days post-bleomycin. The reduction in pulmonary fibrosis was seen when FGF2

overexpression was started both at day zero and seven post-bleomycin. FGF2 overexpression did not result in altered whole lung epithelial gene expression, broncho-alveolar lavage (BAL) cellularity, or BAL total protein. Treatment with intratracheal recombinant FGF2 significantly reduced bleomycin-induced mortality and the number of α SMA+ fibroblasts. *In vitro*, FGF2 strongly inhibited baseline expression of α SMA (*Acta2*), *Col1 α 1*, and *Ctgf* in primary mouse lung fibroblasts, and TGF β 1 induced expression of *COL1A1*, *LOX*, and *ACTA2* in primary mouse and human lung fibroblasts. The effect of FGF2 was abolished by PD173074, a FGFR-specific tyrosine kinase inhibitor. While FGF2 did not suppress phosphorylation of Smad2 or Smad-dependent gene expression, FGF2 inhibited TGF β 1-induced stress fiber formation and serum response factor (SRF) luciferase reporter activity.

Conclusion In summary, overexpression of FGF2 is well tolerated and reduces bleomycin-induced pulmonary fibrosis *in vivo* when given as both a preventative and treatment protocol. FGF2 does not alter either inflammation or whole lung epithelial gene expression post-bleomycin. FGF2 reverses TGF β 1-induced stress fiber formation as well as collagen and α SMA expression *in vitro*, in part through inhibition of SRF-dependent gene expression. These results suggest that FGF2 is antifibrotic through a direct action on lung fibroblasts, leading to decreased collagen expression and differentiation of fibroblasts to myofibroblasts.

B11 ILC2S AND EOSINOPHILS PROTECT AGAINST STAPHYLOCOCCUS AUREUS-INDUCED SEPSIS

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Objective Sepsis is defined as life-threatening organ dysfunction caused by an inappropriate inflammatory response to infection. While this detrimental response remains poorly understood, we and others recently demonstrated that patients with diseases associated with the type 2 immune response (such as asthma and allergies) are protected from becoming septic. We confirmed this observation in a mouse model of *Staphylococcus aureus* (*S. aureus*) bacteremia, wherein mice with allergic airways inflammation were protected from lethal sepsis. The objective of this study was to determine the cellular mechanisms by which type 2 immune responses protect against sepsis.

Methods C57BL/6 mice were treated intratracheally with 100 ng IL-33 for 3 days (or PBS control) to induce innate type 2 allergic pulmonary inflammation, followed by intravenous infection with a lethal dose of USA300 *S. aureus* on day 4. The following day flow cytometry was used to quantify lung type 2 innate lymphoid cells (ILC2s), neutrophils and eosinophils. For survival analysis, mice were monitored for 8 days after infection. To investigate the role of specific cell types in survival, PLZF $^{-/-}$ mice (lacking functional ILC2s, and lacking functional natural killer T cells, or NKT), CD1d $^{-/-}$ mice (lacking functional NKT) and Rag1 $^{-/-}$ mice (lacking all T cells) were used. Inducible eosinophil depletion was achieved by treating iPHIL mice, which express the diphtheria toxin receptor exclusively on eosinophils, with diphtheria toxin prior to infection. To determine the importance of specific type 2

cytokines in protection, mice were injected intraperitoneally with IL-5 and IL-13 prior to infection.

Results Mice pretreated with IL-33 prior to *S. aureus* infection demonstrated an expanded number of ILC2s and type 2 cytokines compared with infected control mice. Infection of PLZF $^{-/-}$ mice resulted in accelerated mortality compared to wild type littermate controls. Moreover, IL-33 did not rescue PLZF $^{-/-}$ mice from death. However, infection of mice deficient in only NKT cells (CD1d $^{-/-}$) or all T cells (Rag1 $^{-/-}$) demonstrated no difference in mortality compared to controls, likely because both strains retained functional ILC2s. Further supporting this conclusion, injection of ILC2-derived cytokines into PLZF $^{-/-}$ mice prior to infection protected mice against lethality. Because ILC2 activation and cytokine secretion leads to eosinophil recruitment, we evaluated granulocyte subsets in the lungs and noted an increase in eosinophils and a decrease in neutrophils in IL-33 treated, *S. aureus* infected mice, compared to mice infected with *S. aureus* alone. Remarkably, inducible depletion of eosinophils after infection abrogated IL-33 mediated protection, revealing a novel role for eosinophils in protecting against sepsis.

Conclusion Type 2 innate immune activation induced by IL-33 to promote secretion of ILC2-derived cytokines induces pulmonary eosinophilia that provides critical protection against *S. aureus*-mediated sepsis. Modulation of the type 2 immune response represents a novel therapeutic target for improving the care of patients with sepsis.

A13 DNA METHYLATION AS A REGULATOR OF THE NEONATAL CD4+ T CELL RESPONSE TO PNEUMONIA

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Objective Neonates with pneumonia have poorer outcomes than older children. CD4+ T cells, including T helper and regulatory T (Treg) cells, play a critical role in coordinating the immune response to pediatric pneumonia in murine models. We hypothesized that DNA methylation—a developmentally dynamic regulator of T cell identity and function—drives a unique CD4+ T cell program in neonates compared with juveniles exposed to lower respiratory tract *E. coli*.

Methods Neonatal (3–4 days) and juvenile (11–14 days) C57BL/6NJ mice received 2.8 million colony forming units of *E. coli* or PBS via aspiration. Lung tissue was harvested 48 hours later for CD4+ T cell isolation by magnetic bead pre-enrichment and fluorescence-activated cell sorting. RNA and genomic DNA were purified and subjected to transcriptional profiling (RNA-sequencing) and genome-wide DNA methylation profiling (modified reduced representation bisulfite sequencing). Differential gene expression and methylation analysis were performed using the R/Bioconductor packages edgeR and DSS as well as the SeqMonk platform with downstream analysis performed in R.

Results Neonates experienced higher mortality than juveniles. We identified 3,932 differentially expressed genes across the four groups using a q-value cutoff of 0.05 in an ANOVA-like test. Unbiased techniques revealed an attenuated lung CD4+ T cell transcriptional response to pneumonia among neonates compared with juveniles. In contrast to neonates, juveniles up-regulated a robust set of immune response genes, including

important pathway components of Th1, Th17, and Treg cells. DNA methylation profiling demonstrated 28,623 differentially methylated CpGs, which preferentially clustered around transcribed start sites and CpG islands. Association analysis revealed that gene promoter methylation and gene expression carried an inverse correlation. Based on these data, we performed methylation difference filtering for promoter CpGs with a methylation directionality (hyper- or hypo-methylated by 25%) opposite to the corresponding gene expression directionality (down- or up-regulated) between groups. This process revealed 643 genes whose promoter methylation status passed the filter. Of these 643 genes, we identified important Th1, Th17, and Treg cell pathway components including *Tbx21*, *Ahr*, *Ikzf3*, and *Ikzf4*.

Conclusion Compared to juveniles, neonatal mice display poorer outcomes and a limited lung CD4⁺ T cell transcriptional response to pneumonia. DNA methylation within the promoters of a core set of T cell response genes is statistically likely to regulate the maladaptive gene expression pattern seen in neonates. Future work with pharmacologic and epigenetic editing tools may help uncover novel therapeutic pathways for pediatric pneumonia.

*A14 TIMING DIFFERENCES IN DIAGNOSIS BETWEEN SOFA, QSOFA, AND SIRS CRITERIA IN A LARGE ICU COHORT

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Objective 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) and quick SOFA (qSOFA) scores as part of the diagnostic criteria of sepsis. Given the complexity of the SOFA score and the lack of specificity of the qSOFA score, there has been concern that adherence to these modalities could result in a delay in recognition of sepsis. Our research contrasts the use of these three scores to diagnosed sepsis in an ICU population.

Method 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, qSOFA score 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 55 years. Greater than fifty percent of patients were African-American or Hispanic. The most common source of infection was pneumonia. On average, it took 58.3 minutes to meet sepsis by SIRS, 273.7 minutes by qSOFA, and 145.4 minutes by SOFA. The average SOFA score was 7.2. The average length of stay was 12.1 days, with an average of 4.7 days in the ICU.

Conclusion In this large, ethnically diverse cohort of septic patients admitted to the ICU, Sepsis-2 criteria for diagnosing sepsis outperformed both the qSOFA and SOFA scores. Given the association between early antibiotic administration and mortality, early recognition of sepsis with Sepsis-2 criteria may still be useful in some settings. This timing difference is an important consideration in future research.

A15 GROUP V SECRETORY PHOSPHOLIPASE A₂ MEDIATES MRSA-INDUCED ENDOTHELIAL PERMEABILITY AND ACUTE LUNG INJURY

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Objective Group V phospholipase A₂ (gVPLA₂) is a secretory enzyme that hydrolyzes membrane phospholipids and initiates eicosanoid biosynthesis. Prior work indicates that it is a critical messenger involved in induction of airway hyperresponsiveness, airway inflammation, and acute lung injury (ALI) caused by LPS or mechanical ventilation. In this study we explored the role of gVPLA₂ in lung endothelial (EC) dysfunction and ALI induced by the clinically relevant stimulus, methicillin-resistant *Staph aureus* bacteria (MRSA).

Method Human pulmonary artery lung microvascular endothelial cells (HPAEC or HLMVEC) were cultured and challenged with heat-killed MRSA ($1-2 \times 10^8$ CFU). Barrier function was determined by transendothelial resistance (TER). LY311727 sPLA₂ inhibitor or monoclonal Ab against gVPLA₂ was used to determine the effects of gVPLA₂ activity. Co-culture studies employing HLMVEC and HCl H441 human lung epithelial cell line were used to assess the permeability effects of MRSA and gVPLA₂. In vivo, gVPLA₂ knockout (KO) mice were used to assess effects on live MRSA-induced ALI ($0.5-2 \times 10^8$ CFU MRSA, IT). ACE antibody-linked liposomes (ACE-NC) were used to overexpress gVPLA₂ in lung EC in gVPLA₂ KO mice. Multiple indices of ALI (BAL protein, etc) were collected 18 hours after MRSA.

Results Heat-killed MRSA induces lung EC permeability in a dose-dependent fashion that is partially reversed by gVPLA₂ inhibition. Similar effects of gVPLA₂ inhibition were observed in human lung EC-epithelial co-culture studies of permeability induced by MRSA. In vivo, gVPLA₂ KO mice were significantly protected against ALI induced by live MRSA. Restoration of gVPLA₂ expression in the lung EC of gVPLA₂ KO mice by ACE-NC reverses the protective effects observed in these mice after MRSA.

Conclusion These results indicate that gVPLA₂ plays a critical functional role in mediating lung EC permeability and ALI induced by MRSA. This work supports a potential therapeutic benefit of inhibiting gVPLA₂ in ALI/ARDS caused by MRSA.

A27 MRSA INDUCES EPIGENETIC CHANGES AND PERMEABILITY IN LUNG ENDOTHELIUM THAT ARE ATTENUATED BY FTY720 S-PHOSPHONATE

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Objective Effective therapies are needed to preserve the critical lung vascular barrier that is disrupted during acute inflammatory diseases such as ARDS. Prior work has demonstrated that FTY720 S-phosphonate (Tysiponate/Tys), an analog of sphingosine 1-phosphate (S1P) and FTY720, is protective against barrier disruption in vitro and in the LPS- and bleomycin-induced models of mouse ALI. An important mechanism by which Tys decreases permeability is by preserving expression of the barrier promoting S1P receptor 1 (S1PR1). In this report, we characterize the epigenetic and inflammatory effects on endothelium caused by methicillin-resistant Staph aureus bacteria (MRSA), an important and clinically relevant stimulus, and Tys.

Method Human pulmonary artery endothelial cells (EC) were used for experiments. Chromatin immunoprecipitation (ChIP) assay, ELISA, immunofluorescence microscopy and western blotting were performed per standard protocols. Heat-killed MRSA (HK-MRSA) were used for EC barrier disruption/injury.

Results Tys demonstrated significant barrier protective effects in EC after HK-MRSA injury, or after exposure to alpha hemolysin toxin, a potent staph aureus product. HK-MRSA induced significant disappearance of VE-Cadherin and ZO-1 proteins from junctional locations within EC, which were reversed by Tys. In addition, HK-MRSA significantly induced release of IL-6, IL-8 and TNF- α , which was inhibited by the S1PR2 inhibitor JTE-013. HK-MRSA induced epigenetic changes in lung EC, including methylation of histone H3 lysine 4, which was reversed by Tys. Exposure to HK-MRSA and Tys significantly increased acetylation of histone H3 lysine 27. Tys and S1P also significantly increased acetylation of the actin-binding protein and important EC barrier regulator cortactin. HK-MRSA and p-FTY markedly inhibited HDAC activity, while Tys treatment had no significant effect. By CHIP analysis, HK-MRSA significantly enriched H3K9Ac in the NFAT binding region of the S1PR1 promoter, which was significantly inhibited by Tys treatment. Furthermore, HK-MRSA increased the expression of S1PR1 mRNA and protein, which was partially inhibited by p-FTY but not Tys.

Conclusion MRSA induces significant barrier disruption, cytokine release, and epigenetic changes in cultured lung EC. Tys potently reverses many of these injurious effects. These results provide additional mechanistic insights into the protective effects of Tys on lung EC function during inflammatory stimuli.

A28

SYNDECAN-1 MEDIATES LUNG ENDOTHELIAL CELL INFLAMMATORY SIGNALING BY INTEGRIN β 4.

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Rationale We previously reported lung endothelial cell (EC) inflammatory responses are mediated by integrin β 4 (ITGB4). In addition, we identified decreased ITGB4 phosphorylation as a key vascular-protective effect of simvastatin, an HMG CoA-reductase inhibitor. To explore the mechanisms involved in regulating ITGB4 phosphorylation we investigated the role of syndecan-1 (SDC1), a cell-surface proteoglycan that binds the ITGB4 cytoplasmic domain, is expressed by EC, and has been implicated as a mediator of ALI. Accordingly, we hypothesized that syndecan-1 mediates ITGB4 signaling associated with vascular inflammation.

Methods Human pulmonary artery EC were treated with simvastatin (5 μ M, 16 h) and lysates were used for Western blotting for ITGB4 and SDC1 or for immunoprecipitation with an ITGB4 antibody followed by Western blotting for SDC1. To investigate a functional link between SDC1 and inflammatory responses regulated by ITGB4 EC were transfected with siRNA specific for SDC1 (siSDC1, 100 mM, 3 d) or non-specific siRNA prior to excessive cyclic stretch (18% elongation, 2 h) followed by immunoprecipitation of ITGB4 and Western blotting with a phospho-tyrosine antibody as well as measurements of inflammatory cytokines, IL-6 and IL-8, in the media. Finally, we utilized SDC1 C-terminal peptide, a competitive inhibitor of ITGB4-SDC1 interaction to assess effects of SDC1 inhibition on LPS-induced ITGB4 phosphorylation and EC barrier function. EC were pretreated with the competitive peptide (30 μ M) or control peptide 30 min prior to LPS (1 μ g/ml, 1 h) followed by Western blotting for total and p-ITGB4. Transendothelial electrical resistance (TER) measurements of EC under similar conditions were performed to assess barrier effects.

Results Simvastatin treatment of EC was associated with dramatically increased ITGB4 and markedly decreased SDC1 expression levels. Simvastatin treatment also abrogated the strong association of SDC-1 with ITGB4 that was present under basal conditions. Moreover, SDC1 silencing significantly decreased ITGB4 phosphorylation after cyclic stretch and attenuated CS-induced expression of IL-6 and IL-8. Finally, LPS-induced ITGB4 phosphorylation and EC barrier disruption measured by TER were both significantly attenuated by inhibition of the ITGB4-SDC1 interaction with the SDC-1 competitive inhibitor.

Conclusions These studies implicate SDC1 as a critical mediator of ITGB4 signaling in lung EC inflammatory responses. Inhibition or knockdown of SDC1 is associated with decreased ITGB4 phosphorylation and an attenuation of agonist-induced inflammatory cytokine expression levels and EC barrier disruption. Our findings suggest SDC1 may serve as a novel target to mitigate lung vascular inflammatory responses in a variety of clinical contexts.

*A29

ABSTRACT WITHDRAWN

*A30

ELUCIDATING THE ROLE OF PHOSPHOLIPASE D IN IDIOPATHIC PULMONARY FIBROSIS AND HOW IT MEDIATES EPITHELIAL INJURY AND APOPTOSIS

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Objective Idiopathic pulmonary fibrosis (IPF) is a chronic and ultimately fatal pulmonary disease characterized by a progressive decline in lung function, leading to respiratory failure and ultimately death. This is due to dysregulated repair of the epithelial injury in the lung, which involves epithelial apoptosis and epithelial to mesenchymal transition (EMT), thereby leading to the deposition of the extracellular matrix in the lung. This study would lead to delineation of the phospholipase D signaling mechanism in IPF to identify new therapeutic targets.

Method To define the role of PLD2 in murine model of pulmonary fibrosis, PLD2 was down-regulated in mice by genetic

manipulation or activity was inhibited by specific validated inhibitors or by over-expression of dominant negative PLD2 mutant. To elucidate the role of PLD signaling in epithelial injury, Beas2B cells were pre-incubated with either PLD1 (VU0155069- 250nM), PLD2 (VU0364739- 500nM) or PLD1 +PLD2 inhibitors prior to bleomycin challenge.

Results Genetic deletion of PLD2 in mice conferred protection against bleomycin induced PF. *PLD2*^{-/-} mice exhibited less inflammation on day 7 and less pulmonary fibrosis on day 21 post-bleomycin challenge compared to wild type mice. GSK3 β and Akt are known to be involved in crucial signaling pathways that regulate cell death and survival. Bleomycin challenge enhanced phosphorylation of GSK3 β at Ser9 leading to its inactivation, which was reversed by inhibition of PLD1 and PLD2. Also, activated Akt as shown by enhanced phosphorylation at Ser473 was reversed upon PLD1 and PLD2 inhibition. Inhibition of PLD1 and PLD2 was necessary to attenuate bleomycin mediated apoptosis of Beas2B cells as evidenced by cleavage of Caspase-3 and PARP.

Conclusion The results presented here suggest that PLD regulates bleomycin-induced pulmonary fibrosis by modulating apoptosis and EMT via Akt/GSK3 β signaling in the epithelial cells, and targeting PLD in epithelial cells may be beneficial against IPF. This work is supported by National Institutes of Health grant P01 HL 98050 to VN.

A47

MECHANOTRANSDUCTION IN ALVEOLAR MACROPHAGES CONTRIBUTES TO LUNG INJURY BY MODULATING PRO-INFLAMMATORY CYTOKINE SECRETION AND MIR-146A EXPRESSION

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Rationale The acute respiratory distress syndrome 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 in a phenomenon called ventilator induced lung injury (VILI). VILI is characterized by the release of pro-inflammatory cytokines and blood-air barrier disruption. Alveolar macrophages (AMs) are critical regulators of the innate immune response and may therefore contribute to the pro-inflammatory response during MV. Although alveolar macrophages (AMs) are critical regulators of the innate immune response, the mechanotransduction

mechanisms by which AMs contribute to VILI are not well understood. In this study we characterize the response of primary human AMs to mechanical forces and identify a novel mechanosensitive microRNA. When overexpressed, this microRNA mitigates the force-induced inflammatory response in AMs. We also observed similar changes in miRNA expression using an *in vivo* model of VILI.

Methods Primary human AMs were isolated via bronchoalveolar lavage (BAL) from lungs deemed unsuitable for transplantation from the Lifeline of Ohio procurement agency. For pressure experiments, AMs were seeded on 0.4 μ m pore transwell permeable supports within 6-well culture plates and subjected to oscillatory pressure for 16 h at 0.2 Hz and 20 cm-H₂O. Following the experiment, cells were harvested and RNA extracted, and media cytokine levels were determined via ELISA. RNA was extracted and analyzed with RT-PCR, cytokine levels were determined via ELISA. C57Bl6/J wild-type mice were ventilated for 4 h with 12mL/kg TV and PEEP=0 cm H₂O to induce VILI. AM depletion was achieved via delivery of liposomal clodronate 24–48 h prior to ventilation. Murine AMs were isolated from BAL following ventilation.

Results *In vitro*, AMs exposed to oscillatory pressure exhibited increased pro-inflammatory cytokine (IL-8) secretion (figure 1B) and increased expression of anti-inflammatory miR-146a (figure 1A). Although pressure caused an increased in both cytokine and miR-146a expression, pressure-induced expression of miR-146a was modest and likely an insufficient compensatory response by cells to reduce force-induced inflammation. To test this hypothesis, we overexpressed miR-146a by ~100-fold and exposed these cells to transmural pressure. As shown in figure 1B, overexpressing miR-146a in AMs completely mitigated the force induced response (miR + pressure). In an *in vivo* model of VILI, miR-146a expression was increased in AMs isolated from the BAL of injuriously ventilated mice and expression decreased when AMs were depleted prior to ventilation (figure 1C). AM depletion *in vivo* also decreased pro-inflammatory cytokine secretion following ventilation.

Conclusion These results indicate that AMs play a role in the mechanotransduction processes responsible for VILI and that miR-146a can regulate these mechanotransduction events. This miRNA may provide a point of therapeutic intervention in mitigating the pro-inflammatory cytokine secretion that occurs during VILI. Ongoing *in vitro* studies are investigating the molecular mechanisms of miR-146a regulation in AMs and *in vivo* studies are using miR-146a knock out mice to further demonstrate the role miR-146a plays in VILI.

Abstract A47 Figure 1 A. MiR-146a expression in human AMs following 16 h oscillatory pressure. B. ILB secretion after application of pressure and overexpression of MiR-146a. C. MiR-146a expression *in vivo* following ventilation with and without AM depletion

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A48

GROUP V PHOSPHOLIPASE A₂ (GVPLA₂) MEDIATES RESPONSES TO METHICILLIN-RESISTANT STAPH AUREUS (MRSA) IN LUNG ENDOTHELIUM

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Rationale Infections are the most common cause of the acute respiratory distress syndrome (ARDS), which is characterized by inflammatory disruption of the alveolar-vascular barrier secondary to activation of the lung endothelium cells (EC). Previous work has demonstrated that the 14-kDa mammalian enzyme group V phospholipase A₂ (gVPLA₂) is activated after LPS and increases pulmonary EC permeability directly through action as a membrane hydrolytic agent. In the current study we characterized the functional role of gVPLA₂ expression in mediating lung endothelial responses to methicillin-resistant Staph aureus (MRSA), an important and clinically relevant stimulus.

Methods Human pulmonary artery or microvascular lung EC (HPAEC or HLMVEC) were cultured and exposed to heat-killed MRSA (1–3 × 10⁸ CFU). In some experiments, EC also were treated with LY 311727 (50mM), a specific group II sPLA₂ small molecule inhibitor, either pre or post MRSA exposure. Barrier function was determined by transendothelial resistance (TER) using the ECIS assay, as well as labeled dextran transwell permeability. Cytokine release was determined by ELISA. Expression of gVPLA₂ was determined by RT-PCR. Mouse pulmonary vascular EC (mPVEC) were isolated from gVPLA₂ KO and C57/BL6 WT mice, sorted by flow cytometry, and then passaged several times until sufficient numbers were obtained for ECIS studies.

Results MRSA significantly increases gVPLA₂ expression in HPAEC within one hour as measured by RT-PCR. MRSA induces IL-8 secretion from HLMVEC, which is attenuated by LY 311727. Heat-killed MRSA significantly increases permeability in human lung EC in a dose-dependent fashion. LY311727 attenuates these effects after either pre or post treatment. In general, isolated mPVEC required substantially higher concentrations of thrombin, LPS, or HK-MRSA to increase permeability than needed for cultured human lung EC. mPVEC isolated from gVPLA₂ KO mice exhibited less permeability after these barrier-disrupting agents than mPVEC from WT mice. **CONCLUSION:** These results demonstrate that gVPLA₂ is upregulated in lung EC by MRSA and participates in mediating inflammatory and permeability effects caused by this clinically relevant stimulus. Strategies targeting this enzyme may have therapeutic potential in ARDS caused by MRSA infection.

A49

SIMVASTATIN UPREGULATES ENDOTHELIAL CELL INTEGRIN B4 EXPRESSION BY PROMOTER ACTIVATION AND EPIGENETIC MODIFICATION

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Objective We previously reported that protection conferred by simvastatin in murine acute lung injury (ALI) is mediated by the upregulation of endothelial cell integrin β4 (ITGB4). However, the mechanisms underlying these effects are unknown. To explore this further, we investigated ITGB4 promoter regulation and epigenetic modifications by simvastatin.

Method Human pulmonary artery EC were transfected with luciferase reporter promoter deletion constructs prior to treatment with simvastatin (5 μM) to identify specific 5' regions within the ITGB4 gene responsible for statin-mediated ITGB4 expression. Regions of interest were then subjected to chromatin immunoprecipitation (ChIP) to identify candidate transcription factors (TFs). Subsequently, EC were transfected with siRNA specific for TFs of interest prior to simvastatin treatment and Western blotting for ITGB4. In separate experiments, EC were pretreated with either a histone deacetylation inhibitor, trichostatin (TSA, 5 μM, 2 h), or a histone methylation inhibitor, 5-aza-2'-deoxycytidine (5-Aza, 5 μM, 2 h) prior to treatment with simvastatin (5 μM, 16 h) followed by RT-PCR and Western blotting for ITGB4 mRNA and protein levels, respectively. Finally, ChIP-qPCR assays were conducted to assess simvastatin effects on ITGB4 promoter methylation as well as specific histone modifications including H₃K₉ acetylation and H₃K₄ trimethylation associated with transcription activation.

Results ChIP assays identified simvastatin-induced NF-κB binding to the ITGB4 promoter. Subsequently, we confirmed that silencing of NF-κB2 specifically inhibits ITGB4 upregulation by simvastatin. Using CHIP-qPCR, we identified H3K9 acetylation and H3K4 trimethylation of ITGB4 promoter target regions by simvastatin. In addition, Inhibition of histone deacetylation (TSA) resulted in increased simvastatin-induced ITGB4 expression while inhibition of histone methylation (5-Aza) was associated with increased ITGB4 expression in response to simvastatin.

Conclusion These data confirm ITGB4 upregulation by simvastatin is mediated by both NF-κB activation of the ITGB4 promoter as well as specific epigenetic changes including DNA methylation and histone modifications. Our findings identify mechanisms of ITGB4 expression regulation which may ultimately lead to novel therapeutic strategies in patients with ALI.

A50

CORTACTIN DEFICIENCY ALTERS LUNG MECHANICS DURING INFLAMMATORY LUNG INJURY

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Objective The pulmonary endothelial barrier is disrupted during inflammatory lung injury and results accumulation of protein rich edema fluid in the alveolar and interstitial spaces. This leads to alterations in gas exchange and lung mechanics characteristic the acute respiratory distress syndrome (ARDS). Peripheral cytoskeletal structures and rearrangements leading to cell membrane lamellipodia are crucial to the maintenance and recovery of endothelial barrier integrity. We have previously identified a critical role for the actin-binding protein cortactin in regulating peripheral cytoskeletal dynamics. In the current study we characterize the effect of cortactin deficiency on lung mechanics in a murine model of lung injury.

Additionally, we investigate the subcellular localization of cortactin under barrier enhancing and disruptive conditions in vitro.

Method Cortactin heterozygote knockout mice ($\pm$) or their wild type (WT) C57/BL6 littermates were subjected to mechanical ventilation 18 hours following administration of intratracheal LPS (5mg/kg). Lung mechanics were measured using the flexiVentTM (Scireq) small animal ventilator. In vitro studies were performed using cultured human pulmonary artery endothelial cells. Subcellular fractionations were taken under control, barrier enhancing or barrier disruptive conditions and relative protein localization determined by western blot.

Results Baseline lung compliance was similar between WT and cortactin ($\pm$) animals (0.036 ± 0.002 mL/cmH₂O vs 0.033 ± 0.001 mL/cmH₂O). Following intratracheal LPS (5mg/kg $\times$ 18 hrs) compliance was significantly reduced in cortactin ($\pm$) mice (0.0239 ± 0.001 mL/cmH₂O) compared to WT (0.0296 ± 0.001 mL/cmH₂O; $p=0.02$) consistent with previous studies demonstrating increased vascular leak after inflammatory injury in cortactin ($\pm$) animals. Analysis of pressure-volume (PV) loops revealed an increased PV loop area in WT mice compared to cortactin heterozygotes (5.36 ± 0.78 vs 3.93 ± 0.56) suggestive of a decrease in recruitable lung among cortactin deficient animals. In vitro treatment of lung endothelial cells with sphingosine-1-phosphate (1 μ M $\times$ 15 min) resulted in a $37\% \pm 7\%$ reduction and a $17\% \pm 4\%$ increase of cortactin in cell membrane and cytoskeletal fractions respectively compared to control ($p=0.04$). No significant change in cortactin membrane localization was found after thrombin (1 U/ml $\times$ 15 min).

Conclusion These data support a protective role for cortactin in the pathophysiology of inflammatory lung injury through regulation of endothelial cell cytoskeletal and membrane dynamics.

A51 DYSREGULATED METABOLISM IN INTERSTITIAL MACROPHAGES MAY CONTRIBUTE TO THROMBOSPONDIN-1 MEDIATED HYPOXIC PULMONARY HYPERTENSION

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Background Hypoxia-induced pulmonary hypertension (PH) is one of the most common causes of cardiovascular disease. The pathobiology of hypoxic PH is complex. Increased density of monocytes and macrophages within the perivascular/adventitial space and metabolic reprogramming due to altered substrate uptake has been implicated in the activation of macrophages. In addition, TGF- β signaling has been identified as necessary and sufficient for many forms of pulmonary vascular disease, including hypoxia-PH. Hif2 α stabilization regulates thrombospondin-1 (TSP-1), and TSP-1 is a known activator of TGF- β . However, it has not been determined exactly which cell populations produce TSP-1, or the mechanisms that result in stabilization of Hif2 α in this compartment specifically which promotes TSP-1-mediated hypoxic PH. Therefore, we hypothesized that under hypoxic conditions a metabolic dysfunction in recruited interstitial macrophages may result in TSP-1 expression and PH.

Methods and results Our preliminary data using flow cytometry on whole lung digest and single cell dispersion in hypoxia exposed 6–8 weeks old female C57BL/6J mice showed a new population of cells which express intracellular TSP-1⁺ compared to control (normoxic) mice. These TSP-1⁺ cells based on cell surface markers were consistent with interstitial macrophages (CD64⁺ CD11b⁺ CD11c⁺ Ly6^{int} MHCII^{lo}). Interestingly, these interstitial macrophages were circulating prior to hypoxia exposure as intraperitoneal clodronate liposomes administered prior to hypoxia resulted in depletion of these cells. TSP-1^{-/-} bone marrow protects against hypoxia-PH and thus suggests that these cells are bone marrow derived. Interestingly, flow sorting of these cells followed by RNA extraction and RT-PCR showed suppression of multiple glycolysis enzymes.

Conclusions Recruited interstitial macrophages could be the major source of TSP-1 and decreased glucose uptake and oxidation may contribute to the phenotype of these pathologic cells that drives hypoxia-induced vascular diseases.

B26 MYD88 REGULATES AIRWAY MUCINS MUC5AC AND MUC5B IN A MODEL OF AGRICULTURAL ORGANIC DUST EXPOSURE RELATED CHRONIC BRONCHITIS

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Objective Organic dust exposure (ODE) contains bacterial cell wall ligands that activate the innate immune system. It leads to chronic bronchitis and asthma symptoms in agricultural workers. MyD88 is central to agriculture ODE exposure-induced lung inflammation, however its role in mucin regulation is unknown. We hypothesized that ODE increases airway mucins and that this response is MyD88-dependent.

Methods Using an established murine model, C57BL/6 wild type (WT) and MyD88 knock-out (KO) mice were treated with intranasal inhalation of saline or ODE daily for 1 week. Muc5ac was marked by lectin UEA-1 which is up-regulated during inflammation and Muc5b was localized by a mouse monoclonal antibody.

Results By immunostaining of lung tissues, ODE exposure increased Muc5ac, and to a lesser extent, Muc5b levels. In comparison to WT, ODE treated MyD88 KO mice demonstrated increased Muc5ac and Muc5b staining area per secretory cell and number of positive secretory cells per airway. Muc5ac and Muc5b airway staining were also increased in saline treated and untreated MyD88 KO mice as compared to WT (figure 1 A-D). Immunoblots for lectin UEA-1 and Muc5b confirmed the enhanced Muc5ac and Muc5b levels from MyD88KO mouse lung homogenates (figure 1 E-F). The WT and MyD88 KO mice treated with ODE and subsequently challenged with nebulized ATP demonstrated a normative decrease in intracellular airway mucins. ODE-induced inflammation increased Muc5ac expression by qPCR in WT and MyD88 KO mouse lung homogenates. The increase in mucin staining and expression in MyD88 KO mice was not explained by neutrophil-mediated inflammation as ODE-induced neutrophil influx, neutrophil elastase levels, and IL-17A were reduced in MyD88 KO mice as compared to WT. Lastly, the ODE mediated in UEA-1 staining was enhanced along with reduced apical mucin secretion in MyD88 KO

Abstract B26 Figure 1

derived mouse tracheal epithelial cells (mTEC) suggesting reduced baseline mucin secretion.

Conclusion Bacterial wall components from ODE trigger a neutrophil-mediated airway inflammation and mucous cell metaplasia. MYD88 signaling is required for this neutrophil-mediated response. However, deletion of MyD88 results in enhanced production and secretion of Muc5ac and Muc5b. This suggests that MYD88 is required to properly regulate the mucin responses following ODE mediated-airway inflammation.

B27 ENDOTHELIAL GROUP V PHOSPHOLIPASE A₂ (GVPLA₂) MEDIATES ACUTE LUNG INJURY CAUSED BY METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA) IN MICE

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Introduction Prior work indicates that the 14-kDa inflammatory secretory phospholipase gVPLA₂ is involved in acute lung injury (ALI) pathogenesis induced by lipopolysaccharide (LPS) in mice. In the current study we characterized the role of gVPLA₂ in ALI caused by MRSA, an important and more clinically relevant stimulus.

Methods 8–12 week old, male homozygous gVPLA₂ knockout (gVPLA₂ KO) mice and C57B6 (B6) as wild type (WT) control were used. Liposomes containing gVPLA₂ expression or

control plasmid were made under sterile conditions and administrated (10mg/kg) to mice by intravenous (IV) retro-orbital injection. The angiotensin converting enzyme (ACE) antibody was conjugated to the liposomes to target the pulmonary vasculature selectively. After 24 hours, mice were challenged with live MRSA (Wild-type USA300 strain) intratracheally (IT) 0.75 × 10⁸ CFU and then allowed to recover for 18 hours before multiple lung injury indices were determined. Bronchoalveolar lavage (BAL) protein and total white blood cells (WBC) were determined.

Results IT MRSA in mice causes a significant increase in BAL gVPLA₂ levels, total BAL protein, and total WBC and neutrophil levels compared to PBS control (18 hours). Mice genetically deficient in gVPLA₂ (KO) receiving control liposomes are significantly protected. In gVPLA₂ KO mice in which liposomes specifically overexpress gVPLA₂ in lung endothelium, BAL protein levels are significantly increased (from 765 ± 267 µg/ml in control liposome to 1290 ± 278 µg/ml in PLA₂ liposome) by 69% (p < 0.05), BAL total WBC recruitment (from 1.1925 × 10⁶ cell/ml in control liposome to 1.815 × 10⁶ cells/ml in PLA₂ liposome) by 52% (p < 0.05). No difference was observed between gVPLA₂ KO with gVPLA₂ liposome and the WT MRSA control.

Conclusion These results demonstrate that gVPLA₂ KO are protected from MRSA-induced ALI, but 'add back' experiments in which gVPLA₂ expression is reconstituted in lung endothelium by liposomes eliminates this protection. Thus endothelial gVPLA₂ regulates ALI caused by MRSA model in mice.

B28 PULMONARY FUNCTION TESTING AS A SCREENING TOOL TO PREDICT INTERSTITIAL LUNG DISEASE

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Objective Interstitial lung disease (ILD) is a category of diffuse parenchymal lung disorders that develops through inflammatory, fibrotic and immunologic pathways and often results in irreversible pulmonary fibrosis. Symptoms are usually non-specific and many times will result in misdiagnosis and delays in appropriate care. Pulmonary function test (PFT) and Chest computed tomography (CT) are two essential tests that are used for diagnosing and monitoring ILD. Since they are widely available and easily accessible, each can be optimal for early ILD detection. The objective of this study is to create and validate an ILD prediction tool, using PFT and Chest CT, that allows early detection of ILD and avoids diagnostic and therapeutic delays in patient care.

Methods Clinical and pulmonary function testing data were extracted from the electronic medical record and chest CTs were reviewed by two chest radiologists. ILD was considered present when non-dependent sub-pleural reticular opacities were observed. Exploratory analysis using logistic regression was conducted to identify clinical and PFT predictors of ILD. A final, parsimonious multivariable model was chosen and included age, total lung capacity, forced expiratory volume in 1 second and diffusion capacity. Selected variables were categorized into ordinal strata with each increasing strata being assigned an increasing number of points. An aggregated ILD PFT score was developed and exploratory analysis conducted to identify optimal strata for test performance characteristic estimation.

Abstract B28 Figure 1

Results Of 668 patients who underwent PFT and CT chest within a six-month timeframe, 650 had complete PFT data and were included in the final analysis. ILD was identified in 130 (20%) patients. The ILD prediction score ranged from 0–9, with each increase in score corresponding to a nearly 2-fold increase in odds of having ILD (OR 1.94; 95% CI: 1.71 to 2.21; $p < 0.0001$). The receiver operator characteristic of the ILD prediction score was 0.8 (figure 1). A score of 3 or higher had a sensitivity and specificity of 0.87 and 0.48, respectively.

Conclusions This ILD prediction tool can effectively rule out ILD in patients presenting with classic ILD symptoms, but results in a high number of false positives. Further research is needed to improve upon these test performance characteristics.

B29 IMPAIRED HYPOXIC PULMONARY VASOCONSTRICTION CAUSE BY ACUTE LUNG INJURY IS MEDIATED THROUGH NUCLEAR FACTOR OF ACTIVATED T-CELLS IN PULMONARY ARTERY SMOOTH MUSCLE CELLS

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Objectives Hypoxic pulmonary vasoconstriction (HPV) is an important physiologic mechanism directing blood flow away from poorly ventilated regions of the lung in order to support adequate gas exchange and oxygenation. Impaired HPV has been implicated in multiple disease processes associated with hypoxemia and inflammation. Canonical transient receptor potential (TRPC) channels have been shown to play an important role in Ca^{2+} entry in pulmonary artery smooth muscle cells, a process central to modulating vascular tone. Nuclear factor of activated T-cells (NFAT) is a calcium-dependent transcription factor with emerging evidence to suggest an important role in inflammatory as well as respiratory disorders. We hypothesize that lipopolysaccharide (LPS)-induced lung inflammation activates NFATc3 leading to impaired HPV through downstream mechanisms which includes downregulated TRPC expression.

Methods Murine lung inflammation is induced by intratracheal instillation of LPS (1–2 mcg/gm body weight) and acute hypoxic pulmonary vasoconstriction is elicited by five minute challenges of 1% inspired oxygen tension using an isolated perfused mouse lung (IPL) preparation. Human pulmonary artery smooth muscle cells were used for *in vitro* experiments and lung injury was modeled using LPS treatment (10 ug/mL). Western blotting and real-time polymerase chain reaction was completed using whole murine lung lysates and human pulmonary artery smooth muscle cells.

Results LPS-induced lung inflammation significantly impairs HPV at 24 hours compared to sham (saline) treatment. In protein isolates from whole mouse lung lysates, LPS-induced lung inflammation is associated with significant increases NFATc3 protein expression at 24 hours which is prevented by pretreatment with a calcineurin inhibitor, cyclosporin A, at both 30 and 100 mg/kg. LPS-induced lung inflammation is associated with decreased mRNA expression of TRPC7, while other subtypes remain unchanged and this effect is prevented with cyclosporine A treatment. Nonspecific Inhibition of TRPC channels using either 2-Aminoethoxydiphenyl borate (2-APB) and pyrazole (Pyr3) significantly diminished hypoxic pulmonary vasoconstriction in an isolated perfused mouse lung model. Treatment of pulmonary artery smooth muscle cells with LPS increases expression of NFATc3 and is associated with decreased expression of TRPC7 confirming the importance of pulmonary artery smooth muscle in these findings.

Conclusion We conclude that LPS-induced lung inflammation impairs hypoxic pulmonary vasoconstriction in mice mediated through NFATc3. Inhibiting NFAT activation using cyclosporine A protected against impaired HPV and was associated with restored mRNA expression of TRPC7. The effects of LPS on

NFATc3 and TRPC7 were confirmed in human pulmonary artery smooth muscle cells as the likely predominant cell type affecting HPV. Ca^{2+} influx in pulmonary artery smooth muscle cells is essential to pulmonary vasoreactivity, therefore decreased TRPC expression seen after lung inflammation may be a major mechanism for impaired HPV during lung injury and targeting this signaling cascade could conceivably identify novel therapeutics.

B30 IDENTIFYING BARRIERS TO PHYSICAL ACTIVITY AMONG SEDENTARY AFRICAN AMERICAN WOMEN WITH ASTHMA

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Objective To identify key barriers to physical activity in African American women with asthma.

Methods Patients that had been seen at least once in the health system over the past 2 years and met the first 3 eligibility criteria (female sex, African American race and age 18–69) were randomly selected to be recruited through mailings. Women were invited to participate in a focus group session after successfully meeting the other 2 eligibility criteria: self-report of <150 min/week of moderate-vigorous physical activity and sub-optimally controlled persistent asthma based on Asthma Control Questionnaire (ACQ) ≥ 1.5 . Ninety-minute focus groups or interviews were conducted to assess barriers to PA, specifically walking. The focus group/interview guide was developed using the COM-B (Capability, Opportunity, Motivation-Behavior) model, designed to incorporate existing theories of behavior change and link a full range of intervention functions that can be effective in eliciting change in a specific target behavior. Potential barriers to PA were identified from the literature and surveys we conducted previously, and were mapped to the following COM-B components: psychological and physical capability, physical and social opportunity and reflective motivation. The questions in the focus group guide targeted these COM-B components and the specific constructs within each component. Audio transcripts of the sessions were examined for pre-conceived themes and then analyzed independently by two coders. Inter-coder reliability was assessed by a third qualitative expert. Descriptive statistics of demographic data was analyzed using R.

Results Eleven focus groups/interviews were held with a total of 20 sedentary African American women with sub-optimally controlled asthma. The focus group participants represented an obese (BMI: $37 \text{ kg/m}^2 \pm 11$), middle-aged (age: 46 years ± 15), low-income population with varying education levels, marital status and dependent-care responsibilities. Median ACQ score were found to be 2.5 ± 1.2 . All 20 women indicated that asthma was a barrier to engaging in PA. Many of the women felt that they did not have sufficient skills or knowledge on how to prevent and treat asthma symptoms during physical activity. Less than half of the women were aware of the benefits that physical activity had on asthma. Personal negative experiences with the effects of asthma that more frequently affect African American women strongly influenced many women's attitudes towards the danger of being physically active with asthma. Specifically, one-third of the women had someone close to them die from asthma, or had been intubated in the past for their asthma. A lack of

properly maintained sidewalks and walking paths were also identified as barriers to walking safety. Most women expressed the need for a support system for women living with asthma, and felt that this was a barrier to engaging in physical activity.

Conclusion We found that African American women were more likely to experience unique barriers to engaging in physical activity. These included a lack of knowledge of the benefits of physical activity for asthma, lack of areas to walk, lack of social support and negative beliefs of capability and consequences of engaging in physical activity with asthma. Obtaining and incorporating the input of a high-risk population, such as African American women with asthma, into a physical activity intervention designed to address their specific barriers to behavior change may ultimately have important implications for improving the standard of asthma care.

B55 NOVEL DRUG BASED THERAPY FOR TREATMENT OF VASCULAR LEAKAGE

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Objective Acute Respiratory Distress Syndrome (ARDS) is a devastating lung disease characterized by severe leakage of plasma proteins in the interstitium and migration of inflammatory cells into the alveolar space. This causes pulmonary insufficiency and eventually multisystem organ failure, morbidity and mortality. Despite recent advances in understanding the epidemiology and pathogenesis of ARDS, mortality due to ARDS remains unacceptably high. Therefore, there is a pressing need for novel strategies that will improve the clinical outcomes of this disease. We have demonstrated that knockout of Microtubule End Binding (EB) protein 3 in endothelial cells or inhibiting EB3 function with a 7-mer allosteric EB Inhibitory (EBIN) peptide significantly attenuated the effect of cytokine storm on lung microvasculature by reducing edema and lung injury in the experimental model of endotoxemia. To optimize physicochemical and biochemical properties of EBIN for future clinical studies we have employed rational design.

Method The binding affinity of EBIN analogs was assessed using Saturation Transfer Difference (STD) by Nuclear Magnetic Resonance (NMR) approach. The binding interfaces of the compounds to target protein were mapped by heteronuclear single quantum correlation (HSQC) NMR. The *in vitro* efficacy of the compounds in inhibiting specific protein-protein interaction was determined by competitive binding assay.

Results We have designed and tested sixty-one compounds, twenty-six of which demonstrating an affinity at least two-times higher than EBIN. Furthermore, the ^{15}N , ^{13}C , and ^2H stable isotope enriched sample of C-terminus of EB3 was prepared and utilized for sequential assignment of backbone resonances using a suite of standard NMR experiments. The obtained signal assignments are sufficient to define the binding interfaces between EB3 and the tested analogs. The HSQC-NMR experiments with selected analogs further indicated their binding to the sites that were remarkably similar to EBIN.

Conclusion These interactions have exerted a long-range effect on the EB3 structure. Our studies establish the workflow for rational drug design to target and allosterically modulate the protein structure and function.

C11 VENTILATOR MANAGEMENT IN ARDS: A SINGLE ACADEMIC CENTER EXPERIENCE

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Objective Acute respiratory distress syndrome (ARDS) is a severe consequence of infection or other inflammatory stimuli and is associated with significant morbidity and mortality. However, the underlying pathophysiology remains incompletely elucidated, which has hindered accurate diagnosis and effective treatment. As part of an ongoing study at our institution, we are collecting clinical information and blood samples from DNA, RNA and protein analysis in order to create a repository of ARDS and control patient samples that can aid in identifying potential ARDS biomarkers. The current study is an initial description of the clinical characteristics of the patients enrolled over a three-year period from 2010 to 2013. **Method** Our patient sample is a single center cohort comprised of 53 patients admitted to our medical intensive care unit between August 2010 and June 2013. Data obtained from a retrospective chart review of the subjects include age, reason for ICU admission, length of ICU stay, mortality, ventilator settings and other parameters.

Results The average age of the subjects in this cohort was 52 years. The average length of ICU stay was 10.7 days, and 17 of the subjects died during their ICU stay. Twenty seven of these subjects had ARDS, and the mortality among these ARDS subjects was 59%. The majority of these subjects with ARDS was concurrently diagnosed with either septic shock, acute pancreatitis, and/or decompensated liver cirrhosis. Of the 41 subjects in the total cohort requiring mechanical ventilation, the average duration of ventilation was 12.5 days. All of these subjects were maintained on volume control ventilation for at least part of their time spent intubated, and three of these subjects were also ventilated with airway pressure release ventilation. Among ARDS patients, 14 of 27 patients (52%) received a tidal volume of 6 mL/kg ideal body weight or less for some duration during their time intubated. The mortality rate among the ARDS subjects receiving low tidal volume ventilation was higher compared those not receiving low tidal volume ventilation (64% versus 46%).

Conclusion In this retrospective analysis of a medical ICU cohort from our institution, adherence to lung-protective ventilation with low tidal volumes was poor, consistent with recent observations made in the multicenter, multinational LUNG-SAFE study. These data will help identify areas of potential improvement in ARDS care and the barriers preventing optimal treatment of this devastating condition.

C12 REGULATION OF IL33 NUCLEOKINE FUNCTION IN COPD

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Objective IL-33 is an airway epithelial progenitor-derived factor that is central to the pathogenesis of chronic airway diseases asthma and COPD. This project aims to elucidate the cellular mechanism by which the IL-33 nuclear factor (nucleokine) is processed and released from airway progenitor cells to

signal as a cytokine and drive inflammation and mucus production.

Method Toward this goal, we have identified multiple IL-33 splice variants in COPD airway cells that exhibit altered expression, distinct cellular localization, and release behavior. These variants lack one or more exons within the N-terminal part of IL-33, which is hypothesized to include the nuclear localization sequence (NLS), chromatin interacting domain and putative cleavage site. To further investigate these transcripts we have developed airway cell lines stably expressing tagged versions of these variants that can be tracked by live-cell microscopy (mCherry/GFP) or immunoprecipitated (IP, FLAG/His).

Results Through these studies, we have found that IL-33 splice variants lacking combinations of exons 3, 4, and 5 exhibit distinct patterns of nucleo-cytoplasmic shuttling and cellular release from intact airway cells. Proteomic studies are in progress to determine the functional implications, including differences in protein and nucleic acid interactions for these variants that lead to altered cellular localization, processing and release from airway cells.

Conclusion Results obtained from this work will provide new insight to the function of this enigmatic cytokine and reveal novel approaches to therapeutically target this highly relevant system in chronic airway disease.

C24 ARTERIOVENOUS METABOLOMICS REVEALS INCREASED CEREBRAL METABOLITE CONSUMPTION IN A PORCINE MODEL OF HEMORRHAGIC SHOCK

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Objective Survivors of critical illness commonly experience acute brain dysfunction in the form of delirium, and chronic brain injury resulting in cognitive and affective disorders. The pathogenesis of these disorders is likely multifactorial, but poorly understood. Invasive brain monitoring has the potential to reveal both metabolic derangements and biomarkers of cellular breakdown to guide therapy, but cerebral oximetry and microdialysis are clinically reserved for patients with direct brain injury, usually from trauma or cardiac arrest. We therefore hypothesized that less invasive measurement of cerebral metabolism using metabolomic analysis of paired arterial and internal jugular blood samples in a porcine model of hemorrhagic shock would reveal limitations of metabolite delivery to the brain and spillage of brain injury markers into the venous cerebral circulation. We also sought to determine if central venous blood, which is readily accessible in critically ill patients, could serve as a surrogate readout of brain metabolism.

Method Swine were fasted overnight with free access to water. General anesthesia was induced, once animals were endotracheally intubated and instrumented, maintained with propofol. Hemorrhagic shock was induced by a combination of hindlimb soft tissue injury and computer controlled hemorrhage to a mean arterial pressure of 30–40 mmHg and oxygen debt of 80 mL/min. Swine were then resuscitated with auto-transfused citrated whole blood and normal saline. Paired internal jugular, mixed venous, and carotid artery blood samples were drawn at baseline, maximum oxygen debt, early resuscitation,

and 120 minutes post resuscitation. Whole heparinized blood was immediately frozen and later analyzed by quantitative ^1H -NMR spectroscopy.

Results Paired samples were collected from 3 swine. As expected, arterial lactate ($p<0.01$) and lactate/pyruvate ratio ($p<0.01$) increased from baseline to peak shock. Surprisingly, we did not observe release of products of anaerobic metabolism into the cerebral venous circulation. Rather, for multiple metabolites, arterial concentration rose in excess of venous concentration, indicating increased *extraction* during shock (multivariate PCA and Hotelling's T^2 $p=0.03$ with *post-hoc* $p<0.05$, $\text{FDR}<0.1$). While cerebral blood flow was not measured directly, under the conservative assumption that cerebral autoregulation was completely compromised and blood flow was proportional to cardiac output, we found that arteriovenous *consumption* of 3-hydroxybutyrate, hypoxanthine, lactate, and multiple amino acids including glutamate increased from baseline to peak shock. There was no correlation between metabolite levels in internal jugular and mixed venous blood.

Conclusion Hemorrhagic shock results in significant changes to the whole blood metabolome. Contrary to our hypothesis that shock would be associated with increased products of anaerobic glucose metabolism in the venous cerebral circulation due to ischemia, we found that shock was associated with increased consumption of amino acids, ketones, and lactate. Furthermore, these metabolomic changes were not evident by examining mixed venous blood, likely due to admixture from the hepatic circulation. Ongoing studies in a porcine model of sepsis and in critically ill patients will determine if arteriovenous differences in cerebral metabolites are associated with critical illness in the absence of severe hemodynamic compromise. Measuring arteriovenous metabolite differences may be a feasible approach for physiologic brain monitoring in critical illness.

C25 VIRTUAL TEACH-TO-GOALTM IS EFFECTIVE FOR TEACHING RESPIRATORY INHALER SKILLS BUT MAY BE LESS EFFECTIVE AMONG OLDER PATIENTS WITH COPD

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Objective While respiratory inhaler technique is a critical self-management skill, many patients fail to use inhalers correctly. Previous studies have shown that in-person Teach-To-Goal (TTG) improves inhaler skills for patients across health literacy levels. However, because inhaler technique skills require subsequent educational reinforcement, we developed a virtual TTGTM (V-TTGTM) intervention to be used across care and home settings. V-TTG was shown to be overall efficacious in reducing inhaler misuse among hospitalized patients. However, concerns about the influence of technology literacy by patients' age may impact the generalizability of these findings after discharge home. Patients with asthma tend to be, on average, younger than patients with COPD. This abstract evaluates whether V-TTG's effectiveness differed among patients with asthma versus COPD who are respectively, on average younger versus older patient populations.

Method This was a secondary analysis of a pre-post study of V-TTG. Patients were assessed for whether they had physician diagnosed asthma versus COPD. Means (paired T-tests) and

dichotomized misuse (yes vs. no; McNemars) analyses were performed.

Results Among 83 participants, the mean age was 48 years, 60% were female, 94% were black, and 51% completed at least high school. About a third had COPD (31%). Patients with COPD were significantly older in mean age (59 vs. 43 years, $p<0.001$). Overall, older patients were not more likely to misuse inhalers prior to education ($p=0.6$), but were more likely to misuse after education ($p=0.03$). Pre-V-TTG, most patients with COPD or asthma misused inhalers (79% and 87%, respectively; $p=0.4$). After V-TTGTM, there were no differences by diagnosis in proportions with misuse (27 vs 23%, $p=0.8$), however, when testing within diagnosis, older patients with COPD were more likely to misuse after education ($p=0.008$), though older age was not associated with asthma patients ($p=0.7$).

Conclusion This study demonstrates that a technology-based learning tool was as effective for inhaler skill instruction among patients of all ages, but that older patients with COPD had a significantly increased likelihood of ongoing inhaler misuse post V-TTG education. Future work is needed to understand if patient repeated use of V-TTG versus in-person education improves inhaler technique among patients with persistent inhaler misuse after one V-TTG educational session.

C46 PULMONARY ASPERGILLOMA DISGUISED AS ACTINOMYCES INFECTION IN A HEALED TUBERCULOUS CAVITARY LESION

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Introduction Aspergilloma or Pulmonary Mycetoma is a saprophytic infection of a diseased lung. It most commonly occurs within a previously healed lung lesion such as tuberculosis, lung abscess, bronchiectasis, lymphoma etc. The incidence of cavitary TB being affected by aspergilloma formation is 11–17%. The most common presenting symptoms are cough and hemoptysis. Actinomycosis on the other hand is a rare infection in immunocompetent individuals. Its association as superinfection in aspergilloma is not well documented.

Case report An immunocompetent HIV negative 30-year-old man originally from Cameroon presented with frank hemoptysis for the past one year. He was diagnosed with primary pulmonary tuberculosis (TB) back home in 2011 but he sought no treatment. He then moved to Korea in 2013 for schooling where he received full course of treatment. Later, he immigrated to USA in 2016 when he first developed off and on episodes of hemoptysis which resolved on their own. TB was ruled out by 3 negative AFB sputum analysis as well as negative TB PCR. Again, in May '17 he started having frank hemoptysis and cough. He was seen at clinic where CT scan of the chest was concerning for LUL cavitation. Additionally, patient had some diffuse areas of tree-in-bud appearance along with a small nodule in left lower lobe. Bronchoscopy was arranged which showed erythematous mucosa. BAL was done which was negative for malignant cells but grew Actinomyces for which he was started on Augmentin but his symptoms failed to resolve even after 3-month course of antibiotics. Next, fungal serology were ordered which confirmed *Aspergillus fumigatus* and finally he was started on Posaconazole.

His symptoms resolved for the next 6 months after which he underwent successful elective left upper lobectomy.

Conclusion Pulmonary mycetoma is a characteristic clinical-radiological lesion due to colonization of aspergillus or candida species in pre-existing pulmonary cavities following a number of diseases. Immunocompromised and high-risk individuals who present with hemoptysis, cough and a history of cavitary lung lesion warrant a diagnostic bronchoscopic evaluation to rule out grave infections prior to undergoing treatment of choice i.e. surgical excision. Serology and sputum analysis is critical for diagnosis as well.

Rheumatology/Immunology/Allergy

A02 PSEUDOVASCULITIS SECONDARY TO SCURVY

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Objective Recognize scurvy as a vasculitis imitator.

Method 56 year old Caucasian female without significant past medical history was admitted for fatigue, shortness of breath and hematochezia for one week duration. She had no known bleeding disorders, was not on any medications and denied taking any over the counter drugs. In hospital she developed a petechial rash to involve the lower extremities (Panel A). It extended over the next few days involving the abdomen and upper extremities. She received a total of five packed red blood cells (PRBC). She underwent colonoscopy and esophagogastroduodenoscopy that showed similar petechial lesions in the entire GI tract but no active site of GI bleeding was found (Panel B). Rheumatology was consulted for suspected systemic vasculitis with cutaneous and GI involvement. Skin biopsy was obtained and prednisone 60 mg was initiated empirically. Two days later the cutaneous petechial lesions worsened. She developed a large hematoma in her right thigh with minimal trauma and splinter hemorrhages under the fingernails (Panel C). Prednisone, which had provided no benefit, was discontinued. Further questioning revealed that she had been eating boiled and pureed food for years without fresh fruits or vegetables due to a subjective throat irritation from these foods.

Results Blood work found a hemoglobin of 5 g/dL and elevated CRP at 37.1 (normal: 0.0–8.0). Coagulation studies and platelet counts were normal. Evaluation for hereditary and acquired bleeding disorders were negative. Autoimmune work up returned with a negative antinuclear antibodies, extractable

nuclear antibodies, ANCA (including: myeloperoxidase, anti-proteinase 3 antibodies) and complement levels were normal. Her ascorbic acid (Vitamin C) serum level was severely low: less than 0.1 mg/dl (normal: 0.6–2).

Pathology results from skin, stomach and colonic mucosa were consistent with non-inflammatory purpura.

Conclusion She was started on vitamin C supplementations with significant improvement. The cutaneous lesions cleared and no recurrent episodes of GI bleed were reported at 3 month follow up. Scurvy can mimic vasculitis.

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B31 A RARE COMPLICATION OF LUPUS

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Purpose Diffuse alveolar hemorrhage (DAH) is a rare and deadly complication of Systemic Lupus Erythematosus (SLE).

Methods 41-year-old male with history of SLE and diabetes mellitus presenting with dyspnea for five months and hemoptysis for one month. He was treated as an outpatient for recurrent episodes of pneumonia with oral antibiotics. The treatment provided no relief and he slowly declined. Because of the lack of improvement, he came to the emergency department. Physical exam was without synovitis, but with oral ulcers (figure 1) and bilateral pulmonary rales. On admission to the hospital, he was initially treated with IV antibiotics for presumed pneumonia. Patient had progressive hypoxic respiratory failure and required orotracheal intubation and mechanical ventilation.

Results Laboratory studies showed mild leukocytosis, platelets of 77, hemoglobin of 10.3 g/dL, INR 1.2 (0.8–1.1), partial thromboplastin time (PTT) 46 (33.7–36.1 seconds).

ANA was 6.3U (<1.0 U), C3 70 mg/dL (75–175 mg/dL), C4 9 mg/dL (14–40 mg/dL), anti-cardiolipin antibody IgG 41.5 (<15 GPL), anti-B2GP IgG 35.7 u/mL (<9.5 u/mL). Urinalysis (UA) with microscopy showed 30 protein, 6 white blood cells, 74 red blood cells, three granular casts.

Negative anti-glomerular basement membrane antibodies, anti-smith, anti-dsDNA, anti-U1RNP, p-ANCA, c-ANCA, and MPO.

Abstract A02 Figure 1

Chest radiograph showed bilateral diffuse interstitial prominence (figure 2). CT chest showed diffuse ground glass and consolidative airspace opacities (figure 3).

Bronchoalveolar lavage (BAL) was with progressively hemorrhagic aliquots.

He was treated with pulse methylprednisolone, plasmapheresis, and cyclophosphamide with improvement of oxygenation and eventual extubation. He was discharged in stable condition.

Conclusion Classic presentation of diffuse alveolar hemorrhage (DAH) includes dyspnea, cough and hemoptysis. Although hemoptysis is present in only 44% of cases at the time of presentation.¹ Chest radiographs typically show bilateral central opacities with peripheral sparing. BAL shows progressively hemorrhagic aliquots, which is diagnostic of alveolar hemorrhage.

DAH is a rare complication of SLE. In a 10 year retrospective chart review of 510 patients admitted for SLE there were 19 episodes of DAH in 15 patients. Etiology of DAH in SLE is unclear. In 8/10 patients, pulmonary capillaritis was present on biopsy.²

DAH in SLE is considered life threatening. Mortality rates have been found to be about 50%.² Despite high mortality rates there are no randomized clinical trials for appropriate treatment. In

a systematic review of 174 episodes of DAH in SLE corticosteroids were almost universally used. Cyclophosphamide was used in 54% of cases, and plasmapheresis was used in 31% of cases.³

Our patient meets American College of Rheumatology classification criteria for SLE with the following 5/11 criteria: Positive ANA, granular casts on UA, thrombocytopenia, oral ulcers and abnormal serum levels of IgG anticardiolipin antibodies.

Abstract B31 Figure 1

Abstract B31 Figure 2

Abstract B31 Figure 3

DAH is a rare and deadly complication of SLE. It is important to keep DAH in the differential of SLE patients presenting with pulmonary symptoms because of its high mortality. Early and aggressive therapy should be implemented to improve outcome. To date, no randomized trials have been published on treatment. Pulse dose methylprednisolone, cyclophosphamide and plasmapheresis resulted in improvement in our patient.

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