Abstracts

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Cardiology/Cardiovascular Disease

A20 MITOCHONDRIAL CALCIUM AND REACTIVE OXYGEN SPECIES CONTROL CARDIAC FIBROBLAST PROLIFERATION
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Objective Cardiac fibroblasts (CFs) exhibit a hyper proliferative phenotype under pathophysiological conditions such as after cardiac injury and/or during repair in response to various stimuli in vivo including angiotensin II (Ang-II). Ang-II stimulation also promotes increased cellular oxidation in CFs, but it is still unclear whether the cellular oxidation and proliferation pathways interact and if so, whether the mitochondrial signaling pathway is involved in this mechanism. Therefore, in this study, we tested our hypothesis that mitochondrial Ca\(^{2+}\) (mtCa\(^{2+}\))-mediated reactive oxygen species (ROS) generation are served as upstream of activating CF proliferative pathway.

Method Primary CFs were enzymatically isolated from 1–2 day or 3-month-old rat hearts, plated, and used for experiments at passage 1. Dominant-negative mtCa\(^{2+}\)uniporter (MCU) and mitochondria-targeted biosensors are transiently transfected into CFs.

Results Using neonatal CFs, we confirmed that Ang-II stimulation induces Ca\(^{2+}\) release from the endoplasmic reticulum (ER). Concomitantly, elevation of cytosolic Ca\(^{2+}\) concentration by Ang-II increased mtCa\(^{2+}\) concentration, confirmed by live cell imaging with mitochondria matrix-targeted Ca\(^{2+}\) biosensor, mtRCamp1h. Moreover, this mtCa\(^{2+}\) uptake was blocked by the expression of a dominant-negative mutant of mtCa\(^{2+}\)uniporter (MCU). Using the adult CFs, we found that Ang-II stimulation also promotes mitochondrial fragmentation and increased mitochondrial superoxide assessed by expressing mitochondria matrix-targeted GFP and loading mitochondrial superoxide-sensitive dye MitoSox Red, respectively. Ang-II stimulation activates proliferative pathways including the ERK1/2-p38 MAPK pathway, which was abolished by the overexpression of dominant-negative MCU or the pretreatment of a mitochondria-targeted antioxidant, Mito-TEMPO.

Conclusion Mitochondrial ROS generation induced by mtCa\(^{2+}\) accumulation via MCU is required for the activation of Ang-II-mediated proliferative pathway in CFs. Thus, MCU-dependent mitochondrial ROS generation may serve as a potential therapeutic target for chronic fibrosis frequently observed in heart failure.

A38 MYOCARDIAL FIBROSIS AND PROGNOSIS IN HEART TRANSPLANT RECIPIENTS
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Abstract A38 Figure 1
Objective Myocardial fibrosis is a well-described histopathological feature in heart transplant recipients. Cardiovascular magnetic resonance imaging (CMR) using the late gadolinium enhancement (LGE) technique is the reference standard for the non-invasive detection of focal myocardial fibrosis. Whether myocardial fibrosis on LGE CMR is independently associated with long-term adverse cardiac outcomes in heart transplant recipients is unclear. We, therefore, sought to determine whether the presence and/or the extent of myocardial fibrosis on LGE CMR was independently associated with long-term adverse cardiac outcomes after heart transplantation.

Method Using a cohort of consecutive heart transplant recipients that underwent LGE CMR, we first determined the prevalence and the patterns of myocardial fibrosis. Next, using Kaplan-Meier and Cox proportional hazards regression analyses, we analyzed associations between myocardial fibrosis and a primary endpoint of major adverse cardiac events (MACE): cardiac death, retransplantation, non-fatal myocardial infarction, coronary revascularization, and heart failure hospitalization.

Results One hundred and fifty-two heart transplant recipients (age, 54±15 years; 29% women; 5.0±5.4 years after heart transplantation) were included. Myocardial fibrosis was present in 18% (37% infarct pattern, 41% non-infarct pattern, and 22% both). Its prevalence was positively associated with cardiac allograft vasculopathy (CAV) grade. Over a median follow-up of 2.6 years, 44 heart transplant recipients (28.9%) experienced MACE. Myocardial fibrosis independently predicted MACE (hazard ratio [HR], 2.52; 95% CI 1.29–4.93; p=0.007) after adjustment for CAV, left ventricular ejection fraction (LVEF), and indexed right ventricular end-diastolic volume (RVEDVI). Every 1% increase in myocardial fibrosis was independently associated with 3% higher hazard for MACE (HR, 1.05; 95% CI, 1.02–1.09; p=0.005). Inclusion of myocardial fibrosis in a model with CAV, LVEF and RVEDVI resulted in a significant improvement in model fit, suggesting incremental prognostic value.

Conclusion In heart transplant recipients, myocardial fibrosis is identified on LGE CMR in 18%. Both the presence and extent of myocardial fibrosis are independently associated with the long-term risk of MACE.

A39 NOVEL PEPTIDE B7–33 AND RELAXIN HORMONES PROTECT CYTOTROPHOBLASTS FROM PREECLAMPSIA PHENOTYPE

Objective Preeclampsia (PreE) is a hypertensive pregnancy disorder, which occurs in approximately 10% of all pregnancies. Recently, a digitalis-like factor, marinobufagenin (MBG) has been implicated as a causative factor in preE. We demonstrated that MBG inhibits the proliferation, migration, and invasion of cytotrophoblasts (CTB) cells. We also showed that hyperglycemia impairs CTBs function via stress signaling. Relaxin is a peptide hormone that allows vasodilation and plays an important role in the process of parturition. The literature suggests potential therapeutic role of H2 relaxin in preeclampsia (PreE), however, there is a controversy on hypotensive action of the peptide. Due to the complex insulin-like structure of relaxin (A- and B- chains, 53 amino acids, 3 disulfide bonds), a novel H2 relaxin B-chain-only peptide variant B7–33 (27 amino acids without any disulfide bonds) has recently been developed.

Objective This single-chain peptide displayed equivalent efficacy to the natural H2 relaxin in several functional assays both in vitro and in vivo. Importantly, B7–33 was shown to have H2 relaxin-like RXFP1 specific effects, particularly in endogenously expressing RXFP1 cells, thus we hypothesized that B7–33 could be an alternative and cost-effective treatment option for PreE compared with H2 relaxin. The Aim of this study is to evaluate whether B7–33 attenuate the in vitro CTB model of PreE phenotype and also to evaluate B7–33 is working through RXFP1 receptor.

Method Human CTBs were treated with DMSO (vehicle) or 0.1, 1, 10 or 100 nM of MBG for 48 h and were co-treated either with B7–33 (25 nM) or relaxin (25 nM) with MBG exposure, while some cells were treated with 5, 10, 25 and 50 nM B7–33 alone. CTBs were also treated with 100, 150, 200, 300, or 400 mg/dl glucose for 48h and were co-treated either with B7–33 (25 nM) or relaxin (25 nM) with glucose exposure. CTB cells were treated with 0, 10, 25, 50 or 100 nM of B7–33 and some cells were pretreated with relaxin antagonist (1.0 μM RXFP1 antagonist). Levels of vascular endothelial growth factor (VEGF), placental growth factor (PIGF), and soluble fms-like tyrosine kinase-1 (sFlt-1) were measured in culture media using ELISA kits. Cell lysates were utilized to evaluate the mTOR by western blotting. Statistical comparisons were performed using analysis of variance with Duncan’s post hoc test.

Results Secretion of sFlt-1 was increased while VEGF and PIGF were decreased in CTBs treated with ≥1.0 nM MBG and ≥150 mg/dl glucose (*p < 0.05 for each). Both B7–33 (25 nM) or relaxin (25 nM) with MBG exposure. CTB cells were treated with 0, 10, 25, 50 or 100 nM of B7–33 and some cells were pretreated with relaxin antagonist (1.0 μM RXFP1 antagonist). Levels of vascular endothelial growth factor (VEGF), placental growth factor (PIGF), and soluble fms-like tyrosine kinase-1 (sFlt-1) were measured in culture media using ELISA kits. Cell lysates were utilized to evaluate the mTOR by western blotting. Statistical comparisons were performed using analysis of variance with Duncan’s post hoc test.

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Conclusion Both B7–33 and relaxin mitigate the MBG-induced and hyperglycemia-induced dysfunction of CTBs by attenuating anti-angiogenic phenotype similar to that seen in PreE. Moreover, the B7–33 induced effect on CTBs was attenuated by 1.0 μM RXFP1 antagonist. This study supports that B7–33 and relaxin are working through the same pathway via RXFP1 receptor. This data also suggests the importance of continuing research of B7–33 in preE prevention.
cardiac conduction system disease. Furthermore, homozygous or heterozygous deletion of the Mybphl gene in mice also causes dilated cardiomyopathy and arrhythmias, confirming MyBP-HL’s importance in the heart. MYBPHL is highly expressed in the atria and encodes myosin binding protein H-like (MyBP-HL), a previously understudied myofilament protein component with homology to cardiac myosin binding protein-C (cMyBP-C). Here, we aim to determine the mechanisms by which loss of MyBP-HL causes conduction system disease.

**Method** We use immunofluorescence super-resolution microscopy, surface and intracardiac ECG recordings, and confocal calcium transient measurements to assess human and mouse heart tissue and cardiomyocytes.

**Results** In the current work, we used super-resolution microscopy on human atrial tissue samples from controls and from a heterozygous MYBPHL R255X mutation carrier to identify MyBP-HL localization. Using immunofluorescence microscopy on control atria, MyBP-HL staining was observed in all atrial cardiomyocytes and showed a myofibrillar pattern with cMyBP-C overlap. Atria from the heterozygous MYBPHL R255X mutant carrier did not show any MyBP-HL-positive cells. We confirmed this using human induced pluripotent stem cell-derived cardiomyocytes carrying the heterozygous MYBPHL R255X variant and healthy control cell lines. These cells showed similar results, with control cell lines exhibiting MyBP-HL staining in a subset of cardiomyocytes, whereas the R255X cardiomyocytes showed no MyBP-HL. These data suggest that the single loss of function allele prevents MyBP-HL expression from the normal MYBPHL allele. In wild-type (WT) mice, we used immunofluorescence microscopy to identify MyBP-HL-positive ventricular cardiomyocytes. In adult and embryonic mice, MyBP-HL co-localized with the ventricular conduction system marker contactin-2 (Ctnn2) near the atrioventricular node and in a subset of Ctnn2-positive Purkinje fibers. We found that adult Mybphl heterozygous ventricles have only 10% as many MyBP-HL-positive cells. Functionally, surface electrometry revealed third-degree atrioventricular block and atrial bigeminy following propranolol treatment in homozygous mice. Intracardiac pacing revealed prolonged action potential propagation time through the His bundles, a shorter atrial relative refractory period and inducible atrial tachycardia. In the absence of MyBP-HL in mice, the atria were enlarged but atrial cell morphology appeared normal. Confocal microscopy to measure calcium transients in isolated atrial cardiomyocytes revealed that Mybphl null cardiomyocytes had an increased occurrence of triggered calcium waves and more heterogeneous calcium release than WT control atrial cardiomyocytes. The finding of dysregulated calcium release coupled with the shorter atrial refractory period and dilated atria describe conditions that could account for the observed atrial arrhythmias, bigeminy, and atrial tachycardia. Super-resolution microscopy revealed disorganized ryanodine receptor distribution in Mybphl heterozygous and null atrial cardiomyocytes compared to WT controls, which may account for aberrant calcium release.

**Conclusion** Using human and mouse model systems, we identified that the MYBPHL R255X heterozygous mutation reduces MyBP-HL protein as to be nondetectable, and that reduced MyBP-HL levels are accompanied by altered atrial and ventricular conduction system function and impaired calcium handling in mice. Together, these data reinforce the importance of MyBP-HL in proper conduction system function and provide targets for further investigation of MYBPHL in human arrhythmia and cardiomyopathy.

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**Abstracts**

**B12 MANIPULATING POTASSIUM CHANNEL SUBDOMAINS TO PREVENT CARDIAC ARRHYTHMIA**

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Objective The human ether-a-go-go related gene (hERG) encodes two subunits, hERG 1a and hERG 1b, that combine in vivo to conduct the rapid delayed rectifier potassium current (IKr). Reduced IKr slows cardiac action potential (AP) repolarization and is an underlying cause of cardiac arrhythmias associated with long QT syndrome (LQTS). hERG 1a contains a long N-terminus that includes a PAS domain that is critical for generating the slow gating behavior of hERG 1a homomeric channels. In contrast, the hERG 1b N-terminus is short and lacks a PAS domain. The absence of this PAS domain enhances current magnitude in heteromeric hERG 1a/1b channels compared to hERG 1a homomeric channels. Most recently, using cardiomyocytes derived from human pluripotent stem cells (iPSC-CMs), we demonstrated that targeted manipulation of the hERG 1a PAS domain using antibody fragments enhances IKr and shortens the action potential in iPSC-CMs. These data suggest that the PAS domain could be a therapeutic target to treat diseases of cardiac excitability.

**Method** We tested the antiarrhythmic potential of antibodies targeting the hERG 1a PAS domain in two iPSC-CM models of long QT syndrome: long QT syndrome type I and acquired long QT syndrome. The antibodies were delivered intracellularly through the recording pipette and we recorded IKr and APs using whole cell patch clamp at physiological temperature (36±1°C). Results iPSC-CMs intracellularly perfused with anti-PAS antibodies displayed APs that were significantly shorter than APs recorded in the absence of the antibodies. Additionally, the antibodies reduced the incidence of early afterdepolarizations in our long QT type I cells during beta adrenergic stimulation.

**Conclusion** Overall, these data demonstrate a proof-of-concept that the hERG 1a PAS domain could be used as a therapeutic target to treat diseases of excitability.

**B13 REGULATION OF MITOCHONDRIAL CALCIUM UPTAKE VIA TYROSINE PHOSPHORYLATION OF MITOCHONDRIAL CALCIUM UNIPORTER**

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Objective Mitochondrial Ca2+ (mtCa2+) overload promotes mitochondrial reactive oxygen species (ROS) generation and apoptosis in various cells/tissues, which is linked to the pathogenesis of various human diseases such as neurodegenerations and heart failure. The main ion channel responsible for mtCa2+ influx is a mtCa2+ uniporter protein complex (mtCUC), which pore structure is formed by the oligomerization of pore forming subunit MCU. We previously reported that
stabilization of Gq-protein coupled alpha1-adrenoceptor (alpha1AR), concomitantly promotes 1) activation of mitochondrial matrix-localized a Ca2+- and ROS-dependent protein tyrosine kinase, proline-rich tyrosine kinase 2 (Pyk2), 2) tyrosine phosphorylation (P-Tyr) of the pore forming subunit of mtCUC, MCU, and 3) the acceleration of mtCa2+ uptake via mtCUC in the cardiac cells. However, it is still unclear 1) whether Pyk2 directly phosphorylates MCU, and if so 2) how Pyk2-dependent P-Tyr of MCU modulate mtCUC channel function as well as mitochondrial Ca2+ uptake profile. In this project, we determined Pyk2-specific P-Tyr site(s) in MCU and investigate the molecular mechanism of P-Tyr-dependent activation of mtCUC.

**Method** Dephospho-mimetic mutants of MCU (MCUY157F, Y288F, and Y316F) were generated by PCR-based site mutagenesis by switching tyrosine (Y) to phenylalanine (F) using wild-type (WT) mouse MCU as a template. P-Tyr levels of MCU were determined by immunoblotting with the general P-Tyr antibody after immunoprecipitation (IP) using the lysates from HEK293T cells stably overexpressing WT- or MCU-YFs. The changes in mtCa2+ levels in response to the cytosolic Ca2+ from HEK293T cells stably overexpressing WT- or MCU-YFs, were determined by immunoblotting with the general P-Tyr antibody after immunoprecipitation (IP) using the lysates from HEK293T cells stably overexpressing WT- or MCU-YFs. The changes in mtCa2+ levels in response to the cytosolic Ca2+ elevation induced by sarcoplasmic (SR)/endoplasmic reticulum (ER) Ca2+-ATPase (SERCA) blocker thapsigargin were assessed under confocal microscopes using the cells expressing mitochondria-targeted Ca2+-biosensor mtCaMP1h.

**Results** Three Tyr residues in human MCU were selected via computational prediction programs as candidates for P-Tyr sites, which are highly conserved across all eukaryotic species including mouse. Direct P-Tyr of MCU by Pyk2 was confirmed by *in vitro* kinases assay using recombinant Pyk2 kinase domain and MCU-Flag purified from HEK293T cells stably overexpressing WT-MCU-Flag. We next used HEK293T cells stably overexpressing wild type (WT)- or MCU-YFs and found that only two Tyr sites (Y157F at the N- and Y317 C-termini of MCU) exhibited increased P-Tyr levels in situ in response to the treatment of alpha1-adrenoceptor agonist phenylephrine (Phe). Overexpression of MCU-WT, Y157F, and Y288F, but not Y316F, significantly increases mtCa2+ uptake in response to cytosolic Ca2+ elevation compared to non-transfected cells. Moreover, *in situ* binding assay by performing IP using the lysates from cells co-expressing GFP and flag-tagged WT-MCUs showed that Phe stimulation enhances oligomerization of MCU. In contrast, binding between MCU-Y316F-Flag and WT-MCU-GFP was markedly reduced compared to that between MCU-WT-Flag and WT-MCU-GFP.

**Conclusion** MCU structure contains Pyk2-specific phosphorylation sites and Pyk2 directly phosphorylates MCU termini. Pyk2-dependent P-Tyr of at C-terminus of MCU enhances MCU oligomerization, which increases mtCUC channel numbers at the inner mitochondrial membrane and accelerates mtCa2+ uptake upon Pyk2 activation. Thus, P-Tyr MCU may serve as an important regulator for ROS overproduction and apoptotic cell death via mtCa2+ overload under pathological condition such as heart failure.

**Objective** Human Immunodeficiency Virus (HIV) infection is associated with an increased risk of thrombosis, and treatment with antiretroviral therapy (ART) does not decrease this risk. The cause of the increased risk is not known, but HIV infection is associated with multiple changes in plasma coagulation proteins, the most common of which is deficiency in the plasma anticoagulant protein S (PS). Despite the prevalence of PS deficiency, its pathologic consequences are unclear because PS concentration does not correlate with thrombin generation in the standard calibrated automated thrombography (CAT) assay. PS functions as a cofactor for the anticoagulant enzyme activated protein C (APC), whose activation requires endothelial cell thrombomodulin (TM). TM is not present in the standard CAT assay, and thus APC is not activated. We hypothesized that PS concentration in plasma from HIV+ patients correlates with thrombin generation, if TM is included in the CAT assay.

**Method** Citrated plasma was collected from 22 consenting HIV+ patients (11 naive samples collected from patients on first diagnosis and 11 samples from patients on ART) and 7 healthy controls.

**Results** Total plasma PS concentration was measured by ELISA. 59.8% (13/22) of HIV+ plasma samples were deficient in PS, compared to the control samples (p=0.018). There was no difference between the naive patients and those on ART, suggesting that ART does not correct PS deficiency (p=0.999). To correlate plasma PS with thrombin generation, we established a modified CAT assay that is sensitive to PS concentration. In the standard CAT assay (citrated plasma incubated with tissue factor and phospholipids), supplementing PS-deficient plasma with 150nM purified PS resulted in only a 12% decrease in total thrombin produced. By contrast, if 20nM TM was included in the assay, then PS supplementation resulted in a 75% decrease in total thrombin. In the presence of TM, a PS dose response was observed in all parameters of thrombin generation, except for the lag time, since APC is not activated until some thrombin has been produced. We next compared thrombin generation in the absence or presence of TM to PS concentration in the patient samples. In the absence of TM, there was no correlation between plasma PS and thrombin generation (R2=0.0008), consistent with previous reports. In the presence of TM, there was a negative correlation (R2=0.1554), with decreased PS being associated with increased thrombin generation. As ART does not affect PS concentration, there was no difference between the naive patients and those on ART in thrombin generation assays measured in the presence of TM. In the absence of TM, thrombin generation was significantly higher in samples from patients on ART, compared to naive samples (16.2% higher total thrombin, p=0.047). This suggests that there is a PS-independent difference between the ART and naive samples, which is masked when the complete anticoagulant system is present.

**Conclusion** More than half of the HIV+ patients evaluated had PS deficiency, consistent with previously published results and this deficiency was not corrected by treatment with ART. PS deficiency does correlate with increased thrombin generation, in a CAT assay that was modified to be sensitive to PS. However, there is also a PS-independent procoagulant effect in the patients on ART. These data demonstrate that the procoagulant risk associated with HIV treatment is multifaceted. One risk factor is likely PS deficiency, while there is at least one PS-independent risk factor associated with ART treatment.
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B25 PARAOXANASE 1 DELETION LEADS TO INCREASED CARDIAC REMODELING AND CARDIAC FIBROSIS IN A DAHL SALT-SENSITIVE RAT MODEL OF CHRONIC KIDNEY DISEASE
Prabhatchandra Dube, Fatimah K. Khalaf, Chyran Mohammed, Amelie DeRiso, Dhanushya Batementti, Tiana Sarsour, Iman Tassavor, Steven T Haller, Eric Morgan, David Kennedy, University of Toledo, OH
10.1136/jim-2019-midwestern2019.8

Objective Paraoxanas (Pon) are hydrolytic enzymes with three distinct isoforms (Pon1, Pon2 and Pon3), all of which exhibit arylesterase, paraoxonase and lactonase activities. Pon-1 synthesis occurs in liver and circulates bound to high-density lipoproteins (HDL, contributing to HDL’s antioxidant, anti-inflammatory and anti-atherogenic properties. Decreased circulating Pon-1 activity is associated with increased oxidant stress and adverse clinical outcomes in the setting of chronic kidney disease (CKD). Whether decreased Pon-1 is mechanistically linked to adverse cardiovascular outcomes in CKD, however, remains unclear. We tested the hypothesis that Pon-1 is cardio-protective in a Dahl salt-sensitive model of hypertensive renal disease.

Methods Experiments were performed on control Dahl salt-sensitive rats (SSMcwi, hereafter called SS rats) and Pon1 mutant rats (designated SS-Pon1em1Mcwi, hereafter called SS-Pon1 KO rats) generated by injecting a CRISPR targeting the sequence into SSMcwi rat embryos. The resulting mutation is a 7bp frameshift insertion in exon 4 of the Pon3 gene. Ten week old, age-matched male and female rats were maintained on high salt diet (8% NaCl, Envigo, Teklad diets, Madison, WI) for up to 12 weeks to initiate the salt-sensitive hypertensive renal disease characteristic of this model. Left ventricular geometry and function were assessed in male SS and SS-Pon1 KO rats at the end of week four of high salt diet via echocardiography and animals were euthanized and hearts processed for histology.

Results SS-Pon1 KO rats had negligible circulating Pon activity when compared to SS as measured by a fluorometric lactonase activity assay. Early mortality was observed in 3 out of 8 (37.5%) male SS-Pon1 KO rats (mean length of time until death = 33 days), while no mortality was observed in female SS-Pon1 KO rats or in either male or female SS rats. SS-Pon1 KO male rats demonstrated a significantly increased (p<0.001) relative wall thickness (0.77 ± 0.05 vs. 0.58±0.02) and fractional shortening (0.62 ± 0.02 vs. 0.53 ± 0.01), as well as significantly increased (p<0.05) mean velocity of circumferential fiber shortening (circ/s, 6.37 ± 0.33 vs. 5.52 ± 0.17) and cardiac index (ml/min/kg, 184 ± 18 vs. 136 ± 11) vs age matched SS rats. No difference in heart rates was observed. Upon histological examination, heart sections of SS-Pon1 KO male rats showed a significant increase in fibrosis and heart-weight-to-body-weight ratio (p<0.05) compared to the age matched SS rats.

Conclusion Our findings suggest that loss of PON-1 in salt-sensitive hypertensive rats leads to a cardiac phenotype consistent with compensated heart failure including increased left ventricular function and hypertrophy as well as increased cardiac fibrosis and mortality.

B35 CARDIOPROTECTIVE EFFECTS OF PARAOXANASE 3 IN A DAHL SALT-SENSITIVE RAT MODEL OF CHRONIC KIDNEY DISEASE
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10.1136/jim-2019-midwestern2019.9

Objective Paraoxanas (Pon) are hydrolytic enzymes with three distinct isoforms (Pon1, Pon2 and Pon3) exhibiting arylesterase, paraoxonase and lactonase activities. While a number of studies have clearly detailed the atheroprotective role of Pon1, Pon3 is also a calcium-dependent glycoprotein with significant antioxidant and anti-atherosclerotic activities. Pon-3 synthesis occurs in liver and circulates bound to high-density lipoproteins (HDL), although significant expression is noted in the kidney as well. PON3 also inhibits oxidative modification of LDL and monocyte activation. Decreased circulating Pon activity is associated with increased oxidant stress and adverse clinical outcomes in the setting of chronic kidney disease (CKD), yet whether decreased Pon-3 is mechanistically linked to adverse cardiovascular outcomes in CKD is unknown. We tested the hypothesis that Pon-3 is cardioprotective in a Dahl salt-sensitive model of hypertensive renal disease.

Methods Experiments were performed on control Dahl salt-sensitive rats (SSMcwi, hereafter called SS rats) and Pon3 mutant rats (designated SS-Pon3em1Mcwi, hereafter called SS-Pon3 KO rats) generated by injecting a CRISPR targeting the sequence into SSMcwi rat embryos. The resulting mutation is a 16bp frameshift deletion in exon 4 of the Pon3 gene. Ten week old, age-matched male and female rats were maintained on normal salt (0.3% NaCl) and high salt (8% NaCl) diets (Envigo, Teklad diets, Madison, WI) for eight weeks to initiate the salt-sensitive hypertensive renal disease characteristic of this model. Left ventricular geometry and function were assessed at the end of week eight of high salt diet via echocardiography using a Sequoia C256 System (Siemens) with a 15-MHz linear array transducer. After eight weeks animals were euthanized and hearts were processed for histology.

Results By 8 weeks, mortality was observed in 2 out of 11 (18.2%) male SS-Pon3 KO rats on high salt (mean length of time until death = 31 days) while no mortality was observed in male SS male rats on high salt. In female rats, by 8 weeks 100% mortality was observed in SS-Pon3 KO rats on high salt diet (mean length of time until death = 67 days) while no mortality was observed in SS female rats on high salt. High salt fed SS-Pon3 KO male rats that survived to the echocardiography study demonstrated significantly decreased left ventricular end-systolic diameter (p<0.05) and end-diastolic diameter (p<0.001), as well as significant increases in left ventricular relative wall thickness (p<0.01) compared to age matched SS rats. Furthermore, SS-Pon3 KO rats demonstrated significantly increased heart-weight-to-body-weight ratio (p<0.05) compared to age matched SS rats.

Conclusion These findings suggest a cardioprotective role for PON-3 in the setting of salt-sensitive hypertensive renal disease.
Background Familial hypercholesterolemia (FH) is an autosomal dominant condition that causes life-long elevation of low-density lipoprotein cholesterol that can lead to premature cardiovascular (CV) events. Approximately one million individuals in the U.S. have FH and it is estimated that half are untreated. Individuals with untreated FH are 20 times more likely to have a CV event than those without FH. At Geisinger, FH is diagnosed several ways: 1) referral to cardiology for uncontrolled hypercholesterolemia or a CV event; 2) evaluation through primary care with variable cholesterol levels and no evidence of CV disease; or 3) identification of a pathogenic (P) or likely pathogenic (LP) variant(s) in genes associated with FH (LDLR, APOB, or PCSK9) from a population genomic sequencing initiative (MyCode Community Health Initiative). Geisinger patients can enroll in MyCode and provide a DNA sample with the expectation they and their primary care physician will be notified if a P/LP variant in an FH gene is identified. Statins are widely available and recommended as first-line therapy. The purpose of this study is to understand patient-perceived barriers and facilitators to FH treatment experienced by individuals with FH.

Method Semi-structured interviews were conducted with individuals with FH. Included individuals must have had FH a problem list diagnosis (ICD 10: E78.01) or a P/LP FH gene variant. Development of the interview guide was informed using the Practical, Robust, Implementation and Sustainability Model. Individuals were asked to describe how they learned about their diagnosis and care they have received, the barriers and facilitators they have experienced, and how they were able to overcome those barriers. Interviews were recorded and transcribed verbatim. Transcripts were assessed for accuracy and independently coded by two reviewers using consensus coding.

Results A total of 25 individuals with FH were interviewed (12 with a genetic diagnosis via MyCode and 13 with a clinical diagnosis). Of those, 72% (18/25) were female and 60% (15/25) were 55 years of age or older. All individuals were white and almost all (24/25) did not identify as Hispanic or Latino origin. Almost half (11/25) had a college degree or some higher education. About half (13/25) reported having private health insurance at the time the interview was conducted. Many individuals described knowing that they had high cholesterol for a long time, or had a family history of high cholesterol, but only recently learned that their high cholesterol condition was due to FH. A few described not experiencing any barriers related to their FH care and felt treated. Most individuals described a variety of barriers, including issues related to medications (e.g., side effects, cost), health insurance (e.g., prior authorization, denial), and the healthcare system (e.g., provider access). Some individuals also described other health or family issues that required attention and prevented them for taking a more active role in management of their own condition. Many individuals stated that their care team was helpful in facilitating their care.

Conclusion Individuals commonly experience many barriers that delay or prevent adequate FH treatment. These barriers are similar to those found in previous studies conducted in patient with routine hypercholesterolemia. Next, we plan to match the barriers and facilitators identified in this study to evidence-based implementation strategies that will be vetted with patient and organizational (providers and administrators) stakeholder groups to inform a future intervention development at Geisinger.
Abstracts

C05 Gq-MEDIATED PKD ACTIVATION INDUCES ABERRANT MITOCHONDRIAL FISSION THROUGH PHOSPHORYLATION OF DLP1 IN CARDIOMYOCYTES
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Objective Gq protein-coupled receptor (GqPCR) signaling is frequently over-activated under pathological conditions. It has recently been suggested that GqPCR signaling induces abnormal mitochondrial morphology, especially small and fragmented mitochondria, and mitochondrial dysfunction in the heart. However, the specific molecular mechanism by which GqPCR signaling causes abnormal changes in mitochondrial morphology and function remains unclear. Therefore, we hypothesized that GqPCR signaling induces aberrant mitochondrial fission and injury, which contributes to cardiomyocyte death and cardiac dysfunction in vitro.

Method Neonatal rat ventricular myocytes were stimulated by the Gq-coupled α1-adrenoceptor agonist, phenylephrine. Mitochondrial morphology was monitored by confocal microscopy and transmitted electron microscopy. Translocation and activation of protein kinase D (PKD) and dynamin-like protein 1 (DLP1) were detected by live cell imaging and/or western blot analysis using the cytosol and mitochondrial-enriched fractions. Time-dependent levels of mitochondrial reactive oxygen species (mROS) and opening of mitochondrial permeability transition pore (mPTP) were measured using fluorescent dyes, MitoSOX-Red and calcine, respectively.

Results We found that PKD activation by GqPCR stimulation translocated to the outer mitochondrial membrane and phosphorylated mitochondrial fission protein, DLP1 at serine 637, resulting in mitochondrial fragmentation. We also found that GqPCR-mediated PKD activation increased mROS generation and mPTP opening, followed by apoptotic signaling activation. These morphological and functional changes in cardiomyocytes were abolished by pharmacological inhibition of PKD with a small molecule PKD inhibitor CPT066101 or genetic inhibition of PKD1 with a dominant-negative mutant of PKD1 or PKD1-targeted siRNA. Importantly, PKD activation, DLP1 phosphorylation at serine 637 and apoptotic signaling activation were concomitantly detected in left ventricular tissues from a transgenic mouse model of left ventricular heart failure with cardiac-specific overexpression of constitutively active Gqα (GqαQ209L). Moreover, similar results were also obtained from right ventricular tissues (but not from left ventricular tissues) from a rat model of pulmonary hypertension treated with the combination of a vascular endothelial growth factor receptor inhibitor, Sugen 5416, and chronic hypoxia for 3 weeks.

Conclusion GqPCR stimulation induces mitochondrial fragmentation and dysfunction through PKD-dependent phosphorylation of DLP1, which likely contributes to cardiac dysfunction during heart failure. These findings suggest that inhibition of GqPCR-PKD-DLP1 can serve as a potential therapeutic target to mitigate mitochondrial fragmentation, mitochondrial injury, and myocardial death during heart failure.

C07 AUTOPHAGY FACILITATES MITOCHONDRIAL BIOGENESIS TO MAINTAIN MITOCHONDRIAL HOMEOSTASIS DURING CARDIAC ISCHEMIA/REPERFUSION INJURY
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Objectives Fifty percent of tissue damage of myocardial infarction results from reperfusion injury. It is crucial to delineate the mechanisms of reperfusion injury as no standard clinical therapy is available. The FDA-approved histone deacetylase (HDAC) inhibitor SAHA has been shown to induce cardiomyocyte autophagy and blunt ischemia/reperfusion (I/R) injury when administered at the time of reperfusion. We hypothesize that autophagy protects the myocardium by facilitating mitochondrial biogenesis and removing damaging Reactive Oxygen Species (ROS) during I/R injury.

Methods Mouse and cultured cardiomyocyte (neonatal rat ventricular myocytes and human embryonic stem cell-derived cardiomyocytes) I/R models were used to investigate the effects of SAHA and autophagy inducer Tat-Beclin on mitochondria. Dependence on autophagy was assessed in by ATG7 knockdown in cardiomyocytes and knockout in mice. The role of PGC-1α in SAHA-mediated mitochondrial biogenesis was analyzed by adenovirus-mediated overexpression and knockdown.

Results Pre-treatment of cardiomyocytes with SAHA before simulated I/R resulted in a four-fold decrease in I/R-induced loss of mitochondrial membrane potential (MMP) and a 30% reduction in cytosolic ROS levels. Intact and total mitochondrial DNA (mtDNA) content and mitochondrial mass were also significantly increased by SAHA pretreatment. In vitro, I/R induced >50% loss of mtDNA content in the border zones of mouse hearts, but SAHA pre-treatment and reperfusion treatment alone reversed mtDNA content and mitochondrial mass to control levels. Loss-of-function of ATG7 in cardiomyocytes or in mouse myocardium abolished the protective effects of SAHA on ROS levels, MMP, mtDNA levels, and mitochondrial mass. Expression of PGC-1α was induced by SAHA pre-treatment in cardiomyocytes and mouse hearts subjected to I/R, and ablation of PGC-1α expression blocked the effects of SAHA on mitochondrial biogenesis in cardiomyocytes. To delineate the effects of autophagy on mitochondria, we used tat-Beclin peptide to induce autophagy in vivo and in vitro. Tat-beclin induced PGC-1α expression and mtDNA content significantly in infarct border zone and in NRVMs subjected to I/R.

Conclusions HDAC inhibition preserves mitochondrial homeostasis and reduces ROS levels in heart tissue subjected to I/R injury by promoting autophagy and PGC-1α-mediated mitochondrial biogenesis. Autophagy facilitates PGC-1α-mediated mitochondrial biogenesis during cardiac I/R injury.
**C09**

**DISRUPTED INFLAMMASOME ACTIVATION BY THE VASCULAR ECTO-APYrase CD39 IN VENOUS THROMBOSIS**

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Objective Venous thrombosis (DVT) is a serious health concern, with growing incidence in an aging population. DVT is marked by sterile inflammation and innate immune activation. Early participants in DVT include endothelial cells, monocytes, and neutrophils which form extracellular traps (NETs) and potentiate thrombosis. The vascular ATP/ADPase enzyme CD39, found on leukocytes and the endothelium is at the nexus of inflammation and coagulation. CD39 dissipates extracellular thromboinflammatory ‘danger’ signals, by phosphohydrolyzing ATP and ADP. We hypothesized that CD39 is a critical enzyme in venous homeostasis, restraining unchecked inflammation and thrombosis in DVT.

Methods Using a physiologic model of restricted IVC flow, DVT was induced in CD39± and WT control mice. Thrombi were assessed by immunohistochemistry, and immunoblots. Neutrophil extracellular trap formation was examined in mature neutrophils. IL-1 beta neutralizing antibodies were used to inhibit the inflammasome effector.

Results CD39± mice had a 2-fold increase in thrombus frequency, a 3-fold increase in clot size, and higher fibrin content. CD39± mice had exaggerated neutrophil recruitment to the growing thrombus. CD39± neutrophils had increased citrullinated histone 3 in vitro, which correlated with enhanced NET formation in CD39± venous thrombi. CD39-deficiency also amplified inflammasome activation with increased NFκB phosphorylation and mature IL-1 beta content in CD39± DVTs compared with WT mice. Using neutralizing antibodies, inhibiting IL-1 beta mitigated the increased thrombosis burden in CD39± mice.

Conclusion CD39 is a critical vasculoprotective ecto-enzyme in venous homeostasis, by tempering inflammation and thrombosis. CD39± mice have increased DVT burden with fibrin deposition, innate immune activation and IL-1 beta release compared with WT mice. Studies are underway delineate relative contributions of leukocytes and the endothelium to CD39-mediated venous protection.

**C38**

**VALIDATION AND REFINEMENT OF THE 2017 AHA/ACC/HRS GUIDELINE RECOMMENDATIONS FOR USE OF IMPLANTABLE CARDIOVERTER DEFIBRILLATORS IN CARDIAC SARCOIDOSIS**


Objective Implantable cardioverter defibrillators (ICDs) are used for the prevention of sudden cardiac death in patients with cardiac sarcoidosis (CS). The latest and the most comprehensive recommendations for ICD implantation in patients with CS are from the 2017 American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS) Guideline for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death. Each of these recommendations is based on separate observational studies or expert opinion, and the recommendations have not been validated together in a single cohort. We aimed to validate and refine the Guideline recommendations for ICD implantation in CS.

Methods We performed this study using a large retrospective cohort of patients with known or suspected CS that underwent CMR. All patients were followed for a composite endpoint of significant ventricular arrhythmia or sudden cardiac death. The discriminatory performance of each Guideline recommendation was tested using time-dependent receiver operating characteristic analyses. The optimal cutoff for the extent of late gadolinium enhancement (LGE) predictive of the endpoint was determined using the Youden index.

Results In a cohort of 286 patients, the Guideline Class I and IIa recommendations identified all patients that experienced either significant ventricular arrhythmia or sudden cardiac death during a median follow-up of 3.2 years. Patients with one or both Class I indications had a significantly higher incidence of the composite endpoint than patients with one or more Class IIa indications. Any LGE on CMR was sensitive but not specific for the identification of patients at risk for the composite endpoint, and a cut-off of >5.7% of the left ventricular mass was optimal. Excluding two of the four Class IIa recommendations – left ventricular ejection fraction (LVEF) >35% and syncope, LVEF >35% and inducible ventricular arrhythmia –resulted in improved discrimination for the composite endpoint.

Conclusions The Guideline Class I and IIa recommendations identified all patients that experienced significant ventricular arrhythmia or sudden cardiac death during follow-up. With regard to the Class IIa recommendation for ICD implantation in patients with LVEF>35% and LGE, we identified a cut-off of 5.7% that provided the highest discriminating performance for the combined endpoint. We identified two of the four Class IIa recommendations that may warrant an upgrade to Class I, and a third that might benefit from either clarification or a downgrade to Class IIb.
Method PubMed, Elsevier, EBSCO, Spring databases and Cochrane Library were searched for relevant articles between January 1985 and November 2017. Based on the different mechanisms of atherectomy, the patients were divided into Orbital Atherectomy (OA) group and Rotational Atherectomy (RA) group. Rates of intraoperative angiographic complications were reported and compared between the two groups and included coronary artery dissection, abrupt vessel closure, persistent no-flow and persistent slow flow. Two independent reviewers selected and appraised studies and extracted data in duplicate. Random-effects meta-analysis was used to pool outcomes across studies. and Cochrane Library were searched for relevant articles between January 1985 and November 2017. Based on the different mechanisms of atherectomy, the patients were divided into Orbital Atherectomy (OA) group and Rotational Atherectomy (RA) group. Rates of intraoperative angiographic complications were reported and compared between the two groups and included coronary artery dissection, abrupt vessel closure, persistent no-flow in RA (1.4% compared to 0.9% in OA), abrupt closures (1.2% compared to 0.66% in RA), and persistent slow flow (2.1% compared to 1.3% in RA). Persistent no flow and dissections were higher in RA (1.2% and 4.2% respectively) compared to OA (0.5% and 2.2% respectively), these rates were not statistically significant based on our analysis.

Conclusion In patients undergoing percutaneous coronary interventions (PCI), Orbital and Rotational Atherectomy techniques have yielded similar outcomes in terms of intraoperative angiographic complications, this might be due to differences between the individual studies, lack of unified definitions of these complications, or merely due to the absence of difference between the two techniques. Continually evolving experience with OA systems and the persistent use of RA.

Dermatology

B29 CHARACTERISTICS OF PATIENTS DIAGNOSED WITH CATASTROPHIC CUTANEOUS CARCINOMATOSIS
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10.1136/jm-2019-midwestern2019.17

Objective Catastrophic Cutaneous Carcinomatosis (CCC) is a dermatologic condition in which a non-organ transplant patient is diagnosed with ten or more nonmelanoma skin cancers in a one year period. We identified patients from a large skin cancer database who had been diagnosed with at least ten nonmelanoma skin cancers in one year. We looked at characteristics of these patients and if they could be diagnosed with CCC. We performed a retrospective chart review at the Brody School of Medicine of dermatology patients with 10 or more cases of nonmelanoma skin cancer in a one year period to identify characteristics of these patients.

Method Brody School of Medicine’s EHR and paper charts were used to review patients diagnosed with 10 or more cases of basal cell carcinomas and/or squamous cell carcinomas in a one year period. The characteristics of the 37 patients eligible for the study were compiled and analyzed to determine correlations. One patient’s chart was unable to be located.

Results Of the 37 patients eligible for the study all were Caucasian with 78% of our patients being males. Approximately half (41%) of our patients were immunosuppressed. Hypertension was common with 70% of our patients having high blood pressure. Eight patients diagnosed with diabetes had a comorbidity of hypertension as well. Twenty-one of 37 patients (57%) were deceased. Of the patients who were deceased 3 (24%) died due to skin cancer. Patients who were immunosuppressed were younger at the onset of their first skin cancer by 15 years. This was a statistically significant difference. There was also a statistically significant difference in the number of basal cell carcinomas; immunocompetent patients had more basal cell carcinomas than immunocompromised patients. Patients who were immunosuppressed showed a greater number of squamous cell carcinomas, however this data was not statistically significant.

Conclusion The data shows that the majority of patients diagnosed with Catastrophic Cutaneous Carcinomatosis will be Caucasian and male. Many CCC patients will have a comorbidity of hypertension. Differences in the rates of squamous cell carcinomas and basal cell carcinomas exist between patients who are immunosuppressed and immunocompetent. Patients with multiple skin cancers suffer significant morbidity and many die from their disease. Management requires a coordinated multispecialty approach.

Diagnosis or Treatment of a Disease Process or Clinical Syndromes

B10 FULMINANT GIANT CELL MYOCARDITIS: A CASE OF EARLY DIAGNOSIS AND PROMPT TREATMENT RESULTING IN GOOD OUTCOME

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10.1136/jm-2019-midwestern2019.18

Introduction Giant cell myocarditis is an autoimmune cause of myocarditis that is very rare and often fatal. This disorder occurs as a result of T-cell mediated inflammation and may respond to immunosuppressive medication. Majority of the patients with giant cell myocarditis present with acute onset rapidly worsening heart failure. Early diagnosis and prompt treatment results in good outcomes. We present here a case of biopsy-proven giant cell myocarditis that presented initially as ventricular arrhythmia.

Case description 64 year-old-male with past medical history of hypertension presented to the emergency department with one-day history of palpitations associated with chest pressure and shortness of breath. An initial EKG showed monomorphic ventricular tachycardia (figure 1), which resolved with procainamide and amiodarone infusion. Transthoracic echocardiogram showed ejection fraction of 40% and cardiac catheterization showed mild non-obstructive coronary artery disease with elevated left sided filling pressures. Cardiac MRI was later performed that showed LV EF of 42%, normal RV structure and function and patchy late gadolinium enhancement in the mid-myocardial basal septum, apical anterior wall and apex (figure 2). Because of multiple episodes of ventricular arrhythmias and persistent heart failure symptoms, RV...
biopsy was performed that showed severe lymphohistiocytic myocarditis with giant cells (figure 3). During the hospitalization, patient had ICD placement, IV steroids and cyclosporine along with goal directed medical management of heart failure with reduced ejection fraction. The patient improved clinically and was discharged home after staying in the hospital for two weeks.

**Discussion** Giant cell myocarditis is a very rare but fatal cause of cardiomyopathy that usually affects middle-aged individuals without previous history of cardiac abnormalities. Early diagnosis is very critical and studies have shown significant improvement in symptoms, transplant free survival and suppression of inflammation with early initiation of immunosuppressive medications. Prior to 1980s, this disorder was diagnosed at the time of autopsy. Recent advances in cardiac imaging including cardiac MRI have resulted in this condition being diagnosed on endomyocardial biopsy. Histologic examination remains the gold standard of diagnosis and second endomyocardial biopsy is often needed to come to the correct
diagnosis. Suspicion of giant cell myocarditis should be kept in mind in rapidly progressive heart failure in previously healthy individuals.

**References**

candidiasis-histoplasmosis co-infection. All but three of these were associated with HIV with low CD4 counts. Of cases not associated with HIV, one patient was diabetic; second was diabetic on steroids for autoimmune thrombocytopenia; no risk factors were identified in the third case.

Both infections are acquired via inhalation. An intact immune system usually controls the infection. For Cryptococcus, about 40% infected individuals develop pulmonary symptoms; in less than 1% cases, there is dissemination to meninges, bones, joints, skin or soft tissues with meningoencephalitis being the most common extra-thoracic manifestation. Histoplasmosis is usually asymptomatic in immunocompetent patients; however, in cases of immunodeficiency, 95% patients develop symptomatic infection. All medicine practitioners frequently manage patients with immunocompromised states: chronic steroid therapy for multiple disease states such as rheumatoid arthritis, elderly, solid organ transplant recipients or patients with hematological malignancies as well as HIV. Co-infections are rare; diagnosis of one fungal disease may result in inadequate evaluation and failure to diagnose the other. Management in such complicated situations may require specialty referrals. Hence, it is important to report these for the knowledge of all general practitioners.

REFERENCES

B22 UTILITY OF CARDIAC MRI IN THE PROGNOSTICATION OF PERIPARTUM CARDIOMYOPATHY
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10.1136/jim-2019-midwestern2019.21

Introduction Peripartum cardiomyopathy (PPCM) is a life-threatening idiopathic form of dilated cardiomyopathy affecting women in the last month of pregnancy up to 5 months postpartum. In the United States, PPCM has an incidence of 1 in 4000 live births and an estimated mortality of 6 to 10%. Cardiac magnetic resonance imaging (CMR) has been used as a radiation free investigative method to assess cardiac structure & function in PPCM. It allows for non-invasive assessment of myocardial edema, fibrosis and necrosis, by assessing for late gadolinium enhancement (LGE). LGE has been used to assess prognosis and functional recovery in non-ischemic cardiomyopathies. Previous cases have shown that the presence of LGE appeared to be associated with a poor prognosis, while the lack of LGE is associated with a good prognosis.

Case description A 28-year old G3P2012 African American female with a past medical history of asthma & pre-eclampsia presented with a 6-day history of shortness of breath, 1 month following normal vaginal delivery of her second child, complicated by pre-eclampsia. On presentation, chest x-ray revealed pulmonary edema, pleural effusions, and cardiomegaly. BNP was elevated at 1651 pg/mL and troponin-I was within normal limits. She was admitted and treated for heart failure in setting of PPCM.

CMR went on to show no abnormal myocardial enhancement, moderate global left ventricular hypokinesis with an ejection fraction of 31%, normal LV size with moderate global hypokinesia, moderate mitral regurgitation and a small pericardial effusion. In view of the absence of myocardial enhancement it was evident that there was no signs of fibrosis, inflammation, or previously existing cardiomyopathy. The patient was continued on guideline-directed medical therapy for heart failure with reduced ejection fraction, which included furosemide, metoprolol, spironolactone and enalapril. Once clinically improved she was successfully discharged home.

On follow-up three months later, she reported no recurrence of SOB, dyspnea, edema or chest pain. She was placed on medroxyprogesterone contraceptive injection and the risks of recurrent pregnancy were explained to her. Follow-up as outpatient was continued, and she remained on metoprolol, spironolactone and enalapril.

Discussion The case presented has several elements conforming with the data present on PPCM; the patient had risk factors of African ancestry, pre-eclampsia and multiparous pregnancy. Protective factors included low level of troponin and diagnosis following delivery. CMR did not reveal any LGE and the patient had functional recovery with a good prognosis following appropriate treatment. Given the lack of LGE and the positive outcome, this case linked the absence of LGE to a good prognosis.

Several case reports and small studies have attempted to examine the prognostic association between PPCM and the observation of LGE on CMR, the majority of which who concluded the presence of LGE is linked to a poor outcome. Conversely, the lack of LGE can predict a good outcome, potentially myocardial recovery. Further large-scale studies are needed to examine LGE on CMR as well as other prognostic factors for PPCM. In expectation, CMR will continue to provide useful diagnostic data in assessing cardiac structure & function, and evaluating myocardial edema, fibrosis and necrosis.

B28 DOUBLE RULE IN: CONCOMITANT ACUTE CORONARY OCCLUSION AND PULMONARY EMBOLIZATION
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10.1136/jim-2019-midwestern2019.22

Introduction Paradoxical coronary embolism is a rare cause of acute coronary syndrome. CT is frequently used for double rule out of obstructive coronary artery disease (CAD) and pulmonary emboli (PE) in patients presenting to the emergency department (ED) with acute chest pain. Concomitant acute coronary occlusion and PE has been reported, but it is rare to see both (double rule in) on the same CT scan.
A 71-year-old female with history of recurrent PE, chronic thromboembolic pulmonary hypertension, and multiple CAD risk factors presented to the ED with chest pain and an elevated troponin. CT angiography of the pulmonary and coronary circulation was performed for a double rule out (single contrast bolus of 120 cc, 2 separate scans, Siemens SOMATOM Definition Flash). It showed recurrent PE, with near complete occlusion of the right pulmonary artery (figure 1). Surprisingly, it also showed a 3 cm long occlusion of the distal right coronary artery (RCA) (figure 2). This lesion was felt to be acute due to absence of any calcification or bridging collaterals. There was no thrombus seen in the left heart chambers. She underwent urgent invasive coronary angiography that confirmed the RCA occlusion (figure 3). Aspiration thrombectomy of the RCA was performed with removal of large thrombus burden (figure 4). There was no underlying plaque seen and hence stent placement was deferred (figure 5). She was deemed to have coronary embolism, and a paradoxical source (with right to left shunt) was suspected given the presence of a new PE. Echocardiography showed a patent foramen ovale (PFO) with right to left shunting (figure 6). She was not a candidate for PFO closure due to severe pulmonary hypertension and right ventricular dysfunction.

Discussion Coronary embolization causes 3% of all acute coronary syndromes, with the embolus being paradoxical in 10–
15% of those cases given the rarity of this condition, a high index of clinical suspicion is required. CT is a useful test to assess for both PE and CAD, and should be performed when the diagnosis is not clear, for eg with a significant elevation in troponin. Once coronary embolization is suspected, cardiac and paradoxical causes should be looked for. Demonstration of venoarterial communication (most often at the atrial level) together with the identification of a venous source of embolus and lack of thrombi in the left heart fulfill the criteria for a presumptive diagnosis of this condition. Whenever possible, PFO closure should be considered.

**Abstract B34**

**AORTOENTERIC FISTULA WITH DUODENAL GRAFT MATERIAL MIGRATION RESULTING IN GASTROINTESTINAL BLEEDING**

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**Introduction** Aortoenteric fistula (AEF) is an abnormal connection between the aorta and the gastrointestinal tract. AEF is a rare but life-threatening condition that requires emergent intervention. It usually results from compression of an abdominal aortic aneurysm (AAA) or after aortic surgery.

**Case Description** A 78-year-old male with a history of abdominal aortic dissection status post repair and mechanical aortic valve on chronic warfarin presented to the emergency department (ED) after feeling unwell for 3 days, associated with upper abdominal and lower back pain, black tarry stool and one episode of hematochezia. While in the ED, he had an episode of hematemesis and was noted to be hypotensive, so he was admitted to the intensive care unit. A Computed tomography (CT) scan of the abdomen and pelvis with contrast showed a calcified aortic plaque with surrounding soft tissue thickening and abutting of the second part of the duodenum, concerning of abdominal aortic dissection without contrast leak (figure 1). Gastroenterology team performed an emergent Esophagogastroduodenoscopy (EGD), which showed blood in the fundus and an ulcer like lesion in the third portion of the duodenum with a graft material concerning for aorto-enteric fistula (figure 2). Vascular surgery took the patient emergently to the operating room and performed an Endovascular Abdominal aortic aneurysm repair to control the acute bleeding. The plan was to do definitive repair for the
aorta and the aorto-enteric fistula once he is more stable. Two days later the patient underwent removal of the aortic graft, duodenal diverticulectomy and duodenotomy repair, and replacement of abdominal aortic graft with HEMASHIELD graft. The graft was found to be infected, so the infectious disease team recommended discharging him home on intravenous IV antibiotics for 6 weeks.

Discussion Aortoenteric fistulae are uncommon but associated with high mortality. It should be considered in the differential diagnosis of upper gastrointestinal bleeding, especially in patients who have an aortic aneurysm or had a repair of aortic disease.

HYPOTHENAR HAMMER SYNDROME: AN OVERLOOKED OCCUPATIONAL VASCULAR PATHOLOGY

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Introduction Hypothenar hammer syndrome occurs due to repetitive trauma to the palmar aspect of the wrist resulting in damage to the ulnar artery and decreased blood supply to the superficial palmar arch. We present here two cases of occupation associated hypothenar hammer syndrome.

Case description 54-year-old male with past history of smoking and hyperlipidemia presented with coldness and discoloration of the right 3rd and 4th digit along with pain in the right wrist. He is a carpenter by profession and used his wrist as a tool to punch in nails into woodwork. Arterial ultrasound showed occlusion of distal right ulnar artery with a collateral vessel originating proximal to the occlusion (figure 1). An arterial angiogram of the hand showed no contrast in the right ulnar artery due to occlusion. There was also abnormal perfusion to the right middle artery, lateral digital artery with...
61-year-old male with past medical history of hypertension and long-standing tobacco use presented to the emergency room with complaint of left middle finger pain for about one week associated with tingling and some discoloration and scab formation under the finger nail (figure 3). He noted going outside may change it more to pale color, and hot shower improve this symptom. He is a mechanic by profession and uses his hand frequently as a tool for pounding and hitting. Arterial ultrasound showed chronic occlusion of the left ulnar artery and a contrast angiogram of the left upper extremity showed chronic distal ulnar artery occlusion just proximal to the radio-ulnar joint with a large collateral reconstituting the ulnar artery at the level of the hamate bone of the wrist. He was started on apixaban and amlodipine and the plan is to see him in clinic in 3 months with repeat Doppler studies.

Discussion

Hypothenar hammer syndrome mostly occurs from repetitive stress injury to the hypothenar eminence from biking, handball, martial arts and in occupational workers who use their hands as tools. The syndrome may occur as a result of acute or chronic trauma to the ulnar artery. This can result in spasm, thrombosis and aneurysm of the ulnar artery. Clinically it presents as pain in the palm or digits associated with cold intolerance. Allen test may be absent and surgical treatment may be needed in cases not resolved by conservative and medical management. High index of suspicion for this syndrome should be kept in mind in patients with repetitive trauma to the wrist.
paroxysmal atrial fibrillation, and autoimmune hepatitis. She presented with left-sided chest pressure and shortness of breath. Troponin T was elevated at 0.11 ng/mL, and an electrocardiogram revealed a non-specific ST-T wave abnormality. Cardiac CT angiography demonstrated a left main coronary artery arising from the right coronary sinus with a course anterior to the pulmonary artery. Coronary angiogram revealed no angiographic stenosis or plaque. Cardiac MRI revealed no angiographic stenosis or plaque. Cardiac MRI angiogram demonstrated a left main coronary artery arising from the right coronary sinus with a course anterior to the pulmonary artery. Coronary angiogram revealed no angiographic stenosis or plaque. Cardiac MRI angiogram demonstrated a left main coronary artery arising from the right coronary sinus with a course anterior to the pulmonary artery.

Discussion ACAOS is a rare finding with variable clinical implications, including association with sudden cardiac death. It is theorized that compression of the coronary artery between the aorta and pulmonary artery can result in ischemia and fatal arrhythmias. Management varies from observation to surgical correction in symptomatic patients. It is unclear whether our patient’s symptoms and MRI findings were related to transient ischemia, to immune globulin embolization, or to a manifestation of her active polymyositis.

**B41** A RARE CASE OF A RAOULTella SPECIES BACTEREMIA IN A NEONATE

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**Introduction** Late onset sepsis (LOS) is a common complication seen in the neonatal intensive care unit (NICU). The most common causative organisms include coagulase-negative Staphylococcus, Staphylococcus aureus, and Escherichia coli. Raoultella species rarely cause LOS in the NICU. However, sepsis due to Raoultella species is commonly associated with intensive care unit stays, indwelling catheters and immunocompromised status. These are characteristics of many patients in a NICU. To date, there have been six reported cases worldwide of Raoultella sepsis in infants. We present a case of LOS in an extremely preterm neonate caused by Raoultella, and the successful treatment to eradicate the organism.

**Case description** A female newborn born at 25 weeks completed gestation and 690 grams by cesarean section due to severe pre-eclampsia was admitted to the NICU. Upon admission, she was started on total parenteral nutrition, respiratory support of bubble continuous positive airway pressure (bCPAP) and empiric antibiotics. Within hours of birth, the abdomen became firm and distended and an abdominal x-ray revealed free air. Emergent laparoscopy was performed which confirmed focal intestinal perforation and bowel ischemia. A 4cm segment of small intestine was removed and an ileostomy was created. On the sixteenth postoperative day, the infant had increased frequency of desaturation events on mechanical ventilation, increased need for oxygen concentration and tachycardia. A septic workup was initiated which revealed an abundance of bands, metamyelocytes and myelocytes and a C-reactive protein of 4.6 mg/dL. Peripheral blood, central line, and urine cultures were obtained and the infant was started on empiric vancomycin and tobramycin. The infant improved and was extubated the following day to bCPAP. The peripheral blood culture was identified as Raoultella species and the central line and urine cultures remained negative. A lumbar puncture was performed and found no evidence of meningitis. Consultation with pediatric infectious disease was obtained, and because the infant showed evidence of clinical illness which had led to the evaluation for sepsis, the decision was made to treat for LOS. The organism demonstrated resistance to ampicillin and sensitivities to cefepime, cefotaxime, cefazidime, ceftriaxone, ciprofloxacin, gentamicin, piperacillin/tazobactam, and trimethoprim-sulfamethoxazole. A repeat blood culture obtained 2 days after initial culture and after the infant had been on antibiotics for 48 hours was negative. Antibiotic coverage was narrowed to ceftazidime as a single agent for a total course of 14 days after first negative culture. The infant did well thereafter and was weaned off parenteral nutrition and transitioned to room air.

**Discussion** This Raoultella infection represents the first case in our neonatal intensive care unit of this species and was successfully eradicated with a 14 day course of a third generation cephalosporin. Medical literature is sparse on Raoultella infections in neonates and potential sources. A study performed on enteral feeding tubes in otherwise asymptomatic neonates revealed that 11% of isolates represented organisms of the Raoultella species. This could illustrate a possible source for infection. Though it is unclear how this infant acquired the infection, we suspect translocation from bowel injury, translocation from feeding tube or as a contaminant from a visitor or caregiver are all possible etiologies. This case illustrates a case of LOS in an extremely preterm infant who presented with commonly-seen, non-specific clinical symptoms, and was due to a Raoultella species.

**B42** PELIOSIS HEPATIS AND COMMON VARIABLE IMMUNODEFICIENCY

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**Introduction** Peliosis hepatis is a rare condition characterized by blackish-blue blood-filled cavities in hepatic parenchyma caused by dilatation of hepatic sinusoids. Peliosis hepatis has previously been described in patients with secondary immunodeficiency, including HIV, tuberculosis, and cancer. Medications such as azathioprine, cyclosporine, and oral contraceptives have been implicated in peliosis hepatis as well. We present the first case of peliosis hepatis in a patient with a primary immunodeficiency, common variable immunodeficiency (CVID).

**Case description** A 44-year-old African American male presented to our hospital with gastrointestinal bleeding and elevated liver function tests. The patient’s medical history included CVID (diagnosed in 2012) and chronic kidney disease. Records from 2012 revealed no cirrhotic morphology, however, the patient had jaundice, regenerative nodules on liver pathology, and low immunoglobulin levels when he was initially diagnosed with CVID. The patient was transferred to our hospital in 2015 for management of his liver failure and CVID. The patient had not been receiving IVIG regularly for his CVID and his IgG days before presenting to our hospital was 283 mg/dL. Patient received an infusion of intravenous immunoglobulin prior to transfer. On arrival at our hospital, an MRI of the abdomen was performed which revealed a cirrhotic liver, a 5 x 3cm lesion, and numerous poorly defined nodules which had decreased enhancement. A CT-guided liver biopsy revealed peliosis hepatis and nodular regenerative hyperplasia, along with fibrosis not consistent with cirrhosis (figure 1). The patient denied alcohol use, drug abuse, and
was negative for HIV and Bartonella antibodies. No other etiology of his liver disease was found. The patient succumbed to his disease.

Discussion Peliosis hepatitis is a rare condition that previously was reported to occur in patients with secondary immunodeficiency. Diagnostic work up of a patient with peliotic lesions should include testing for both primary and secondary immunodeficiencies, a thorough medication history and Bartonella Ig testing. The etiology of peliosis hepatitis in patients with primary immunodeficiencies remains unclear but may lead to liver failure or even death. Further research to reveal the underlying mechanisms of peliosis hepatitis in primary immunodeficiency is needed.

Abstract C10 Figure 1 Perisinusoidal fibrosis

was unresponsive and pulseless in bed. Cardiopulmonary resuscitation was performed with successful return of spontaneous circulation after 12-minutes. Further ICD interrogation revealed that he was in ventricular fibrillation at 170 bpm pre-arrest, however, the defibrillator threshold was set at 180 bpm. Unfortunately, he remained in critical condition and expired one day later.

Discussion This case highlights the difficulty in determining appropriate telemetry use. While our patient appeared to be hemodynamically stable, continuous telemetry monitoring may have been able to prevent this poor outcome. While the American Heart Association (AHA) has outlined a guideline for the appropriate use of cardiac monitoring, its final use is determined by the physician’s clinical judgement. Based on the AHA, patients are classified into class I (monitoring indicated), class II (monitoring may be of benefit), and class III (monitoring not indicated). Despite our patient’s extensive medical and cardiac history, he did not have class I or II indications such as typical chest pain, newly diagnosed coronary lesion, undergoing coronary angiography or ablation, pacemaker or defibrillator placement, acute heart failure, or syncope. Physicians need to use clinical judgement when assessing for appropriate use of cardiac monitoring while at the same time preventing over use. Cardiac monitoring may aid is early detection of cardiac arrest, however, current medical research has yet to reveal any change in outcomes for such cases.

APPROPRIATE USE OF TELEMETRY: INDICATION VERSUS GRATIFICATION

Julien Feghaly, Zachary Oman, Ariana Mooradian. St Louis University Hospital, MO

Introduction Physicians are often in a dilemma in determining the appropriateness of starting continuous cardiac telemetry monitoring on a variety of patients presenting to the hospital. Most physicians would agree that telemetry monitoring is warranted for patients with syncope, arrhythmias, myocardial infarction, or following cardiac surgery. However, other situations are less clear such as patients with abdominal pain, stable pulmonary embolism, atypical chest pain, or rate controlled atrial fibrillation.

Case description A 79-year-old male with past medical history of end stage renal disease (ESRD) on hemodialysis, heart failure with reduced ejection fraction status-post implantable cardiac defibrillator (ICD) placement, coronary artery disease with one drug eluting stent in his right coronary artery, chronic atrial fibrillation, and colon cancer status post left hemicolecotomy presented with a 3-day history nausea, epigastric and umbilical abdominal pain, with reported black stool following dialysis. Upon admission he was found to have ileac artery stenosis with an elevated lactic acid of 16.6 mmol/L. but was deemed too high risk for surgical intervention given his complex comorbidities. He was not started on telemetry as there was no concern for acute heart failure, despite his history of chronic hypotension (average: 90/50 mmHg) secondary to ESRD and chronic heart failure with reduced ejection fraction (25–30%) & severely decreased left ventricular systolic function. On day 3 of the admission, he was found unresponsive and pulseless in bed. Cardiopulmonary resuscitation was performed with successful return of spontaneous circulation after 12-minutes. Further ICD interrogation revealed that he was in ventricular fibrillation at 170 bpm pre-arrest, however, the defibrillator threshold was set at 180 bpm. Unfortunately, he remained in critical condition and expired one day later.

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APICAL HYPERTROPHIC CARDIOMYOPATHY: A DIAGNOSTIC DILEMMA

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Introduction Apical hypertrophic cardiomyopathy (AHCM) is an uncommon morphologic variant of Hypertrophic Cardiomyopathy (HCM) in which the hypertrophy of the myocardium predominantly involves the apex of the left ventricle. We present a case of asymptomatic man with EKG and Nuclear stress test findings concerning for ischemia but MRI displaying Apical hypertrophic cardiomyopathy.

Case description 48 year old male with no significant past medical history initially came for a routine physical examination and had an electrocardiogram done that was significant for left ventricular hypertrophy with ST segment depressions in the anterolateral and inferior leads (figure 1). Nuclear stress test showed perfusion defects in the apex and antero-septal wall along with hypokinesis of the corresponding walls (figure 2). Echocardiogram showed LVEF of 61% with normal left ventricular wall thickness without any systolic anterior motion of the mitral valve. MRI with late gadolinium enhancement showed normal LV size with vigorous systolic function and complete apical cavity obliteration with thickening of the apical LV segments consistent with apical hypertrophic cardiomyopathy (figure 3). No evidence of late gadolinium enhancement to suggest myocardial fibrosis or scar was found. Based on objective data, the plan was made to have genetic testing done so as to help identify specific variants of HCM for him and his family. Since he did not have poor prognostic factors for sudden cardiac death, no Implantable Cardioverter Defibrillator (ICD) was placed for primary prevention of malignant arrhythmias. This case highlights that Apical HCM...
A high index of suspicion for AHCM should be maintained in a person with evidence of apical wall motion abnormalities on stress testing but no clinical or biochemical signs of cardiac ischemia.

Discussion

Apical hypertrophic cardiomyopathy (AHCM) is a rare variant of HCM where left ventricular hypertrophy is confined to the cardiac apex. AHCM can be incidental in nuclear stress imaging as well as echocardiogram. A high index of suspicion for AHCM should be maintained in a person with evidence of apical wall motion abnormalities on stress testing but no clinical or biochemical signs of cardiac ischemia.

Echocardiogram is the initial diagnostic tool in the evaluation of AHCM and shows hypertrophy of the LV apex. MRI allows better overall assessment of the degree and extent of LVH in HCM patients than echocardiography. Routine use of echocardiogram without contrast does not exclude AHCM, thus MRI and contrast echocardiography are superior in diagnostic accuracy. AHCM rarely gets diagnosed as ischemic disease based on both EKG and stress test imaging findings. AHCM patients usually do not have LVOT obstruction but may have mid-ventricular obstruction.

Introduction

Systemic amyloidosis is characterized by extracellular deposition of pathologic insoluble fibrillar proteins. Although there are many different types of amyloidosis, two types account for over 95% of all cardiac amyloidosis: immunoglobulin light chain amyloidosis (AL) and transthyretin amyloidosis (aTTR). The two types have distinct prognoses and treatments - AL cardiac amyloidosis has a median survival from diagnosis of less than 12 months while aTTR has a median survival of 3–5 years. Cardiovascular magnetic resonance (CMR) is commonly used to make the diagnosis of cardiac amyloidosis. There are some data that CMR could also be used to determine the subtype. We describe a case where cardiac amyloidosis was diagnosed in a patient with risk factors for both AL and aTTR subtypes, where an endomyocardial biopsy was ultimately performed to identify the subtype.

Case description

An 86-year-old male with chronic atrial fibrillation, chronic kidney disease, monoclonal gammopathy of undetermined significance (MGUS) for four years, and heart failure was found incidentally to have a left atrial mass during an MRI of the abdomen and lower extremities performed to evaluate a popliteal aneurysm. A CMR was subsequently performed which demonstrated that the left atrial mass was a thrombus. Additionally, the patient was found to have diffuse subendocardial LGE in the LV, RV and the atria, which is pathognomonic for cardiac amyloidosis.
subendocardial late gadolinium enhancement (LGE) in a non-coronary distribution, which was consistent with cardiac amyloidosis. Given his history of MGUS, AL cardiac amyloidosis was likely. However, as an octogenarian, he was also likely to have aTTR cardiac amyloidosis. CMR cannot reliably identify the subtype of cardiac amyloidosis; while diffuse subendocardial LGE is more often seen in AL cardiac amyloidosis, it may also be seen with earlier stages of aTTR cardiac amyloidosis. Therefore, to clarify the subtype, an endomyocardial biopsy was performed, which revealed aTTR cardiac amyloidosis.

Discussion Both MGUS and aTTR cardiac amyloidosis are diseases of the elderly; autopsy studies show a prevalence of nearly 25% of aTTR cardiac amyloidosis over age 80, and the prevalence of MGUS is 7.5% among those 85 years of age or older. MGUS could lead to AL cardiac amyloidosis. However, AL cardiac amyloidosis is a rare condition, with only around 1500 new cases diagnosed annually in the US. Thus, the presence of MGUS may lead clinicians to incorrectly assume that they are dealing with AL cardiac amyloidosis when in fact, the elderly patient with MGUS is statistically more likely to have another disease associated with aging - aTTR cardiac amyloidosis. For this reason, an endomyocardial biopsy should be performed to identify the subtype of cardiac amyloidosis even when clinical and imaging features may suggest one of the two main types of cardiac amyloidosis.

C13 CHRYSEO BACTERIUM INDOLOGENES BACTEREMIA IN CIRRHOSIS

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Introduction CHRYSEO BACTERIUM INDOLOGENES is a gram negative rod bacteria which can be found in soil, plant, water sources and food products. In the hospital setting it can be isolated from wet surfaces and water sources. CHRYSEO BACTERIUM INDOLOGENES is rarely recovered from humans and has been implicated as a causative agent in hospital acquired pneumonia, bacteremia, peritonitis, urinary tract infection and catheter related infections. Possible risk factors include indwelling devices, prolonged exposure to broad-spectrum antibiotics, Immunosuppression, and old age. We present a rare case of ventilator associated pneumonia in a cirrhotic patient presenting with upper GI bleeding.

Case presentation A 62 years old Caucasian man with past medical history of diabetes mellitus, hypothyroidism, bipolar disorder, alcohol abuse, hemochromatosis and liver cirrhosis. Liver cirrhosis was complicated by portal hypertension with known history of esophageal and gastric varices, hepatic encephalopathy and ascites. The patient presented to our medical center with general weakness, dizziness, dyspnea on exertion and melena. At admission he was hypotensive with BP of 87/30 and HR of 90 BPM. The physical exam was notable for pallor, jaundice, spider angiomata, 85 cm, and soft abdomen without tenderness. Blood work up revealed HB of 4.4, INR 1.8, Cr 1.6 (baseline 0.6), total bilirubin 2, ALT 146, AST 268, and ALKP 73. He was intubated for airway protection and planned for upper endoscopy. Intravenous ceftriaxone, proton pump inhibitor and octreotide were started. Given evidence of bleeding gastric varices on upper endoscopy her underwent BRTO and placement of transjugular intrahepatic portosystemic shunt (TIPS). On the second day of admission and while still ventilated he developed a fever with rising WBC. Sepsis work up revealed bilateral infiltrates on CXR, negative urine analysis, and diagnostic paracentesis ruled out spontaneous bacterial peritonitis. Antibiotic coverage was broadened from ceftriaxone to ceftazidine and vancomycin. He continued to have intermittent low grade fevers with thick bronchial secretion and repeated CXR demonstrated worsening infiltrates. He underwent bronchoscopy which showed: friable, erythematous airways, thick/stringy gold tinged mucus in RMSB. Secretions also in RML and RLL which were therapeutically aspirated. BAL done in RML with 20 cc of cloudy mucus removed. Sputum culture was positive for CHRYSEO BACTERIUM INDOLOGENES. Levofloxacin was added according to sensitives with resolution of fever and he was successfully extubated.

Discussion CHRYSEO BACTERIUM INDOLOGENES is considered a rare infectious causative agent in human. The vast majority of cases are nosocomial infections with predisposing factors such as indwelling catheters, comorbidities and immunosuppression. Morality is high with prolonged hospital stay. Although most data on CHRYSEO BACTERIUM INDOLOGENES comes from Asia and particularly from Taiwan, in recent years there has been increasing reports in the USA as well. The main manifestation being bacteremia, catheter-related infections, hospital acquired pneumonia, peritonitis, UTI and cellulitis. Although other morbidities such as DM, COPD, malignancy, ESRD play a major role as predisposing factors, liver cirrhosis is rarely reported in such patients. Recent reports have shown increasing resistance to aminoglycosides, tetracyclines, chloramphenicol, erythromycin and colistin. In our case, the microbiology data showed a similar sensitivity profile similar to what has been recently published. Increasing awareness in the hospital setting for infection with CHRYSEO BACTERIUM INDOLOGENES is warranted.

C14 A RARE CASE OF INFECTIOUS PSEUDOANEURYSM DUE TO ASPERGILLUS FLAVUS IN THE SETTING OF RENAL TRANSPLANT

Samia Adl, Joseph Bennett, Rebecca Pauly. University of Missouri Kansas City, MO

Introduction Renal transplant is currently the preferred treatment for end-stage renal disease, particularly given improvements in surgical techniques and immunosuppressive agents. Frequent complications following renal transplant include acute or chronic graft rejection, nephrophathy secondary to immunosuppressive agents, or infections in setting of immunosuppression. Vascular complications may occur including renal arterial stenosis and vascular thrombosis.1 Pseudo-aneurysms are particularly rare, with mycotic aneurysms reported in <1% of patients after renal transplant.2 We present a case an infected pseudo-aneurysm involving the renal artery anastomosis resulting in transplant nephrectomy.

Case report 77-year-old gentleman with Type 2 diabetes, hypertension and end stage renal disease underwent deceased-donor renal transplantation. Two months following later, he was admitted for an acute kidney injury (AKI); creatinine (Cr) increased from a baseline 1.3 to 2.7. A renal biopsy showed mildly active cellular rejection. He was treated with high dose subclavian portosystemic shunt (TIPS). On the second day of admission and while still ventilated he developed a fever with rising WBC. Sepsis work up revealed bilateral infiltrates on CXR, negative urine analysis, and diagnostic paracentesis ruled out spontaneous bacterial peritonitis. Antibiotic coverage was broadened from ceftriaxone to ceftazidine and vancomycin. He continued to have intermittent low grade fevers with thick bronchial secretion and repeated CXR demonstrated worsening infiltrates. He underwent bronchoscopy which showed: friable, erythematous airways, thick/stringy gold tinged mucus in RMSB. Secretions also in RML and RLL which were therapeutically aspirated. BAL done in RML with 20 cc of cloudy mucus removed. Sputum culture was positive for CHRYSEO BACTERIUM INDOLOGENES. Levofloxacin was added according to sensitives with resolution of fever and he was successfully extubated.

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intravenous steroids. Patient was re-admitted within 3 weeks with worsening Cr of 3.8. He was initially treated as pre-renal AKI with intravenous fluids. However, a repeat biopsy was performed as Cr did not improve beyond 2.1. During ultrasonography for renal biopsy, a possible renal artery aneurysm was noticed. A formal renal ultrasound showed a 3cm × 3.4cm × 4 cm aneurysm proximal to the renal artery anastomosis to the right external iliac artery. A pelvic arteriogram was performed which showed a large pseudo-aneurysm arising directly off the right external iliac artery. Renal transplant artery was patent with sluggish flow from distal side of aneurysm. Stent placement by Interventional Radiology was considered but deferred due to proximity of aneurysm to anastomosis. Patient underwent exploratory laparotomy. Significant inflammation and scar tissue surrounding the hilum of the transplanted kidney and necrotic tissue and purulence within the pseudo-aneurysm was noted. It was felt that the arterial flow to the transplanted kidney could not be restored; hence resection of the infected pseudo-aneurysm and transplant nephrectomy was performed. Post operatively patient was started on Continuous renal replacement therapy (CRRT). Renally dosed vancomycin, meropenem, and micafungin were started. Bacterial and fungal blood cultures remained negative. Fungal cultures from the pseudo-aneurysm grew Aspergillus flavus on 3 separate samples. The patient was transitioned to Isavuconazonium for 6 weeks. Pathology of explanted kidney showed transmural necrosis of the renal artery, no evidence of rejection, and scattered micro-abscesses within parenchyma. As patient improved clinically, he was transitioned to intermittent hemodialysis.

Discussion Infectious pseudo-aneurysms are a rare entity with potentially devastating consequences. Chung et al summarized all 30 reported cases of infectious pseudo-aneurysms in literature; all except 4 resulted in graft nephrectomy. Patients can present with hemorrhagic shock, fever, abdominal pain, pulsatile mass and rarely, with AKI or asymptomatically. Treatment has to be individualized, but early diagnosis and management may allow preservation of a renal allograft. All physicians frequently encounter acute renal injuries. Given increasing prevalence of patients with renal transplants, it is essential to have increased awareness about such rare but critical complications in renal transplant recipients to allow for appropriate early diagnosis, management and timely referral to relevant specialties. In doing so, a delayed diagnosis, such as renal dysfunction attributed initially to poor volume status in our patient, can be avoided.

REFERENCE


Introduction Xanthogranulomatous pyelonephritis is a rare and severe form of chronic pyelonephritis. This is usually seen in patients with recurrent UTIs or chronic urinary tract infections and obstructive uropathy. When it is associated with chronic UTIs, the causative organisms are E. coli and Proteus. It is more commonly seen in women than men. CT and ultrasound may help in making the diagnosis, but cannot confirm it. The diagnosis is usually confirmed with a functional scan and biopsy upon nephrectomy. It is sometimes complicated by fistula formation. Once diagnosed, nephrectomy has to be performed.

Case presentation The patient is a 47 year old female with a prior history of kidney stones with nephrostomy tube placement in 2010, who presented to the hospital for complaints of severe right flank pain and swelling that was worsening. This was not associated with dysuria, hematuria, urinary frequency, fever, chills nor any other symptoms. Her course started in 2011 with several calculi in the right uretero-pelvic junction and emphysematous pyelonephritis. She was seen by Urology and a ureteral stent was inserted. The patient was lost to follow up, but returned with recurring symptoms in 2012 to the Urology office. At that time, she was found to have a non obstructing renal calculus and an encrusted retained ureteral stent. The ureteral stent was replaced with another stent. Nephrostomy tube was inserted to aid in the drainage and lithotripsy performed for the obstructing renal calculus. She also underwent several ureteroscopies for the calculus burden and was eventually free of calculus in 2013. She did not have any more complaints including flank pain since then until she presented to the hospital in 2018.

During this admission, lab work showed a urinary tract infection with E. coli that was pansensitive. She did not have any leukocytosis. CT of the abdomen showed findings suggestive of severe right pyelonephritis with possible phlegmon. She was admitted and started on broad spectrum antibiotics, which were tapered to oral Bactrim after 3 days. She underwent incision and drainage and was discharged home with

Abstract C16 Figure 1
A RARE CASE OF SERRATIA ENDOCARDITIS IN A PATIENT WITH CHRONIC MYELOID LEUKEMIA

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Introduction Serratia species are gram negative bacilli of the Enterobacteriaceae group of bacteria. The genus Serratia consists of at least 20 species and S. marcescens is the main human pathogen. S. marcescens has been associated with urinary tract infections, pneumonia, and bloodstream infection. Endocarditis caused by Serratia species has been described, particularly in intravenous drug users. There are case reports in HIV patients and in patients with prosthetics heart valves, but it has never been reported in patients with chronic myeloid leukemia (CML). We report a case of Serratia native valve endocarditis in a patient who presented with multiple symptoms and newly diagnosed with chronic myeloid leukemia during the same admission.

Case description We report a 40-year-old Caucasian male with history of bicuspid aortic valve presented to our hospital with left upper quadrant abdominal pain, nausea, vomiting, diarrhea, urinary urgency/incontinence and lethargy of two days duration. Patient also had sudden onset of dizziness, rigor, and low back pain one day prior to presentation. He visited an urgent care center where he was negative for influenza and subsequently sent home. On presentation to the hospital, his body temperature was 103.1 F and laboratory studies showed WBC of 79,000 TH/UL (ref range 4,000–11,000 TH/UL) mild transaminitis with aspartate transaminase-78 IU/L (ref range 15–46 IU/L), alanine transaminase of 58 IU/L (ref range 0–49 IU/L), total bilirubin of 3.2 mg/dl (ref range 0.2–1.3 mg/dl), serum creatinine 2.4 mg/dl (ref range 0.6–1.3 mg/dl). Urinalysis showed white count of 11–20/HPF, 6–10 RBCs/HPF, leukocyte esterase and nitrites were negative but large bacteria were present. CT of abdomen and pelvis showed mild hepatomegaly, mild splenomegaly and possible splenic infarcts. CT of head without contrast was performed due to acute encephalopathy which showed no acute intracranial process. Trans-thoracic echocardiogram showed normal EF of 55%, no valvular vegetation, bicuspid aortic valve with mild stenosis (mean gradient 21 mmHg), and elevated central venous pressure. Platelet count was 170 TH/UL (ref range 140–400 TH/UL) on presentation but dropped to 40 TH/UL on third day of hospitalization. Lactate dehydrogenase elevated at 1801 IU/L (ref range 313–618 IU/L), D-dimer was significantly elevated, INR 2.2 and PTT 24.5 sec (ref range 11.4–15.0 sec), Duplex ultrasound of lower extremities was done which was negative for thrombosis. Hematology team performed bone marrow biopsy due to leukocytosis to rule out malignant process.

Patient was empirically treated with ceftriaxone and vancomycin for possible sepsis. Urine culture grew Serratia marcescens. Patient continued to have fever, chills and developed neck stiffness the following day of admission, hence lumbar puncture was performed to rule out meningitis. CSF analysis showed white count of 1747/UL (ref range 0–5/UL), RBC <3,000/UL (ref range 0–5/UL), neutrophils 91% (ref range 0–6%), CSF glucose 39 mg/dl (ref range 40–70 mg/dl), and CSF protein 102 mg/dl (reg range 15–60 mg/dl). Doxycycline was added to cover any tick-borne illnesses due to recent history of hiking.

Infectious disease was later consulted Blood and CSF cultures turned out negative. CSF meningitis PCR panel was negative. A wide range of bacterial, viral, fungal serologies including tick panel and hepatitis panel were performed all of which was negative. On day 6 of hospitalization transesophageal echocardiogram was performed as patient continued to have high-grade fever with chills and left upper quadrant abdominal pain. It showed linear echo density measuring 1.9 cm noted on the aorta aspect of the aortic valve concerning for vegetation. The intervalvular fibrosa appeared mild thickened, although may not be diagnostic for abscess. MRI of brain was

Abstract C16 Figure 2

instructions to continue Bactrim for another 5 days. However, the patient returned to the hospital 3 weeks later with complaints of drainage from the incision site and increasing lethargy. Lab work done in this visit did not show a UTI. When CT of the abdomen and pelvis was done, and it showed findings that were suggestive of xanthogranulomatous pyelonephritis and perinephric abscess. She was started on empiric antibiotics and was seen by Urology. She was started on Ertapenem for 3 weeks and was planned for a MAG3 scan after the completion of antibiotics for viable kidney function. When the scan was performed, her right kidney was non functional and nephrectomy was performed.

Discussion Xanthogranulomatous pyelonephritis is a rare form of pyelonephritis that usually results from chronic damage from repeated infections. Even though the above patient has a history of obstructing renal stones in the past, she had been calculus free since 2013 and had no complaints since then. She presented to the ED 5 years later with a urinary tract infection. She was found to have severe pyelonephritis, for which she was treated with incision and drainage and antibiotics. Of note, XGP was not seen on the CT scan at presentation. However, when she returned 3 weeks later, she was found to have XGP. It is unusual to have such a rapid progression and destruction of the renal parenchyma.

REFERENCES

Abstracts

C18 A RARE CASE OF SERRATIA ENDOCARDITIS IN A PATIENT WITH CHRONIC MYELOID LEUKEMIA

1Annapoorna Singh, 2Daulath Singh. 1UMKC School of Medicine, MO; 2Loyola University Medical Center, IL;
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done which showed multiple brain abscesses secondary to septic emboli from aortic valve endocarditis. Ceftriaxone was discontinued and meropenem was added to vancomycin and doxycycline. Anticoagulation was not initiated for splenic infarcts due to multiple brain abscesses.

Bone marrow biopsy showed hypercellular marrow with no increased blast population. Molecular testing was positive for BCR-ABL, consistent with the diagnosis of chronic myeloid leukemia. MRI with/without contrast of brain was repeated due to the worsening symptoms of occipital headache, new onset blurring of vision, diplopia, nystagmus, vertigo, transient right facial droop and left transient visual field defect. It showed acute new infarct in the right cerebellum, new abnormal flow within right vertebral artery suggestive of acute occlusion, demonstration of abnormal flow in the left vertebral artery suggestive of subacute or chronic occlusion, and multifocal lesions involving cerebellum, bilateral occipital lobes, parietal lobes consistent with multifocal abscesses with edema. Patient was then started on IV heparin for anticoagulation due to the risk of emboli propagation. At this time, Vancomycin and doxycycline were discontinued and patient was treated with meropenem and linezolid for endocarditis.

Patient had a repeat ultrasound of the abdomen that showed large splenic abscess which prompted open splenectomy. The decision was made to perform mechanical aortic valve replacement following the splenectomy for source control. Aortic valve vegetation was sent for microbiological analysis. Post- surgery, patient developed confusion, worsening of the headache and drowsiness. CT head without contrast was done to avoid thrombosis/bleeding complications. Patient continued to have thrombocytosis, plateletpheresis was done to avoid thrombosis/bleeding complications.

About 10 days into his admission, patient was found to have progressively worsening thrombocytopenia with platelets counts ranging 1,091–1,841 TH/μL (ref range 140–400 TH/μL). Patient’s thrombocytopenia was thought to be secondary to splenectomy however underlying infections/sepsis and CML could also might have contributed. Hematology recommended Hydroxyurea and the dose was gradually increased to 1 gram twice daily. Patient’s neurological status gradually improved and repeat CT scan of the head showed progressively decreasing fourth ventricle size and the tube was taken out on the 25th day of admission. Heparin infusion was discontinued following the external ventricular drain removal and patient was transitioned to warfarin for prosthetic aortic valve. Meanwhile, splenic abscess culture grew Candida albicans, hence was treated with fluconazole.

Serratia marcescens DNA was detected with 16S rRNA gene primer set in the aortic vegetation after about 3–4 weeks of admission. Patient continued to have thrombocytopenia, hydroxyurea dose was increased to 2 g daily and plateletpheresis was done to avoid thrombosis/bleeding complications.

Patient was treated with 6 weeks course of meropenem for Serratia endocarditis. Patient was initiated on treatment for chronic myeloid leukemia prior to discharge.

Discussion Serratia species are facultatively anaerobic gram-negative bacillus of the Enterobacteriaceae group of bacteria. Serratia species are motile and can adhere to cells via fimbriae. The genus Serratia consists of at least 20 species, of which eight are known to cause infections in humans. Serratia marcescens is the main human pathogen. S. marcescens produces a few different hemolysins that are toxic to different cell types. S. marcescens and several other Serratia species encode an inducible, chromosomal AmpC beta-lactamase, although it is typically expressed at low levels. The low levels at which this enzyme is typically expressed, AmpC beta-lactamase mediates resistance to several beta-lactam antibiotics, such as penicillin’s and first generation cephalosporins.

Endocarditis is most commonly caused by gram positive bacteria and among the gram-negative organisms, Escherichia coli is the most common pathogen followed by Pseudomonas aeruginosa and Klebsiella pneumoniae as reported in a 26 Italian centers prospective cohort study. The genitourinary tract source, immunosuppression and the presence of a cardiac implantable electronic device were found to be associated with GNB endocarditis. In another 12 years prospective cohort study of hospitalized patients from Oct 2002 to Dec 2014, among the 284 patients, 3 bacterial species were isolated—Staphylococcus aureus, Pseudomonas aeruginosa and Serratia marcescens. Gram negative bacillus bacteremia patients exhibited higher levels of comorbid conditions (hospital acquired infection, malignancy and recent surgery). In the same study GNB endocarditis patients were more likely to have bacteremia originating from a gastrointestinal/genitourinary source.

Serratia species has been occasionally recognized as the cause of healthcare associated bacteremia due to the contamination of blood products, cleaning solutions and inadequate sterile techniques with intravenous medications. However, a recent population-based study of Serratia species infections including bacteremia in Canada, showed that 65% of infections were community acquired infections and similar reports from Australia revealed that 47% of bacteremia episodes were started in the community. Although marcescens species is the most common cause of endocarditis in the Serratia genus, cases of Serratia liquefaciens IE were reported in a patient with intravascular central catheter related suppurative thrombophlebitis.

Infective endocarditis by S. marcescens was first described in the medical literature as a case series of 19 patients observed in the San Francisco Bay Area, 12 of which were intravenous drug users. Endocarditis caused by Serratia marcescens is seen most commonly in IVDU and in one report it caused 14% of all addict-associated endocarditis. Among these patients, most cases of right-sided endocarditis were cured by antibiotics alone and most cases of left-sided endocarditis treated medically alone did not survive. Most other cases of endocarditis due to S. marcescens have occurred in patients with prosthetic heart valves. Only two cases of native valve endocarditis due to S. marcescens were reported in the literature. Both had right-sided involvement and indwelling intravenous catheters at the time of diagnosis and both were successfully treated medically. An experimental endocarditis rabbit model using S. marcescens confirmed the significance of the presence of an indwelling catheter in the development of endocarditis.

In IVDU, injection of foreign antigens can precipitate antibody production that leads to immune complex deposition on valvular surfaces, which forms nidi for bacterial adhesion. Studies showed that IVDUs have ‘immunologic dysregulation’ even when not HIV infected. It has been noted that HIV seropositive patients with CD4 cell counts>350 cells/μL had an OR of 2.31 for developing infective endocarditis, whereas those with a CD4 cell count<350 cells/μL had an OR of 8.31. Patient with abnormal immune functioning may not be able to clear bacteria and are at risk of severe sepsis. The prognosis of endocarditis is also influenced by immune status
of the patient. The evolution of vegetation size, its mobility and consistency, the extent of the disease, and the severity of valvular regurgitation were related to late complications. With therapeutic options including modern antibiotic treatment and early surgical intervention, IE turned out to be a curable disease.

There had been a case report of ciprofloxacin resistant Serratia marcescens in the Non-Hodgkin lymphoma who was receiving ciprofloxacin for neutropenic prophylaxis but there have no reports in chronic myeloid leukemia patients.

There are several unique features in our reported case. As mentioned, he had no usually reported risk factors for Serratia endocarditis like intravenous drug use, cardiac devices, prosthetic heart valve and endovascular catheters. He had left sided endocarditis with involvement of the native aortic valve which was not initially detected on the transthoracic ECHO. Serratia endocarditis is commonly left sided even in IVDU. Forty percent of Serratia marcescens endocarditis are on aortic valve and septic embolization is very common. Mortality rates are high with just medical therapy, so a combination of medical and surgical management is recommended for left sided endocarditis by Serratia. Most cases of right sided endocarditis resolve with appropriate antibiotic administration without the need for further surgical management. Like reported cases, our case was found to have left sided valvular involvement that needed surgical intervention due to progressive embolic phenomena despite being on medical therapy and size of the vegetation (1.9 cm). Another unique feature is the patient survived after such a morbidity hospital course and multiple surgical procedures. He had underlying chronic myeloid leukemia which might have led to immunocompromised state and subsequent superinfection with Serratia from the urinary source. Based on our search, this is the first reported case in the literature of a patient with left sided Serratia endocarditis and underlying CML.

Abbreviations
CML - Chronic Myeloid Leukemia; HPF - High power field; CT - Computed Tomography; EF - Ejection fraction; CSF - Cerebrospinal fluid; PCR - Polymerase chain reaction; INR - International Normalized Ratio; PTT - Partial thromboplastin time; GNB - Gram negative bacteria; HACEK - Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella; IVDU - Intravenous drug user; ECHO - Echocardiogram; IE - Infective Endocarditis.

REFERENCES
chemistry workup was non-revealing with negative viral hepatitis serologies, negative Anti-Nuclear Antibody Screen, Anti-Smooth Muscle Antibody, Anti-Mitochondrial Antibody, IgM, IgA and normal IgG Subclasses 1,2,3,4. Liver biopsy showed massive hepatic inflammation with evidence of hepatic necrosis with microvesicular steatosis consistent with toxic metabolic liver injury. The patient slowly recovered after stopping Disulfiram.

Discussion Disulfiram is a thiamine derivative which is a potent inhibitor of aldehyde dehydrogenase activity leading to elevated serum acetaldehyde levels. Elevated acetaldehyde causing flushing, headache, nausea, vomiting, diaphoresis, palpitations, chest pain, dyspnea, and confusion. The mechanism of hepatic injury is idiosyncratic hypersensitivity. Disulfiram liver injury can be variable from mild aminotransferases elevation to severe hepatitis with hepatic failure and potential death. Chronic Disulfiram ingestion can lead to asymptomatic mild elevation of aminotransferases up to 2–3 times the ULN in 20–30% patients. Only less than 1% of patients will develop severe hepatitis with remarkable aminotransferase elevation (50x ULN), which can cause hepatic failure with coagulopathy and jaundice. The mortality rate is 10% in patients with severe hepatitis. Alcohol-induced liver injury has a similar histological presentation with evidence of steatohepatitis and formation of Mallory bodies but to a lesser degree than that is seen with Disulfiram induced hepatitis. It is crucial to understand the variable potential of Disulfiram in alcohol abuse patients and differentiate severe hepatic injury from Disulfiram rather alcohol hepatitis. The approach for those patients with severe hepatitis from Disulfiram requires hospitalization and urgent liver biopsy confirming the diagnosis. Careful monitoring for signs of hepatic failure with a change in mental status and coagulopathy is crucial in patients with remarkable elevation in liver enzymes. Clinicians should be able to differentiate between alcohol liver injury and Disulfiram hepatic injury, which can be fatal.

Abstracts

PROXIMAL WEAKNESS, PAIN, AND CACHEXIA: A CASE OF DIABETIC AMYOTROPHY

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Introduction Diabetic amyotrophy is an incapacitating illness, distinct from other forms of diabetic neuropathy. Characterized by lower extremity weakness, with a predilection for proximal muscles, often with sparing of sensation, it is accompanied by severe pain and weight loss, and often improves with control of diabetes. After exclusion of alternative causes, EMG helps to confirm the diagnosis. The natural course is variable, as most experience 2–18 months of debility, with gradual, but often incomplete improvement in strength, despite persistent muscle wasting. Improvement is often seen with control of diabetes. After exclusion of alternative causes, EMG helps to confirm the diagnosis.

GASTRIC OUTLET OBSTRUCTION IN CROHN’S DISEASE (CD): A CASE REPORT AND LITERATURE REVIEW

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Introduction Crohn’s disease (CD) is an autoimmune disease and subtype of Inflammatory Bowel Disease. CD may involve the entire gastrointestinal tract from mouth to anus with the most affected areas being the ileum and proximal colon. Proximal gut is not a common site for CD disease activity. Distal gastric antrum and duodenum are most commonly affected especially in young patients. Here we detail the case of a patient with this disease pattern presenting for a serious complication as a result, a gastric outlet obstruction (GGOO).

Case summary A 26-year-old male was diagnosed with CD in 2007. He had a severe course requiring a sub-total colectomy and end ileostomy which was complicated by ileitis and peristomal cellulitis in the past. The patient presents with generalized weakness and an episode of coffee ground emesis. He was afibrile and vital signs were stable. Physical examination was remarkable for a previous laparotomy scar and right end ileostomy bag. Laboratory findings revealed a WBC count of

normal. Sensation to fine touch is normal. There is no dysmetria or pronator drift. A postural tremor is noted.

Labs are notable for hypercalcemia (calcium 12.2 mg/dL), AKI (creatinine 1.23 mg/dL), hypokalemia (potassium 2.8 mEq/L), and microcytic anemia (Hgb 10.5 g/dL). Given bone pain, hypercalcemia, renal insufficiency, anemia, and weight loss, there is concern for multiple myeloma; however, hypercalcemia is found to be due to primary hyperparathyroidism. Alternative causes for hypercalcemia are excluded—including, but not limited to—multiple myeloma, vitamin D intoxication, granulomatous disease, HIV, neoplasm, and hyperthyroidism.

HbA1c is 8.0%. Thyroid function, vitamin B12, folate, CPK, ESR, CRP, and C3/C4 values are normal. A heavy metal panel is normal. Lyme disease titer is negative. Titers for ANA, ANCA antibodies, and rheumatoid factor are negative. CSF reveals increased protein (55 mg/dL) and a non-reactive VDRL. CT-chest/abdomen/pelvis reveals no mass. MRI-cervical/thoracic/lumbar spine reveals no mass or disc disease. Radiographs of the femurs reveal mild OA. EMG is consistent with proximal bilateral lumbarosacral polyradiculopathy (left > right) without distal peripheral polyneuropathy.

Given asymmetric, proximal leg weakness, pain, and weight loss—after having ruled-out other potential causes for myelopathy, namely mass lesion, inflammatory-, or neoplastic-processes—and with supportive EMG findings, the diagnosis of diabetic amyotrophy is made. Patient is started on prednisone, pregabalin, metformin, cinacalcet, and discharged. Two months later, pain has improved; however, weakness persists and has become symmetric, with 2/5 muscle strength in both proximal legs.

Discussion Diabetic amyotrophy is a rare complication of diabetes. Initially described as occurring asymmetrically, many patients develop progression to bilateral leg involvement. The natural course is variable, as most experience 2–18 months of debility, with gradual, but often incomplete improvement in strength, despite persistent muscle wasting. Improvement is often seen with control of diabetes. After exclusion of alternative causes, EMG helps to confirm the diagnosis.
14,500/mcL, K of 3.3 mEq/L, Cl 78 mEq/L and a creatinine of 1.85 mg/dL, CRP level of 11.5 mg/L and ESR level of 75 mm/hr. Abdominal-Pelvic CT scan showed thickened esophagus walls with mucosal enhancement, stomach distension to with fluid gas level, inflammation and edema at the level of the pylorus and non-dilated small bowel. Surgery and Gastroenterology were consulted and recommended bowel rest with temporary intermittent NG suction and methylprednisolone at 1 mg/kg daily intravenously. Upper endoscopy (EGD) showed normal esophagus, gastric fundus and body. There was significant pre-pyloric, pyloric channel and duodenal bulb edema without an evidence of fibrous strictures or ulceration. Multiple biopsies were obtained from the stomach and duodenum showing mild nonspecific inflammation with mild acute and chronic nonspecific gastritis with gastric antral and fundic type mucosa. The duodenal biopsy revealed normal duodenal mucosa. The patient subsequently improved with intravenous steroids and was able to tolerate normal diet.

**Discussion**

CD can involve the upper gastrointestinal tract but is not often recognized and sometimes missed as most patients are asymptomatic or presenting with dyspepsia. CD can present as GOO if CD activity involves the pyloric area. GOO is defined as a mechanical obstruction at the pyloric gastric region which can lead to postprandial vomiting and abdominal pain. GOO in CD presenting with post-prandial abdominal pain and vomiting can be an initial presentation of CD but can also become chronic where symptoms may last for years without an CD diagnosis. CD presenting with GOO is usually asymptomatic in 63% of patients. Pyloric stenosis can occur secondary to inflammation from CD. The majority of reported cases with biopsies reveal no evidence of granulomatous formation in around 67–70% of patients with granulomas seen in 30–33%. The role of EGD is limited especially in patients with an early presentation of proximal gut CD involvement presenting with signs of dyspepsia; as opposed to the patients presenting with GOO in which an EGD become an extremely helpful diagnostic tool. Mucosal inflammation at the pyloric region is the most common finding with a cone shaped mucosal malformation as shown in prior case series. Inflammatory markers are extremely helpful especially in patients presenting with symptoms and abdominal imaging supporting GOO. Diagnosis should be considered based on symptoms, EGD, imaging studies and multiple biopsies. There are no clear guidelines on which CD patients get GOO or when to suspect CD in GOO. Different approaches have been utilized for patients with symptomatic foregut CD which can include a primarily medical approach, endoscopic balloon dilation and surgery.

### Abstract C31

**HEPATOCELLULAR CARCINOMA WITH TUMOR THROMBUS EXTENDING FROM THE PORTAL VEIN TO THE RIGHT ATRIUM**

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**Introduction**

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors. Tumor thrombus formation in advanced HCC stages is common and usually involves the hepatic or portal veins. The formation is tumor thrombus is considered a poor prognostic factor. Herein, we report a rare case were the thrombus extended to the of Inferior Vena Cava (IVC) reaching the right atrium without affecting the hemodynamic status.

**Case description**

A 59-year-old male with a history of untreated Hepatitis C and 50 pack-year smoking, presented...
with melena, cramping abdominal pain and palpitations for 5 days. Physical examination was remarkable for tachycardia and epigastric tenderness. The patient was started on Octreotide and Pantoprazole infusions with prophylactic Ceftriaxone. He had an Esophagogastroduodenoscopy which showed grade 3 esophageal varices with findings of suggestive of recent bleeding associated with a large amount of blood in the gastric body that required banding (figure 1). Computed tomography of the abdomen and pelvis showed multiple liver masses with an intraluminal IVC mass extending from the hepatic vein into the right atrium (figure 2). A Magnetic Resonance Imaging (MRI) of the abdomen confirmed the diagnosis of HCC. His Alpha-fetoprotein level was 53,320 ng/ml. A CT scan of the chest confirmed the presence of a tumor thrombus in the IVC extending to the right atrium. Oncology team determined that the patient was not a candidate for surgical or ablative therapies. Since his symptoms improved during his stay, he preferred to avoid any intervention for his thrombus. Therefore, he was discharged with a plan to receive palliative treatment with sorafenib as outpatient.

**Discussion**

Tumor thrombus formation is common in HCC. However, expansion of the thrombus to IVC and right atrium is rare and indicate a poor prognosis.

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**C32 PYELONEPHRITIS: A CLINICAL OR RADIOGRAPHIC DIAGNOSIS?**

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**Introduction**

Urinary tract infections (UTIs) are extremely common. They are classically diagnosed by clinical impression and lab abnormalities; imaging is not always necessary or indicated. Now with readily available computed tomography (CT) imaging, it is possible that cases are being over treated or the clinical picture skewed by what could be incidental or non-specific radiographic findings.

**Case description**

A 62-year-old female with a history of systolic heart failure, morbid obesity, chronic obstructive pulmonary disease, diabetes, hypertension, chronic pain, and stage III chronic kidney disease presented with right flank pain of four days duration. This was not associated with fever, dysuria, or suprapubic pain. Laboratory results were significant for a white blood cell (WBC) count of 12.3 and serum creatinine 2.7 (baseline 2.2). Urinalysis (UA) showed several squamous epithelial cells and urine culture ultimately grew urogenital flora, though the sample was taken after a dose of Ceftriaxone. CT abdomen without contrast showed mild right perirenal fat stranding. She was continued on Ceftriaxone for three days and transitioned to oral Cefpodoxime on discharge. Flank pain persisted after a week of antibiotic treatment and normalization of WBC. Patient was soon readmitted with nausea, vomiting and interstitial edema. Her last hemoglobin A1C (HgbA1c) she had was 5.3% 11 months prior to presentation. In ED, her vital signs were unremarkable except for tachypnea, physical examination was remarkable for mild generalized distress, generalized abdominal tenderness, and wrist joints deformities. Her fevers and chills. It is classically associated with flank pain and urinary symptoms such as dysuria, frequency, or urgency. Typical laboratory abnormalities include leukocytosis, pyuria, positive leukocyte esterase and, depending on pathogenic organism, positive nitrite in urine. One literature review warns that patients may present without fever, but indicated the vast majority of patients presented with some form of urinary tract symptom and 90% of patients had positive urine cultures. Though CT imaging is largely accepted as the modality of choice for evaluating acute pyelonephritis, recent recommendations specify that imaging should include non-contrast as well as delayed contrast administration for best visualization, which our patient did not undergo. Radiologic findings of fat stranding and interstitial edema are not isolated to pyelonephritis and may occur with many other clinical entities including metabolic derangement, medications, and stones. A study looking at imaging and clinical aspects of patients treated for pyelonephritis found that the ‘classical triad’ of pyelonephritis including fever, costovertebral angle pain, and dysuria was present in 87% of cases which was much higher than previously reported. The consensus among radiologists is that imaging is important for assessment of complications, but the accepted practice is that the diagnosis of acute pyelonephritis is usually clinical. The appropriate action in this case was to treat as pyelonephritis given the above imaging findings, acute kidney injury, and leukocytosis. However, this clinical course was a good opportunity to re-evaluate the role of diagnostic imaging in UTIs and how readily available imaging may unduly influence the decision to treat.

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**C33 ASSOCIATION BETWEEN CREST SYNDROME AND ACUTE DIABETES MELLITUS TYPE ONE; CASE REPORT IN AN ELDERLY PATIENT**

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**Objective/Introduction**

Scleroderma disorders are groups of autoimmune disorders which can be divided into localized and systemic. Limited scleroderma involves CREST syndrome (Calcinosis, Raynaud phenomenon, Esophageal dysmotility, Scleroderma, and Telangiectasia). Type one diabetes mellitus (T1DM) is characterized by pancreatic beta cells destruction which is usually autoimmune in etiology. Although both T1DM and CREST (Calcinosis, Raynaud phenomenon, Esophageal dysmotility, Scleroderma, and Telangiectasia) are autoimmune diseases, they rarely coexist. Up to our knowledge, there are only 3 cases where both diseases co-existed, and all of them had T1DM since childhood. We present a 67-year-old female with known history of CREST who presented with diabetic ketoacidosis as the first manifestation of T1DM.

**Methods**

We describe a 67-year-old female with medical history significant of CREST syndrome without previous history of elevated blood glucose level who presents to the emergency department (ED) with nausea, vomiting and abdominal pain of 1 day duration. She used to have normal blood glucose levels on her routine laboratory workup and the last hemoglobin A1C (HgbA1c) she had was 5.3% 11 months prior to presentation. In ED, her vital signs were unremarkable except for tachypnea, physical examination was remarkable for mild generalized distress, generalized abdominal tenderness, and wrist joints deformities. Her glycemic control was uncontrolled with diagnosis of diabetic ketoacidosis, she was transferred to the intensive care unit (ICU) where she was monitored for 2 weeks. Her T1DM and CREST were confirmed by an expert in autoimmune disease who performed autoantibody testing, which was positive for Smooth muscle and Antinuclear antibodies. The patient was discharged on October 13, 2019.
INITIALLY MISDIAGNOSED HEPATOCELLULAR CARCINOMA WITH BRAIN METASTASIS

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Introduction Brain metastasis is rare in hepatocellular carcinoma (HCC) and more commonly seen in lung cancer. HCC incidence is on the rise in the United States and carries a poor prognosis making early detection paramount. Risk factors associated with hepatocellular carcinoma include chronic hepatitis infection and advanced liver disease. We report a rare case of hepatocellular carcinoma with an unusual presentation that initially led to misdiagnosis.

Case description A 69-year-old man presented with progressive blurry vision, weight loss of 9 kg for three months and associated low back pain. He was a 25-pack-year smoker. Physical examination showed supraclavicular and posterior cervical lymphadenopathy. Normal extraocular movements, equal and reactive pupils, and no extremity weakness or deficits. Laboratory tests showed an elevated aspartate aminotransferase (AST), alkaline phosphatase and total bilirubin. A computed tomography (CT) scan of the head showed a 2.2 × 2.7 × 2.6 cm mass with surrounding vasogenic edema in the right posterior parietal lobe. CT of the chest abdomen pelvis showed a 2.5 × 2.2 cm speculated right upper lung mass, a 11.1 × 5.3 cm right hepatic lobe lesion, multiple hepatic and pulmonary nodules and lytic lesions of the spine. Magnetic resonance imaging (MRI) of the brain and spine confirmed the above findings with no hemorrhage noted. The patient underwent a biopsy of his left cervical lymph node. He was discharged home with a preliminary diagnosis of metastatic lung cancer given the presence of brain metastasis. A week later while undergoing simulation for radiation therapy, he reported worsening blurry vision and forgetfulness. Repeat CT brain showed acute intracranial hemorrhage. Pathology results consisted of epithelioid tumor cells forming a nested architecture with moderate pleomorphism, hyperchromatic nuclei and moderate amounts of cytoplasm. Immunostaining demonstrated diffusely positive tumor cells for hepatocyte antigen; most compatible with a hepatocellular carcinoma. Given his Child-Pugh score of 11 and the extent of his disease, the patient opted for hospice care and passed away four days later.

Discussion HCC is more common among males comprising 73% of all cases. In the U.S, Hepatitis C, alcoholic cirrhosis and nonalcoholic liver disease are the most common pathogenic factors. Here we report a case of HCC with brain metastasis (BM) where the presenting symptoms were neurological. What makes this even more rare is that he did not have history of cirrhosis, viral hepatitis or HIV. While metastatic disease accounts for 24% of deaths in hepatomas (most commonly to the lung), liver failure and bleeding have been shown to be responsible for a higher mortality. The incidence of BM has been reported to be 0.24% (7/3100 cases) in a Korean study and 0.74% (3/403 cases) in a U.S based study. HCC brain lesions are more likely to cause intracranial hemorrhage and could benefit from early surgical removal or radiation. Though the pathology results are unlikely to have affected immediate treatment or prognosis, this case highlights an opportunity for discerning clinical evaluations based on available epidemiology in hypothesizing disease course as well as an opportunity to reflect on how certain clues in a patient’s history may lead clinicians to assume, or anchor, on an initial impression.
Involves IgM and occurs at temperatures below core body temperature. cAIHA can be secondary to infections (mycoplasma or infectious mononucleosis), or lymphoproliferative disorders. Here, we present a rare case of green tea associated cAIHA.

Case description An 84 year old male with a history of hairy cell leukemia (HCL) presented to clinic for routine clinical surveillance. The patient reported new dyspnea on exertion, lightheadedness, and palpitations for the past 3 weeks, which were getting progressively worse. He denied any signs of overt blood loss and a recent cardiac evaluation was unremarkable. He completed treatment for HCL six years ago and achieved a complete remission based on end of treatment bone marrow biopsy. He had no new medications or dose modifications of the existing ones in the past 3 months. Examination was notable for tachycardia. Complete blood count (CBC) showed a marked drop in hemoglobin from baseline approx 14 g/dL (8 weeks prior) to 7.8 g/dL. Labs showed undetectable haptoglobin (less than 30 mg/dL), elevated indirect bilirubin (1.5 mg/dL) and LDH (218 U/L, normal less than 190 U/L) consistent with a hemolysis. He had a cold auto-antibody with positive DAT for C3. Upon further questioning, the patient reported green tea consumption, between 2.5 and 3 L daily for the past 5 weeks. He was advised to stop green tea as it was felt to be the likely culprit for his current clinical condition. Repeat CBC showed continued improvement in his hemoglobin (9.5 g/dL in 2 weeks, 12.4 g/dL in 4 weeks and 14 g/dL in 12 weeks) with resolution of his symptoms. Given the temporal relation of his presentation to green tea and improvement of hemoglobin after cessation of green tea (without any other intervention), the cAIHA, in this case, is potentially related to excess green tea consumption.

Discussion cAIHA is a rare condition with an incidence of about 1 case per million population year. It is infrequently associated with disease progression in patients with HCL. Given the acuity of presentation for this patient and lack of involvement of other cell lineages, alternative causes were sought, which lead to the hypothesis of potential green tea consumption and cAIHA. Green tea has long been used as a complementary or alternative medicine with potential anti-tumor and anti-oxidant effects and is commonly consumed due to the same reasons, and in some instances, excessively, such as in our case. This case highlights the importance of avoiding excess intake of green tea to prevent unknown and serious adverse events.

Abstracts

C40 ADENOCARCINOMA FOLLOWING TREATMENT OF LYMPHOMA: DOES RITUXIMAB INCREASE RISK OF SECONDARY MALIGNANCY?

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Introduction Rituximab is a CD20 monoclonal antibody known to be effective treatment for lymphoma. Due to its immunosuppression, there has long been discussion of potential for increased risk of secondary primary malignancy (SPM) with its use. Esophageal cancer is growing in incidence in the United States (US). Here we present an unusual case of esophageal cancer following successful treatment of lymphoma with rituximab-based chemotherapy, and explore whether pre-existing risk factors or chemotherapy is more likely to explain our patient’s disease development.

Case description 69-year-old male with a history of chronic obstructive pulmonary disease, 55-year tobacco history, follicular lymphoma transformed to diffuse large B-cell lymphoma, and recurrent pleural effusions presented with progressive shortness of breath and hemoptysis for three days. His lymphoma had been treated with a combination of resection, rituximab-based chemotherapy, and radiation; he had been in remission for two years. On arrival, computed tomography (CT) chest revealed several lung nodules, localized right effusion and simple left effusion. Initial impression was metastatic lung cancer and the patient underwent thoracentesis. Fluid collected indicated an exudative process and cytology revealed adenocarcinoma. Positron emission tomography (PET) scan showed increased uptake at the distal esophagus and he underwent biopsy by esophagogastroduodenoscopy (EGD). He was diagnosed with metastatic esophageal adenocarcinoma. The patient was briefly started on trastuzumab therapy as the mass was HER2 positive but did not tolerate it well. He subsequently elected to pursue palliative care.

Discussion Esophageal cancer incidence is growing in the United States. The majority of the world, as well as the US in previous decades, rank squamous cell carcinoma as the primary malignant esophageal histology. Changes in lifestyle, the growing obesity epidemic and associated dietary habits have led to adenocarcinoma as the most common esophageal malignancy in the US. The diagnosis carries high mortality and literature estimates that patients have <3% 5-year survival rate. Rituximab is a well-established treatment for non-Hodgkin lymphoma, but due to its immunosuppression there has long been discussion of potential for increased risk of secondary primary malignancy (SPM). One population based study from Taiwan estimated the risk of SPM following non-Hodgkin lymphoma to be 1–8%. However, recent literature indicates that the theorized risk may be less compelling than previously thought. Fleury et al. found that at median 6 year follow up there was no significant difference in SPMs between groups treated with and without rituximab and additionally found that prolonged use of the drug such as in maintenance therapy also did not affect risk. Due to its efficacy against lymphoma, rituximab should be continued where clinically indicated and efforts to prevent SPM should be aimed at modifiable risk factors.
with a large, oozing, right facial mass [figure 1]. The mass started as a pimple and was progressively getting worse over the last two years. Over time, she was more aware of the mass, so she avoided leaving the house. As the mass progressed it caused diminished vision of her right eye. She reported losing 25 pounds over the last year. Computed tomography maxillofacial showed large, irregular right facial mass with erosion of the right maxillary sinus and 10 mm posterior extension into the inferior aspect of the right orbit elevating the ocular globe and right inferior rectus muscle [figure 2]. Due to the patient’s agitation, magnetic resonance imaging was not done.

Biopsy result showed a moderately differentiated squamous cell carcinoma. Maxillofacial surgery, Ophthalmology, and Otolaryngology evaluated the patient and they agreed that the patient is not a surgical candidate, given her refusal for any intervention. Oncology was consulted, and they recommended palliative radiation of the mass, but the patient also refused any radiation and wanted to be discharged home. After a discussion with the patient and her family, she decided to go to a skilled nursing facility, and not pursue any further treatment.

Discussion Cutaneous SCC is a preventable disease if it was caught early. It is possible for SCC to reach a giant size if it was neglected. The risk of invasion increases with the size of the lesion. Surgery is the optimal treatment, but if surgery is not an option, chemotherapy or radiotherapy can be used. Our patient had limited options due to the size and the invasion of the underlying structures.
A RARE CASE OF CLEAR CELL CARCINOMA PRESENTING AS VARIANT ANGINA

Nikhil Malhotra, Ihab Hassanieh, Ghassan Daher, Michael Lim. Saint Louis University, MO

Introduction We present an interesting case of variant angina with associated ST segment elevations and marked troponin elevation in a patient diagnosed with ovarian clear cell carcinoma.

Case description A 64 year old female with diabetes and hyperlipidemia was admitted with pressure-like chest pain radiating to her left arm with associated nausea and vomiting. The initial EKG showed ST segment elevations in Leads II and III (see figure 1). Troponins were trended to a peak of 29. The patient was administered Aspirin 325, Plavix 600, initiated on a Heparin drip and taken for emergent left heart catheterization (LHC). LHC showed normal coronaries and the patient was presumed to have had coronary vasospasm. ECHO showed normal systolic and diastolic function. The patient was treated with Diltiazem PO which helped her chest pain. During admission, patient had persistent abdominal pain, nausea, vomiting and a palpable abdominal mass which prompted a CT abdomen and pelvis with contrast. CT A/P showed a 12 × 8 × 14 cm pelvic mass and subsequent work-up revealed elevated CA 125 of 613 and CA 19-9 of 363. Eventually, the patient underwent exploratory laparoscopy resulting in a bilateral salpingo-oophorectomy, hysterectomy, omentectomy, and lymph node biopsy. Pathology showed high grade (3) pT1a pN0 clear cell carcinoma that was 15 cm at its greatest dimension. Patient has since completed 3 courses of Carboplatin and Taxol with no subsequent evidence of disease.

Discussion While chemotherapy, particularly platinum-based therapies such as Carboplatin, have been known to induce coronary vasospasm, a case of variant angina secondary to the cancer itself has yet to be described in the literature. The possibility of intestinal ischemia from ovarian cancer mass effect leading to a supply-demand mismatch of the coronaries provides a theory for this patient’s presentation.

Abstract C44 Figure 1
**Dietary Isoleucine Is a Key Regulator of Metabolic Health**

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**Objective**

Obesity and diabetes are increasing around the world, and effective and sustainable interventions are urgently needed. Protein restricted (PR) diets promote metabolic health and longevity in both rodents and humans, but the precise dietary components that mediate these benefits have not yet been identified. Recently, we found that a diet with reduced levels of the three branched-chain amino acids (BCAAs; leucine, isoleucine, valine) recapitulates many of the beneficial effects of a PR diet, improving glycemic control and promoting leanness in both lean and diet-induced obese mice. However, the role each of the three individual BCAAs plays in the metabolic response to PR, and the molecular mechanisms these amino acids engage, are unknown. Thus the purpose of this study is to determine the role of individual BCAAs in mediating the metabolic effects of protein restriction and to identify the key BCAA regulating the metabolic response to PR.

**Method**

We study the role of individual BCAAs in regulating the metabolic health by examining the metabolic phenotypes of individual BCAA restricted diets and PR diets replenished with normal level of individual BCAAs in young, lean, healthy mice and in obese mice preconditioned with a high-fat, high-sucrose Western diet. To identify the mechanisms by which individual BCAA restriction produces similar effects as PR, we employed transcriptional and metabolomic profiling to compare the effect of restricting individual BCAAs with PR. To determine if suppression of mTORC1 signaling is required for the effects of a single BCAA restricted diet, we utilized a mouse model of constitutive hepatic mTORC1 activity and examined the metabolic responses to a single BCAA restricted diet.

**Results**

Here, we identify distinct metabolic effects arising from restriction of leucine, isoleucine, and valine by 67%. Surprisingly, we find that specific restriction of leucine does not improve glucose homeostasis and body composition, while restriction isoleucine or valine alone promotes glycemic control and prevents fat accretion. Isoleucine restriction promotes the strongest metabolic response, improving hepatic insulin sensitivity, and recapitulates the effects of a PR diet at the level of the transcriptome and metabolome. Furthermore, we observed that ‘addback’ of leucine or valine had negligible effects on the metabolic impact of a PR diet, addback of isoleucine blunted the beneficial metabolic effects of PR. Surprisingly, we find that the beneficial metabolic effects of BCAA or isoleucine restriction do not require reduced activity of hepatic mTORC1, a protein kinase that is agonized by branched-chain amino acids. Restriction of isoleucine is sufficient to rapidly restore metabolic health to diet-induced obese mice, improving glucose tolerance and promoting leanness. Finally, in a population based human sample we find that percent of total dietary protein from isoleucine levels is positively associated with BMI (p<.05).

**Conclusion**

Our results suggest that isoleucine is a key metabolic amino acid that strongly impacts the metabolic health of both mice and humans, and reducing dietary isoleucine levels could be a novel approach for the treatment and prevention of obesity.
Abstracts

Interestingly, aHepPPARγKO mice fed a HFCF diet for 24 weeks showed increased body weight, adiposity, high levels of insulin and c-peptide in plasma, and glucose intolerance as compared to control mice fed a HFCF diet. Nevertheless, aHepPPARγKO mice showed reduced levels of plasma alanine aminotransferase and reduced expression of hepatic genes involved in inflammation and fibrosis: monocyte chemotactic protein 1 (Mcp1), tumor necrosis factor α (TNFα), transforming growth factor β1 (TGFβ1), collagen type 1 α1 (Col1a1), metalloproteinase 13 (Mmp13), and TIMP Metalloproteinase Inhibitor 1 (Timp1), as compared to control mice fed a HFCF diet. Picrosirius red/fast green and hematoxylin/eosin stained liver sections supported the changes in gene expression related to steatosis, inflammation, and fibrosis.

Conclusion Hepatocyte PPARγ may not be an essential factor for the development of steatosis induced by HFCF diet. However, the significant reduction in hepatic fat accumulation and the attenuation of NASH in aHepPPARγKO mice fed a HFCF diet, despite glucose intolerance, high insulin levels and increased adiposity, strongly suggested that loss of hepatocyte PPARγ expression slowed the development of NASH. Ongoing studies are assessing hepatic mechanisms regulated by TZD-mediated activation of hepatocyte PPARγ that may serve to promote NASH.

A18 SEX AND STRAIN DETERMINE THE METABOLIC RESPONSE TO DIETARY PROTEIN LEVEL

Cara L Green, Heidi H Pak, Victoria Flores, Nicole E Cummings, Katherine Kreddell, Shany E Yang, Deyang Yu, Jay L Tomasiewicz, Sabrina N Dumas, Dudley W Lamming. University of Wisconsin-Madison, WI

Objective Low protein-high carbohydrate diets are associated with improved metabolic parameters such as glucose tolerance, insulin sensitivity, reduced adiposity, and increased longevity in rodents and even humans. However, the vast majority of research on protein restriction (PR) has been completed in male C57BL/6J mice. Recent work in the calorie restriction (CR) field has highlighted that sex, genetic background (strain), and the level of restriction are all important factors to consider in the response to CR. Method: We have therefore endeavored to characterize the response of young male and female C57BL/6J and DBA/2J mice, strains which are known to have different metabolic responses to CR, and a genetically heterogeneous strain of mice (UM-HET3), to two different levels of PR: a 33% restriction (21% protein diet vs a natural source 14% low protein (LP) diet) and a 67% restriction (21% protein diet vs. a 7% very low protein (VLP) diet).

Results Whilst male C57BL/6J mice robustly respond to PR, it was interesting to note that most responses only occurred on the VLP diet, not on the LP diet. After 3 months of consuming either Control, LP or VLP diet, all mice showed an increase in body weight (BW), fat mass (FM) and lean mass (LM), however mice on VLP diets had a significantly lower body weight and lean mass relative to Control-fed mice. In contrast, while weight also increased over the same time period in male DBA/2J mice, no effect on body composition was observed. The lack of response in DBA/2J mice was mirrored with respect to changes in glucose homeostasis and energy balance, as whilst the VLP diet improved glucose tolerance and insulin sensitivity, and increased energy expenditure of male C57BL/6J mice, none of these changes were seen in male DBA/2J mice. Intriguingly, food intake and respiratory exchange ratio (RER) were increased in both strains, which may suggest that the increase in energy expenditure is the driving force behind the metabolic benefits of PR. Interestingly, in the genetically heterogeneous HET3 male mice, whilst glucose tolerance and gluconeogenesis were improved and fasting blood glucose was decreased on the VLP diet, insulin sensitivity, weight, fat mass and lean mass were unchanged, suggesting that in HET3 mice, metabolic changes were insulin- and weight-independent. In female HET3 mice the effects of low protein diets were far less pronounced, which may indicate that the response to PR is in part modulated by male sex hormones, although some effects, such as decreased fasting blood glucose were conserved on the VLP diet. Improved glycemic control in males may be due to a more proficient ability to switch metabolic substrate to carbohydrate on PR, as whilst RER increased in males, it was unchanged in females.

Conclusion Our data illustrate the complexity of PR in the context of metabolism, and highlight the importance of testing the robustness of dietary interventions to improve metabolic health. The improvements in metabolic health seen in our strong responders to PR (C57BL/6J mice), are thought to contribute to increased lifespan and health span. However, benefits without lean mass loss (as in male HET3s) may be more beneficial later in life to alleviate issues associated with restriction, such as sarcopenia. Some of these benefits are thought to be conferred through increased energy expenditure, which is thought to occur in part through activation of proteins such as fibroblast growth factor 21 (FGF21), which has previously been shown to be sex specific. Disentangling the genetic and sex contributions to these effects are of paramount importance to understand the underlying pathways.

A26 UNCOVERING THE ROLE OF FASTING AND REDUCED CALORIC INTAKE IN THE METABOLIC BENEFITS OF CALORIE RESTRICTION

Heidi H Pak, Cara L Green, Nicole E Cummings, Jacqueline A Brinkman, Shany E Yang, Deyang Yu, Jay L Tomasiewicz, Matthew H Wakai, Dudley Lamming. University of Wisconsin-Madison, WI

Background As the global population ages, developing interventions that can prevent or delay age-associated diseases, including cancer, heart disease, type 2 diabetes, and Alzheimer’s disease is of increasing importance both to promote healthy aging and to reduce health care costs. Calorie restriction (CR) is a simple dietary intervention that extends both lifespan and healthspan in mammals including rodents and non-human primates. However, an abstemious CR diet is notoriously difficult to maintain; understanding the physiological and molecular mechanisms by which CR promotes health may allow the development of effective CR-mimicking dietary regimens or pharmaceuticals.

Over the last few years, it has become apparent that the interval between meals may be just as important as what we eat and when we eat it. Research into feeding paradigms have found that time-restricted feeding (TRF) - where animals have access to food for only a portion of the day - has metabolic benefits, protecting mice and perhaps humans from the negative metabolic effects of a high-fat, high-sucrose ‘Western’ diet. Similarly, meal-fed mice, which are fed a nearly ad
livitum portion of food but consume it during a short portion of the day, have extended lifespan relatively to truly ad libitum fed animals. These findings significantly complicate the interpretation of CR studies done in a laboratory setting, as CR-fed animals are typically fed only once per day, consuming their food in 1–3 hours. Thus, in contrast to ad libitum fed mice which have unrestricted access to food, CR fed mice are essentially fasted for approximately 22 hours per day.

**Objective** A largely overlooked question that has yet to be answered is whether the metabolic health benefits of CR arise solely from the reduction in calories, or if an enforced period of daily fasting is also required. Here, we distinguish fasting dependent and independent effects by utilizing multiple feeding paradigms to determine if the metabolic effects of CR are mediated by reduced caloric intake, or also require prolonged fasting.

**Method** We randomized male C57BL/6J mice to either an ad libitum diet or to one of three CR regimens in which calories were restricted by 30%: 1) animals fed once per day during the light period; 2) animals fed three equal meals during the course of the 12 hour dark period; and 3) animals provided with ad libitum access to a diet diluted with indigestible cellulose.

**Results** We observed that all three CR regimens had similar effects on weight and body composition, fasting blood glucose levels and glucose tolerance. Surprisingly however, we found that only CR mice that were fed once daily had improved sensitivity to insulin, a phenotype of CR that has been suggested to mediate many of CR’s beneficial effects on longevity.

**Conclusion** We conclude that while many of the metabolic benefits of a CR diet are mediated by reduced caloric intake, the prolonged fasting induced in CR mice fed once a day mediates the effects of CR on insulin sensitivity.
across different muscle groups as well as upon voluntary wheel running and Pgc1α overexpression (mTg).

**Results** We demonstrate that in vivo enhancers specify muscles in accordance with myofiber composition, show little resemblance to cultured myotube enhancers, and identify glycolytic and oxidative muscle-specific regulators. Moreover, we find that voluntary wheel running and mTg, which stimulate endurance performance in mice, result in markedly different changes to the epigenome. Exercise predominantly leads to enhancer hypoacetylation, whereas mTg causes hyperacetylation at different sites. Integrative analysis of regulatory regions and gene expression revealed that exercise and mTg are each associated with myocyte enhancer factor 2 (MEF2) and estrogen-related receptor (ERR) signaling and transcription of genes promoting oxidative metabolism. However, exercise was additionally associated with regulation by RXR, JUN, SIX, and other factors.

**Conclusion** Overall, our work defines the unique enhancer repertoires of skeletal muscles in vivo and reveals that highly divergent exercise-induced or PGC1α-driven epigenomic programs direct partially convergent transcriptional networks.

### Abstracts

#### A42 REGULATION OF BODY WEIGHT AND COMPOSITION BY DIETARY HISTIDINE

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The increasing prevalence of obesity is a serious threat to global health, placing many humans at increased risk of many diseases, including diabetes, cancer, and Alzheimer’s disease. An intervention is urgently needed to put an end to this epidemic. Low protein (LP) diets are associated with a decreased risk of diabetes in humans, and we and others have demonstrated that a low protein diet promotes leanness and glycemic control in lean and obese rodents. In a short-term randomized clinical trial, LP diets also promote leaniness and glycemic control in humans. However, the specific dietary components altered in a LP diet that promote metabolic health have not been fully characterized.

We previously determined that reduced consumption of dietary essential amino acids mediates the metabolic response to a LP diet, with the branched-chain amino acids playing a crucial role. However, we observed that reduced intake of the other six essential dietary amino acids also lead to changes in body composition. Here, we report our finding that dietary histidine plays a key role in the metabolic response to an LP diet. Specific restriction of dietary histidine by 67% reduces weight gain of young, growing C57BL/6J mice, reducing both adipose and lean mass gain; surprisingly, no effect on glucose metabolism was observed. Specifically restricting histidine promotes rapid weight loss with reduction of both adipose and lean mass, but with an overall reduction in adiposity. This effect is not mediated by decreased food consumption but instead is associated with increased energy expenditure.

To determine the potential relevance of our findings to the human obesity epidemic, we analyzed population health and nutrition data gathered from over 600 Wisconsin residents. Surprisingly, in confirmation of animal findings, in a population-based sample of humans, carefully adjusted models show increasing percent of dietary protein from histidine is positively associated with significant increases in body mass index (BMI) (p<.01). Overall, our data suggest that dietary histidine is an important regulator of body weight and composition in both mice and humans, and suggests that dietary guidelines and clinical interventions based on reduced levels of histidine may be an effective means to intervene in the obesity epidemic.

#### B04 DECREASED CONSUMPTION OF BRANCHED-CHAIN AMINO ACIDS PROMOTES LIFESPAN AND HEALTHSPAN IN WILD-TYPE AND PROGEROID MICE

Nicolle E Cummings, Elizabeth N Konoon, Alexis T Mitchell, Colin Boyle, Saha Ahmad, Allison C Rodgers, Abigail Radcliff, Elizabeth M Williams, Timothy Hacker, Dudley W Lamming, University of Wisconsin – Madison, WI

Calorie restriction (CR), or reduced calorie intake without malnutrition, robustly improves metabolic health and extends lifespan in model organisms, including mammals. While CR evenly restricts the intake of protein, carbohydrate, and fat, only recently has research explored reducing intake of these macronutrients selectively. In the last decade, restricting intake of dietary protein has proven in flies and mice to mediate longevity. Low protein, high carbohydrate diets have since shown to strongly improve metabolic health in both mammals and humans. Our lab has focused research into low protein diets, by investigating which amino acid(s) specifically reduced in a low protein diet mediate its beneficial effects. By using amino acid defined diets, we have shown that branched-chain amino acids (BCAAs; leucine, isoleucine, and valine) are critical in improving metabolic health in mice. Low BCAA diets improve glycemic control in young, wild-type mice, as well as diet-induced obese mice, even while mice are still consuming a high fat, high sugar Western diet.

**Objective** Since then, our research has expanded to investigating the role dietary BCAAs may play in longevity. We hypothesized that reducing dietary BCAAs could promote healthspan and lifespan in mice.

**Method** To test this, we fed reduced BCAA diets to young and aged wild-type mice, as well as two mouse models of Hutchinson-Gilford Progeria Syndrome, a disorder of rapid aging. Over time, we assessed metabolic health, cardiovascular health via echocardiography, frailty, survival, and cause of death when possible.

**Results** A Low BCAA diet fed to female LMNA<sup>G609G</sup> mice extends median lifespan by up to 83%. In LMNA<sup>G609G</sup> mice, both males and females are metabolically healthier, though lifespan extension is not observed. In aged wild-type mice, we find that reducing dietary intake of BCAAs promotes healthspan, metabolic health, and slows frailty onset, while also decreasing cancer onset in females specifically. When Low BCAA diets are implemented in wild-type mice at weaning, a robust lifespan extension is observed in males.

**Conclusion** These results collectively suggest reducing dietary BCAA intake may be highly translatable in promoting healthspan and treating age-related disease.
**B06** SHORT-TERM METHIONINE DEPRIVATION IMPROVES METABOLIC HEALTH AND INDUCES PERSISTENT EPIGENETIC CHANGES


Objective The global epidemic of obesity has driven an increase in the prevalence of type 2 diabetes, which affects more than 30 million Americans (12.2% of adults over the age of 18, 25.2% of adults 65 and older); obesity is also a risk factor for many other diseases of aging. Despite the urgent need for many adults to lose weight, long-term compliance with reduced-calorie diets is low. As a way to induce rapid weight loss, we have developed a short-term regimen in which methionine, an essential amino acid and a precursor for the methyl donor S-Adenosyl methionine (SAM), is depleted. We recently showed that methionine deprivation (MD) promotes metabolic health in young mice of both sexes, reduces adiposity and improves glycemic control in diet-induced obese mice of both sexes. As obesity and obesity-related metabolic disorders mainly inflict the elderly, we here compare the metabolic impact of MD on young (6-month-old) and aged (22-month-old) C57BL/6J male mice, and also examined whether the beneficial effects of MD on metabolic health persist after ceasing MD and switching back to a normal control diet.

Method 6-month-old and 22-month-old C57BL/6J male mice were fed either the normal control diet or the methionine-deficient diet for 3 weeks. Then, the MD-fed mice were switched back to the normal control diet for 5 weeks. We examined body weight, body composition, glucose and insulin tolerance, food intake, activity and energy expenditure before, during and after mice were subject to MD.

Results We found that MD reduces fat mass and body weight similarly in both young and aged mice, and improves glycemic control regardless of age. Interestingly, glucose tolerance was more improved in aged mice compared to young mice. Switching MD-fed mice back to a normal control diet resulted in the restoration of normal glycemic control; these mice also rapidly regained lost weight and adipose mass. Intriguingly, despite the relatively transient effect of MD on metabolic health, we found persistent effects of MD-feeding on the hepatic epigenome.

Conclusion Taken together, these findings provide evidence that short-term MD may be an effective way to temporarily improve metabolic health and to reprogram the mammalian epigenome of both young and aged male mice.

**B18** REDUCED FOXO1 SIGNALING ATTENUATES NEGATIVE SIDE EFFECTS OF MTORC2 INHIBITION

Sabrina N Dumas, Dudley W Lamming. University of Wisconsin-Madison, WI

Objective The mechanistic Target Of Rapamycin (mTOR) is a central regulator of whole-body metabolism that is indispensable for coordinating anabolic and catabolic pathways in response to nutrient levels, and is found in two complexes: mTOR complex 1 (mTORC1) and mTORC2. mTORC1 is the canonical target of rapamycin, and is acutely inactivated by rapamycin, whereas mTORC2 is only inactivated following long-term, chronic exposure to rapamycin. Importantly, inhibition of mTORC1 by rapamycin leads to increased health- and lifespan; whereas the ‘off-target’ inhibition of mTORC2 by rapamycin results in undesirable side effects including dysregulated glucose and lipid metabolism. The best characterized substrate of mTORC2 is AKT, a key regulator of numerous cellular metabolic processes; in the liver, mTORC2 regulates glucose and lipid metabolism via AKT signaling. FOXO1 is an important hepatic transcription factor that is phosphorylated by AKT, and deletion of FOXO1 is known to promote glucose homeostasis in the context of hepatic insulin resistance.

Method To examine the role of FOXO1 in the metabolic phenotypes of cells with reduced mTORC2 activity, we treated AML12 cells, a murine liver cell line, with either a FOXO1 inhibitor (AS1842856), or a mTOR kinase inhibitor (Torin1).

Results Quantification of both total fatty acids and fatty acids of specific lipid species revealed novel results. Total fatty acid analysis revealed a sharp increase in the well-known proinflammatory fatty acid arachidonic acid (AA) with mTOR inhibition; excitingly, this increase in AA was suppressed by FOXO1 co-inhibition. Total phospholipid levels were decreased with mTOR inhibition and remained decreased with FOXO1 co-inhibition. However, the proportion of arachidonic acid was sharply increased with mTOR inhibition and restored to control levels with FOXO1 co-inhibition. A similar trend was seen in diacylglycerols but not in the free fatty acid fraction, where arachidonic levels were undetected. Glucose levels mirrored arachidonic acid levels, in that, mTOR inhibition led to significantly increased intracellular glucose levels, and FOXO1 co-inhibition brought levels down to control levels.

Conclusion We conclude that activation of FOXO1 may account for many of the metabolic phenotypes induced by inactivation of hepatic mTORC2, and that inhibition of FOXO1 may be a viable strategy to rescue hepatocytes from the consequences of mTORC2 inhibition.
Abstracts

ABLATING ADIPOSE CREB3L3 PRESERVES METABOLIC HEALTH DURING OBESITY

We are recruiting 16 male subjects for this randomized, controlled, single-blind study, aged 35–65 with BMI 28–35 and hemoglobin A1c 5.7%–6.4% or fasting glucose 101–125 mg/dL. At a screening visit, a 4-day food diary is collected to calculate baseline caloric and protein intake so that subjects will maintain overall total protein and calorie intake while on study diets. A taste test is done to assess palatability of the low BCAA and whey protein powder. If subjects meet screening criteria, they are randomized to low BCAA diet vs. control protein diet. A personalized dietary plan is provided with a goal of replacing 2 meals a day with a beverage prepared with protein powder to reduce BCAA intake by 66% in the low BCAA arm. At baseline and after 2 months on diet, we obtain waist circumference, body weight/BMI, fasting glucose, insulin and HgA1C, oral glucose tolerance, resting metabolic rate with indirect calorimetry, DXA for body composition, and jumping mechanography to assess muscle function. Stool samples are also collected to analyze the microbiome, and fasting blood samples for measurement of amino acids and other metabolites. Liver transaminases, total protein, albumin and prealbumin levels are measured for safety assessment. Every week, compliance and side effects are assessed with a phone call. Subject experience with the beverage is assessed with a survey at each in person visit. After one month on diet, an interim visit measures BMI, review of a food diary, and lab draws to assess metabolic status. The dietary intervention is discontinued after 2 months. A final visit 2 weeks after stopping the diet completes the study with another measurement of body weight, fasting metabolic labs, and safety labs. Subjects are called weekly to assess for adverse events or new medical issues.

Results/Conclusion This trial is ongoing. Currently, 10 of 16 subjects have completed the trial. To date, one subject on BCAA diet was dropped for noncompliance but all others have successfully completed the study with good compliance. No significant safety concerns or side effects have been noted. We do not yet have adequate data to compare the effect of diet on metabolic parameters. In conclusion, our early results suggest that replacement of two meals a day with a protein powder lacking BCAA for up to two months is a safe and feasible intervention. Ongoing analysis will determine if this intervention impacts metabolic health.

At baseline, the adipose tissue becomes supersaturated with lipids, leading to inflammation, the release of free fatty acids into the bloodstream, and the development of metabolic syndrome. However, a small obese subpopulation does not develop metabolic syndrome and has been deemed to have ‘metabolically healthy’ obesity (MHO). Our lab has created a mouse model that mimics MHO, via adipose-specific ablation of the ER-bound transcription factor cyclic-AMP Responsive Element Binding Protein 3-like-3 (CREB3L3). We have discovered that CREB3L3 is not only expressed in adipose tissue, but selectively downregulated in the ‘metabolically protective’ subcutaneous fat in obese mice and human patients. We hypothesized that CREB3L3 downregulation could contribute to the healthier metabolic profile of subcutaneous fat during obesity, so we created a CREB3L3 fat-specific knockout (KO) mouse. CREB3L3 KO mice had enhanced diet-induced obesity following 12 weeks of high-fat diet feeding and significantly larger inguinal white adipose tissue (iWAT) and epidydimal white adipose tissue (eWAT) compared to wild type controls. Unexpectedly, the KO mice do not exhibit the reduction in glucose tolerance or insulin sensitivity that would be expected with their more obese phenotype, which is likely due to the enlarged adipose tissues. The KO mice do not exhibit the expected dyslipidemia or hepatic steatosis, suggesting that the KO adipose tissue sequesters lipids away from these spaces. Additionally, the KO iWAT and eWAT have reduced inflammatory marker expression, suggesting that CREB3L3 plays a role in adipose inflammation. Indeed, we observed that obese mice overexpressing CREB3L3 via direct injection of a CREB3L3 adenovirus into the iWAT and eWAT had marked upregulation of IL-1B and MCP1 in both of these tissues. Together, these data suggest that adipose ablation of CREB3L3 preserves metabolic health during obesity by allowing the adipose tissue to meet the body’s lipid storage demands via healthy expansion.

Epidemiology/Health Outcomes/Quality Improvement/Bio-Informatics

CHARACTERIZING FATIGABILITY IN HOSPITALIZED PATIENTS WITH ANEMIA

Cyrus Alavi, Mitch Prochaska, Sarah Bradbury. University of Chicago, IL.

Objective Fatigability describes how fatigued a patient is at any given level of activity, and is measured as the degree of fatigue a patient experiences after performing a specific amount of activity. The National Institute of Aging has suggested that fatigability is an important measure in patients with conditions where fatigue is a prominent symptom, such as hospitalized patients with anemia. This is because fatigue is the primary symptom of anemia, and both hospitalization and anemia-related fatigue are associated with declines in activity and functional capacity. As such, measuring fatigability in hospitalized patients with anemia could provide hospitalists information about the severity of patients’ fatigue, and how fatigue may be interfering with their functional capacity. Moreover, fatigability could be used to predict future functional decline or disability post hospitalization. However, fatigability has not been previously described in hospitalized patients with anemia. The purpose of our study was to establish the clinical reliability of fatigability, by characterizing the association between fatigability and patient’s clinical (i.e. Hb, comorbidities) and demographic characteristics.

Method From 6/2017–1/2018, hospitalized general medicine patients with a Hb<10g/dL were approached for an inpatient interview at hospital admission. Fatigability was measured using the Pittsburgh Fatigability Scale (PFS). The PFS contains 10 questions that measure fatigue in the context of specific

CO2

ABLATING ADIPOSE CREB3L3 PRESERVES METABOLIC HEALTH DURING OBESITY

1Maximilian McCann, 1Guifen Qiang, 1Shengjian Li, 1Yanliang Li, 1Victoria Gil, 1Kezhong Zhang, 1Chong Wee Liew. 1University of Illinois at Chicago, IL; 1Wayne State University, MI

During obesity, the adipose tissue becomes supersaturated with lipids, leading to inflammation, the release of free fatty acids into the bloodstream, and the development of metabolic syndrome. However, a small obese subpopulation does not develop metabolic syndrome and has been deemed to have ‘metabolically healthy’ obesity (MHO). Our lab has created a mouse model that mimics MHO, via adipose-specific ablation of the ER-bound transcription factor cyclic-AMP Responsive Element Binding Protein 3-like-3 (CREB3L3). We have discovered that CREB3L3 is not only expressed in adipose tissue, but selectively downregulated in the ‘metabolically protective’ subcutaneous fat in obese mice and human patients. We hypothesized that CREB3L3 downregulation could contribute to the healthier metabolic profile of subcutaneous fat during obesity, so we created a CREB3L3 fat-specific knockout (KO) mouse. CREB3L3 KO mice had enhanced diet-induced obesity following 12 weeks of high-fat diet feeding and significantly larger inguinal white adipose tissue (iWAT) and epidydimal white adipose tissue (eWAT) compared to wild type controls. Unexpectedly, the KO mice do not exhibit the reduction in glucose tolerance or insulin sensitivity that would be expected with their more obese phenotype, which is likely due to the enlarged adipose tissues. The KO mice do not exhibit the expected dyslipidemia or hepatic steatosis, suggesting that the KO adipose tissue sequesters lipids away from these spaces. Additionally, the KO iWAT and eWAT have reduced inflammatory marker expression, suggesting that CREB3L3 plays a role in adipose inflammation. Indeed, we observed that obese mice overexpressing CREB3L3 via direct injection of a CREB3L3 adenovirus into the iWAT and eWAT had marked upregulation of IL-1B and MCP1 in both of these tissues. Together, these data suggest that adipose ablation of CREB3L3 preserves metabolic health during obesity by allowing the adipose tissue to meet the body’s lipid storage demands via healthy expansion.

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Method From 6/2017–1/2018, hospitalized general medicine patients with a Hb<10g/dL were approached for an inpatient interview at hospital admission. Fatigability was measured using the Pittsburgh Fatigability Scale (PFS). The PFS contains 10 questions that measure fatigue in the context of specific
activities. PFS scores range from 0–50, with higher scores indicating greater fatigability (higher fatigue at lower activity). Patients’ hemoglobin (Hb) values and clinical data were abstracted from hospital administrative data. Patients who received a transfusion prior to the PFS measurement were analyzed separately since transfusion affects Hb and could confound the association with fatigability. Linear regression was used to test the association between fatigability (PFS) as the dependent variable, and patient Hb and Charlson Comorbidity score (CCS) as predictor (independent) variables, controlling for age, race, and gender.

Results 467 patients completed the inpatient PFS. The median age of the sample was 55 (IQR 39–68) years old, 61% (n=293) were female, 77% (n=360) were African American, with a median CCS of 2 (IQR 1–5). The median PFS score of the sample was 33 (IQR 25–38), and the median Hb was 8.9g/dL. In regression models, a Hb 7–8g/dL (β=2.7, p=0.04) compared to Hb≥9–10, and higher CCS (β=0.8, P<0.001) were associated with increased fatigability.

Conclusion Severity of anemia and number of comorbidities are predictive of higher fatigability (higher fatigue at lower activity) during hospitalization. This suggests that fatigability is reliably associated with expected clinical characteristics during hospitalization, and could be measured and used by hospitalists to clinically evaluate the severity of a patient’s fatigue, and how that fatigue may be affecting their functional capacity.

C23 EVALUATION OF A COMMUNITY WELLNESS WORKER PILOT PROGRAM FOR LATINO MOTHERS AND INFANTS  
1Natalie Guerrero, 1Alissa Small, 2Carmen Valdez, 3Mariela Quesada Centeno, 1Sarah Webber, 1University of Wisconsin School of Medicine and Public Health, WI; 1University of Texas at Austin, TX; 3Centro Hispano, WI

Objective Community wellness workers (CWWs) or promotoras are peer educators from within their community who advocate for and educate community members. CWWs are increasingly utilized to promote community health and well-being. Prosperar is a CWW-led intervention in Madison, Wisconsin for Latina mothers in the first year postpartum. Its aim is to directly address maternal wellness through social support and education. Because there are no established standards for CWW training, varying approaches are used based on perceptions of local needs. Little is known about how CWWs perceive their training and its impact on their community. Our objective is to understand the factors that shape, facilitate, and complicate Prosperar promotora training and program implementation.

Method We conducted semi-structured focus group interviews with 6 promotoras pre-implementation of the program, at 9 months post-implementation, and at 18 months post-implementation. Data was transcribed verbatim. Then two study team members (authors NG and AS) coded the interviews independently, met to compare coding and reach agreement in code definitions, and a complete consensus codebook was finalized. Transcripts were coded using this final codebook.

Results The main themes identified included (1) reflections on how experiences in motherhood and within their countries of origin informed the formation of support groups and complemented their training, (2) aspects of training that facilitated implementation of support groups and encouraged capacity-building within the community, and (3) content areas of training and support group experiences that were barriers to program implementation. With regard to personal experiences, a promotora stated, ‘We carry a bag with different experience, and coming from different countries, too. I think the training that you guys gave us, it was a complement, a very huge, very important complement for our work.’ Increased knowledge and social support were key factors of training and support groups that positively impacted the CWWs, the participating mothers, and the community. One promotora said, ‘I feel like more empowering, and knowledge that makes me open doors to another persons, so they would like to know more about the maternal health or infant health.’

Conclusion Promotoras identified multiple facilitators of effective training and implementation of Prosperar, a CWW-led intervention, including increased knowledge and social support, which should be applied to future CWW-led programs. The identified barriers will be used to further adapt the training aspects of Prosperar.
Abstracts

Practitioners (F&GPs) and receipt of influenza vaccination; in the 2.41+ F&GPs per 1,000 group (the highest stratum), the adjusted odds ratio is 1.15 [95% CI: 1.12 – 1.19]. Other than the number of Pharmacists or F&GPs in an area, the strongest predictor of receiving an influenza vaccine was age (those who were 65 years or older were nearly 3 times as likely to report receiving an influenza vaccine compared to those 18 -24 years old).

Conclusion Higher pharmacist employment levels are associated with larger odds of receiving an influenza vaccine. This association suggests that pharmacists play an important role in delivering this key preventative medicine and public health intervention.

C27 PROTECTIVE EFFECT OF DIETARY FIBER INTAKE ON INFLAMMATION AND RESPIRATORY MORBIDITY IN THE ADULT NHANES POPULATION (2007–2012)
Muhammad A Saeed, Alam Morshed, Elizabeth Lyden, Corrine K Hanson, Tricia D LeVan. University of Nebraska Medical Center, NE
10.1136/jim-2019-midwestern2019.63

Objective High intake of dietary fiber may have anti-inflammatory properties and be protective against respiratory morbidity. In this study, we examined the relation of dietary intake of fiber with inflammation, respiratory symptoms and lung function among adults who participated in the 2007–2012 National Health and Nutrition Examination Survey (NHANES).

Method We analyzed data from adults 19–79 years of age (n=13,147) with complete information on fiber intake, total calorie intake, body mass index (BMI), smoking status and poverty level. Fiber intake was categorized into quartiles. Respiratory morbidities included asthma, COPD, wheeze, cough, and phlegm. Asthma was defined as a yes to two questions: Were you ever told you have asthma? And do you still have asthma? Chronic obstructive pulmonary disease (COPD) was defined as FEV1/FVC <0.7. Cough and phlegm were defined as reported cough and phlegm production for most days in the past three months respectively. Wheezing was defined as wheeze or whistling in the chest in the past one year.

Lung function was assessed using pre-bronchodilator spirometry values and forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) were expressed as% predicted. Serum C-reactive protein (CRP) was used as a biomarker of inflammation. Exclusion criteria included current pregnancy, implausible intake of total calories, and spirometry measurements not conforming to the American Thoracic Society standards (grades C, D and F).

Results We found that individuals with the lowest intake of fiber (quartile 1) had a higher odds for asthma (OR 1.3; 95% CI 1.1–1.6), wheeze (OR = 1.3; 95% CI 1.1–1.5), cough (OR = 1.7; 95% CI 1.3–2.1) and phlegm (OR = 1.4; 95% CI 1.1–1.8) when compared to those with the highest intake of fiber (quartile 4). Data for COPD did not reveal a dose-dependent relationship with high fiber. Also, an increase in dietary intake of fiber was positively correlated with FVC (L),% predicted FVC, FEV1, and predicted FEV1 in a dose-dependent manner (P<0.001 for all comparisons). All results were adjusted for gender, age, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic or other), BMI (kg/m2), income: poverty ratio, smoking status (never, former, current) and total energy intake (kcal). Congruent with these results, we found that increased intake of dietary fiber was associated with a decrease in CRP (n = 8195; P<0.07).

Conclusion Our findings suggest that a low intake of dietary fiber is associated with an increased prevalence of asthma, cough, phlegm, and wheeze as well as decreased lung function. In concordance, low intake of fiber was correlated with increased CRP levels. These results suggest that dietary interventions may be a management approach to treating respiratory morbidity.

C29 SERUM PROTEOMIC ANALYSIS IN THORACIC SURGERY PATIENTS WITH DELIRIUM
Sikandar H Khan, Russell Purpura, Anthony Perkins, Sujuan Gao, Babar Khan. Indiana University School of Medicine
10.1136/jim-2019-midwestern2019.64

Background and objectives Delirium is a leading post-operative complication in non-cardiac thoracic surgery patients, with an incidence as high as 50%. The pathophysiology of delirium is not well defined. We performed an exploratory proteomic analysis to identify serum proteins associated with delirium in thoracic surgery patients.

Methods Blood samples were collected from 56 patients (28 with delirium, 28 without delirium) enrolled in PEPOD, a randomized double-blind clinical trial. Inclusion criteria of the parent trial were: English speaking, adults aged 18 or older, undergoing thoracic surgery at our tertiary-care academic medical center. Exclusion criteria of the parent trial were history of schizoaffective disorder, Parkinson’s, severe dementia, alcohol abuse, haloperidol allergy, neuroleptic malignant syndrome. Blood samples were collected pre-operatively, and on post-operative day 1. Trypsin-digested protein samples were labeled with TMT 10plex isobaric bars, eluted with 3-hour acetoni-trile gradient with mass spectrometry. Bioinformatics analysis was performed using Thermo Proteome Discoverer and STRING web-based tools. Between-group differences in median abundance ratios were analyzed using Kruskal-Wallis.

Results Three proteins with greater increase in median abundance ratio in the delirium group were identified: Coagulation factor IX (delirium-negative: 1.13, IQR: 0.99-1.18, delirium-positive: 1.18, IQR: 1.08-1.26, p=0.047), phospholipid transfer protein (delirium-negative: 0.94, IQR: 0.88-1.06, delirium-positive: 1.05, IQR: 0.97-1.11, p=0.029), and mannosyl-oligosaccharide 1,2-alpha-mannosidase (delirium-negative: 1.36, IQR: 1.34-1.44, delirium-positive: 1.48, IQR: 1.35-1.60, p=0.043).

Conclusions Our study identified three proteins with greater increase in median abundance ratio in the delirium group. This hypothesis generating study may guide further work in proteins associated with postoperative delirium.
Using CMS Data to Project Economic Burden of Antineoplastic Drugs in the United States

Keith D Huff, Eric N Huff, Kayla Link, Eric Kruep, Butler University, College of Pharmacy and Health Sciences, IN; Southern Illinois University Edwardsville College of Pharmacy, IL; Kruep Outcomes Research Technology, FL

Objectives Many data-driven researchers have interest in using large data sets to answer various questions. Although these data sets may be very insightful to a particular hypothesis, the data type, inclusion, completeness, and most importantly, access, are all concerns to whether or not important questions can be answered. Today, in the health care sector, the best data comes at a price. If a student or independent researcher does not have the ability to pay for access to large data sets that can easily cost thousands to millions of dollars, it is difficult to perform basic analyses and generate quality data driven evidence. Of the free data sets available for public use, we evaluated the Centers for Medicare and Medicaid Services (CMS) data to evaluate the capacity for predicting antineoplastic and total drug spend in the United States.1

Methods A data extraction was performed from the CMS website, specifically from Medicaid Analytic eXtract MAX Rx zip files for the years 2006 to 2009. These data tables included Medicare-Medicaid dual eligibles, non-duals, and all Medicaid beneficiaries combined. Annual total reimbursement spend data was first compiled from the U.S. National Prescription Drug Table N.1a from the CMS MAX Rx All Beneficiaries file. Table N.1a contained characteristics of Medicaid beneficiaries with at least one month of pharmacy benefit coverage, by basis of eligibility as total pharmacy spend in U.S. dollars for all beneficiaries in MAX 2006–2009. Secondly, annual spend data for antineoplastic agents was compiled from the U.S. National Prescription Drug Table 6 in MAX 2006–2009.

Results Total annual U.S. pharmacy reimbursement was $22.3 billion in 2009. Total annual U.S. antineoplastic drug reimbursement was $315.5 million in 2009, representing 1.2% of total spend. An 11 year projection estimates total Rx reimbursement at $29 billion in 2020. Similar trends project antineoplastic drug reimbursement spend at $586 million in 2020. Thus antineoplastic drug spend represents 2.0% of total Rx reimbursement spend in the U.S. Medicaid and Medicare population.

Conclusion Based on this analysis, we predict that both antineoplastic drug and total drug reimbursement spend will continue to increase throughout the year 2020, which is validated by other studies evaluating total drug spend.2 Additionally, antineoplastic drug spend is increasing at a faster pace when compared to total annual drug spend. More importantly, we are able to demonstrate that it may be feasible to answer basic research questions using CMS data sets. Many factors may play a role in the ability to perform analyses. First, complicated and very specific data is difficult to isolate in these aggregated data sets. Not all state data was available (data excluded HI, ID, ME, MO, NH, OK, UT, and WI), eluding to other data gaps within the tables. Lastly, a significant weakness using these data is the age. The most recent drug spend data was from 2009 and was prepared for public use in November 2012. Without projection models to quantify CMS drug spend, this publicly available data has the risk of being obsolete. Although free to use, caution should be used designing studies around the CMS data sets, as completeness, aggregate specificity, and age of the data are restraining.


Gastroenterology/Clinical Nutrition

Acute Liver Injury: The Role of Acetaminophen

Shana Kothari, Michael Kalinowski, Elizabeth Brindise, Matthew Kubeszko, Rogelio Silva. University of Illinois at Chicago/Advocate Christ Medical Center, IL

Objective Acute ischemic hepatopathy, or shock liver, is diffuse hepatic injury due to hypoperfusion and accounts from 1 to 2.5 percent of patients admitted to an intensive care unit. This phenomenon leads to a profound elevation in aminotransferases. Recent studies have shown that N-Acetylcysteine (NAC) provides mortality benefit and improves transplant-free survival in patients that have non-acetaminophen induced acute liver injury, however there have been no studies that show the effects on ischemic hepatopathy from cardiogenic, septic, or hypovolemic shock. In studies utilizing murine models, NAC has been shown to be beneficial in ischemic injury by eliminating reactive oxygen species and attenuating hepatic apoptosis. We aim to evaluate and compare the trend of hepatic function tests, use of vasopressor requirements, and length of intensive care stay for patients admitted with ischemic hepatopathy who received the 72-hour-NAC protocol compared to those who did not.

Methods In this retrospective single-center study, we identified all patients with ischemic hepatopathy from cardiogenic, septic, or hypovolemic shock from January 2015 to December 2017. Chart review was performed and data trends in transaminases, bilirubin, coagulation tests, creatinine, vasopressor requirements, and the number of intensive care days were collected. All data was checked for normality and subsequently compared between the two groups with Wilcoxon rank sum and Pearson chi-square test, with p<0.05 considered significant.

Results A total of 20 patients with ischemic hepatopathy were included in our study; 10 patients received the 72-hour-NAC protocol and a control group of 10 patients did not receive NAC. The median age (range) was 65 (35,82) in the NAC group and 64.5 (44,89) in the control group (p=0.437), with 7 male patients (70%) in each group. There was no significant difference in mortality between the two groups. A rapid statistical improvement in the aspartate aminotransferase (AST) (-94.6% vs -72.7%, p=0.023) and creatinine (-32.7% vs 12%, p=0.01) was observed in the NAC group compared to the non-NAC group. Median vasopressor days were fewer and length of stay was higher in the NAC group compared to the control, but not statistically significant.

Abstract A02 Table 1  Clinical characteristics and trends between patients with and without 72-hour NAC protocol

<table>
<thead>
<tr>
<th></th>
<th>No NAC (n=10)</th>
<th>NAC (n=10)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>64.5 (44,89)</td>
<td>65 (35,82)</td>
<td>0.449</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7/10 (70%)</td>
<td>7/10 (70%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3/10 (30%)</td>
<td>3/10 (30%)</td>
<td></td>
</tr>
<tr>
<td><strong>Length of Stay (in days)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital Admission</td>
<td>12.5 (6,36)</td>
<td>16 (3,188)</td>
<td>0.545</td>
</tr>
<tr>
<td>Intensive Care Admission</td>
<td>6 (3,31)</td>
<td>12 (3,188)</td>
<td>0.306</td>
</tr>
<tr>
<td><strong>Intensive Care Unit Location</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult Surgical Heart Unit</td>
<td>3/10 (30%)</td>
<td>6/10 (60%)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular Transplant Unit</td>
<td>0/10 (0%)</td>
<td>1/10 (10%)</td>
<td></td>
</tr>
<tr>
<td>Medical Intensive Care Unit</td>
<td>7/10 (70%)</td>
<td>3/10 (30%)</td>
<td></td>
</tr>
<tr>
<td><strong>Shock Etiology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiogenic</td>
<td>6/10 (60%)</td>
<td>8/10 (80%)</td>
<td>0.342</td>
</tr>
<tr>
<td>Hypovolemic</td>
<td>1/10 (10%)</td>
<td>1/10 (10%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Septic</td>
<td>3/10 (30%)</td>
<td>1/10 (10%)</td>
<td>0.276</td>
</tr>
<tr>
<td><strong>Vasopressor Days</strong></td>
<td>5.5 (2,26)</td>
<td>4.5 (1,120)</td>
<td>0.688</td>
</tr>
<tr>
<td><strong>Laboratory Trends</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate Aminotransferase (AST)</td>
<td>-72.7 (-97,-53)</td>
<td>-94.6 (-98,-33)</td>
<td>0.023</td>
</tr>
<tr>
<td>Alanine Aminotransferase (ALT)</td>
<td>-60 (-75,-20)</td>
<td>-61 (-87,-25)</td>
<td>0.706</td>
</tr>
<tr>
<td>International Normalized Ratio (INR)</td>
<td>-32.5 (-50,25)</td>
<td>-16.7 (-66,111)</td>
<td>0.505</td>
</tr>
<tr>
<td>Prothrombin Time (PT)</td>
<td>-31.1 (-48,23)</td>
<td>-3.2 (-67,113)</td>
<td>0.290</td>
</tr>
<tr>
<td>Creatinine (Cr)</td>
<td>12.0 (-42,46)</td>
<td>32.7 (-57,-16)</td>
<td>0.010</td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>25.5 (-47,166)</td>
<td>-15.6 (-58,229)</td>
<td>0.227</td>
</tr>
<tr>
<td>Platelet Count</td>
<td>-27.1 (-85,74)</td>
<td>-31.3 (-71,17)</td>
<td>0.821</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>3/10 (30%)</td>
<td>3/10 (30%)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

*Values are presented as median % change (range). Change is calculated as (initial value – value at 72 hours) / initial value x 100.

1 In NAC group, 2 patients were excluded as they were on coumadin and had higher goal INR.
2 In NAC group, 1 patient was excluded and in non-NAC group, 4 patients were excluded due to continuous renal replacement therapy requirement.
Conclusion Based on our data, NAC use is associated with improved renal function at 72 hours. We believe that the observed increase in length of stay is an indicator of disease severity between the two groups. The NAC group appeared to have a trend to a more rapid improvement of AST, alanine aminotransferase (ALT), and bilirubin compared to the control group, however only AST reached statistical significance, likely from the small sample size. This pilot study shows some clinical benefit of NAC as a treatment modality of ischemic hepatothropy, however higher-powered, randomized controlled trials are needed to further validate this observation.

A10 GHRELIN-INDUCED ADIPOSE TISSUE DYSFUNCTION: ROLE IN ALCOHOLIC STEATOSIS
Karuna Rasineni, Kurt L Knight, Carol A Casey, Kusum K Kharbanda. Department of Internal Medicine, University of Nebraska Medical Center, Research Service, Veterans’ Affairs Nebraska-Western Iowa Health Care System Omaha, NE
10.1136/jim-2019-midwestern2019.67

Background Fatty liver, or steatosis, is the earliest and most common response to chronic ethanol intake. Previous studies have shown that chronic ethanol consumption leads to increased adipocyte tissue lipolysis and increased free fatty acid delivery to the liver, ultimately resulting in the development of hepatic steatosis. The adipose-liver axis is modulated by the hormone insulin as well as adipocyte-derived chemokines and adipokines such as C-C-motif ligand 2 (CCL2) and adiponectin, respectively. We and others have reported that alcohol administration alters the circulating levels of insulin, adiponectin and other adipokines in humans and animal models. Ghrelin is a hormone that is secreted primarily from the stomach and its levels are increased by chronic alcohol consumption. Since ghrelin inhibits insulin secretion from pancreatic β-cells, it can indirectly affect adipocyte tissue metabolism. Because adipose tissue expresses the ghrelin receptor, we hypothesized that ghrelin may also directly regulate adipocyte function.

Methods Adipocytes (3T3-L1 preadipocytes) were cultured in complete media and differentiated using standard protocols. After 3 days of differentiation, the cells were exposed to ghrelin (10nm) in insulin-supplemented growth media for 5–8 days until evidence of sufficient lipid droplet formation. The adipocyte lysates were prepared and the media collected for subsequent analyses. Free fatty acids, glycerol, CCL2, adiponectin and other adipokines were measured in the conditioned media and triglycerides levels were determined in adipocyte lysates.

Results Ghrelin treatment resulted in increased free fatty acid and glycerol release along with decreased triglyceride levels in the adipocytes. Ghrelin treatment to the adipocytes also significantly inhibited secretion of adiponectin, a hepato-protective hormone that reduces lipid synthesis and promotes lipid oxidation in the liver. Furthermore, ghrelin treatment significantly increased secretion of CCL2, an important chemokine, known to increase hepatic steatosis and liver injury.

Conclusions Ethanol-induced increased circulating ghrelin directly enhances adipocyte lipolysis, thereby increasing the amount of free fatty acids released for the subsequent uptake by the liver that ultimately results in fat accumulation in the liver. In addition, ghrelin-mediated decrease in adiponectin along with an increase in CCL2 can directly promote development of fatty liver. We predict that inhibiting the alcohol-induced ghrelin increase could prevent the development of fatty liver disease directly by improving adipose tissue metabolism and indirectly via normalizing circulating insulin levels.

A31 A COMPARISON OF CHARACTERISTICS IN LEFT VENTRICULAR ASSIST DEVICE PATIENTS WITH AND WITHOUT GASTROINTESTINAL BLEEDING
Michael Kalinowski, Shana Kothari, Matthew Kobesko, Greta Josephson, William Cotts, Sunil Pawar, Antone Tatooles, Rogelio Silva, Imad ElHabbab. University of Illinois at Chicago – Advocate Christ Medical Center, IL
10.1136/jim-2019-midwestern2019.68

Objective Left ventricular assist device (LVAD) therapy is a form of mechanical support for patients with advanced heart failure as either a bridge to heart transplant or destination therapy. The association between gastrointestinal bleeding (GIB) and LVAD recipients is well established. There has been reported literature comparing demographics and clinical associations between patients with and without GIB, however, no studies have analyzed multiple device types. The objective of this study is to further understand the characteristics and associations of two commonly utilized LVAD types, Heartmate II (HMII) and Heartware, in patients with and without GI bleeding events.

Method This was a single-center retrospective study analyzing and comparing randomly selected patients from a population of 425 HMII and 193 Heartware recipients from 2007 to 2018. Chart review was performed and data pertaining to demographics, baseline laboratory values, home medications, LVAD therapy intention and parameters, and echocardiogram reports were collected. Univariate analysis was performed using t-tests, Mann-Whitney U, and Pearson chi-squared tests.

Results A total of 101 HMII and 101 Heartware LVAD patients were included in this study; 46 HMII recipients (45.5%) and 44 Heartware recipients (43.6%) developed at least one GIB event. Of those, 56.5% and 40.9% of patients re-bled, respectively (p=0.141). Among the Heartware group, there was a higher median age among the patients with GIB compared to those without (59.11 ± 11.3 vs 52.1 ± 16.0; p=0.026). HMII patients with a history of GIB pre-LVAD implantation bled more often post-LVAD implantation (10.9% vs. 0% p=0.004). There was higher median therapy days among GIB groups in both the HMII (1017 vs. 422; p=0.001) and the Heartware recipients (668 vs. 356; p=0.003). Baseline hemoglobin was lower in the GIB group compared to the non-GIB group in both HMII (10.3 vs 11.3; p=0.010) and Heartware recipients (10.0 vs 11.0; p=0.001). Patients prescribed angioten-sin II receptor blockers had less occurrence of GIB in both HMII (23.9% vs 54.6%; p=0.002) and Heartware groups (18.2% vs 40.4%; p=0.017).

Conclusion This study highlights that a lower baseline hemoglobin is associated with development of GIB in patients with Heartware and HMII LVADs. Importantly,
both groups showed a protective association with reduced occurrence of GIB among patients taking angiotensin II receptor blockers. The use of proton pump inhibitors showed no association in GIB occurrence. Further development of the association between angiotensin II receptor blockers and GIB effect in LVADs are warranted. Multivariate analyses to validate these associations are in progress.
A COMPARISON OF FIRST TIME GASTROINTESTINAL BLEEDING EVENTS BETWEEN HEARTMATE II AND HEARTWARE LEFT VENTRICULAR ASSIST DEVICES

Michael Kalinowski, Shana Kothari, Matthew Kobeszko, Greta Josephson, William Cotts, Sunil Pauwaa, Antonne Tatooles, Imad Elkhamb, Rogelio Silva. University of Illinois at Chicago – Advocate Christ Medical Center, IL

10.1136/jim-2019-midwestern2019.69

Objective Left ventricular assist devices (LVADs) are an established therapy for patients with advanced heart failure. Gastrointestinal bleeding (GIB) is a common adverse event following LVAD implantation. There is limited literature comparing bleeding events between Heartmate II (HMII) and Heartware LVADs. Previous studies have suggested that HMII recipients bleed more often than those of Heartware. The aim of this study was to further understand gastrointestinal bleeding, endoscopic treatment, and the potential device differences between HMII and Heartware patients.

Method This was a single-center retrospective study analyzing and comparing randomly selected patients from a population of 425 HMII and 193 Heartware recipients from 2007 to 2018. Chart review was performed and data pertaining to demographics, LVAD therapy intention and parameters, LVAD and bleeding characteristics were collected. All data were analyzed and compared using SPSS software (IBM, Armonk, NY). The primary outcome measure was the incidence of GIB requiring intervention.

Results A total of 193 patients (mean age: 56 ± 13 years) were included in the analysis. The incidence of GIB requiring intervention was higher in the Heartware group (36.1%) compared to the HMII group (23.0%). The median number of bleeding episodes per patient was 1 (range: 1-7) in the Heartware group and 0 (range: 0-4) in the HMII group (p = 0.035). The primary site of bleeding was the upper gastrointestinal tract in 75% of cases. The overall mortality rate was 9.5% (18 patients). The comparison of GIB characteristics, findings, and intervention between heartmate II and heartware recipients is shown in the table below.

<table>
<thead>
<tr>
<th>General Information</th>
<th>Heartmate II (n=46)</th>
<th>Heartware (n=44)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent Bled</td>
<td>45.5% (46/101)</td>
<td>43.6% (44/101)</td>
<td>0.778</td>
</tr>
<tr>
<td>Bleeding site identified</td>
<td>65.2%</td>
<td>71.5%</td>
<td>0.593</td>
</tr>
<tr>
<td>Percent that Bled &lt; 30 days after implant</td>
<td>23.9%</td>
<td>18.2%</td>
<td>0.510</td>
</tr>
<tr>
<td>Percent that Bled &gt; 30 days after implant</td>
<td>76.1%</td>
<td>82.8%</td>
<td>0.435</td>
</tr>
<tr>
<td>Therapy Days</td>
<td>1017 (207-3750)</td>
<td>668 (30-3164)</td>
<td>0.049*</td>
</tr>
<tr>
<td>Days to First Bleeding Event</td>
<td>200 (5-2757)</td>
<td>156 (9-2197)</td>
<td>0.743</td>
</tr>
<tr>
<td>Percent of Patients that Rebled</td>
<td>56.5%</td>
<td>40.9%</td>
<td>0.141</td>
</tr>
<tr>
<td>Reduced Right Ventricular Systolic Function</td>
<td>41.3%</td>
<td>68.2%</td>
<td>0.010*</td>
</tr>
<tr>
<td>Hospital Length of Stay (days)</td>
<td>18.3 ± 23.6</td>
<td>22.3 ± 31.3</td>
<td>0.209</td>
</tr>
<tr>
<td>Mortality During GIB Admission</td>
<td>0.0%</td>
<td>4.6%</td>
<td>0.143</td>
</tr>
</tbody>
</table>

Demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Heartmate II (n=46)</th>
<th>Heartware (n=44)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.5 ± 9.8</td>
<td>59.11 ± 11.3</td>
<td>0.138</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>84.8%</td>
<td>68.2%</td>
<td>0.069</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>50.0%</td>
<td>36.4%</td>
<td>0.196</td>
</tr>
<tr>
<td>Black/African American</td>
<td>32.6%</td>
<td>59.1%</td>
<td>0.012*</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>13.0%</td>
<td>4.5%</td>
<td>0.158</td>
</tr>
<tr>
<td>Asian</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.000</td>
</tr>
<tr>
<td>Native American</td>
<td>2.2%</td>
<td>0.0%</td>
<td>0.325</td>
</tr>
<tr>
<td>Other</td>
<td>2.2%</td>
<td>0.0%</td>
<td>0.325</td>
</tr>
</tbody>
</table>

Device Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Heartmate II (n=46)</th>
<th>Heartware (n=44)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device Therapy Goal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bridge to Transplant</td>
<td>19.6%</td>
<td>47.7%</td>
<td>0.005*</td>
</tr>
<tr>
<td>Destination therapy</td>
<td>80.4%</td>
<td>52.3%</td>
<td>0.005*</td>
</tr>
<tr>
<td>Prior History of GI Bleed Prior to LVAD</td>
<td>10.9%</td>
<td>0.0%</td>
<td>0.024*</td>
</tr>
<tr>
<td>Prior History of Endoscopy</td>
<td>60.9%</td>
<td>29.6%</td>
<td>0.003*</td>
</tr>
</tbody>
</table>

Initial GI Presenting Sign

<table>
<thead>
<tr>
<th>Variable</th>
<th>Heartmate II (n=46)</th>
<th>Heartware (n=44)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematemesis</td>
<td>2.2%</td>
<td>6.8%</td>
<td>0.292</td>
</tr>
<tr>
<td>Hematochezia</td>
<td>17.4%</td>
<td>15.9%</td>
<td>0.850</td>
</tr>
<tr>
<td>Melena</td>
<td>45.7%</td>
<td>47.7%</td>
<td>0.850</td>
</tr>
<tr>
<td>FOBT</td>
<td>23.9%</td>
<td>18.2%</td>
<td>0.510</td>
</tr>
<tr>
<td>Obscure Anemia</td>
<td>10.9%</td>
<td>9.1%</td>
<td>0.945</td>
</tr>
</tbody>
</table>

Endoscopic Diagnostic Yield

<table>
<thead>
<tr>
<th>Variable</th>
<th>Heartmate II (n=46)</th>
<th>Heartware (n=44)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Endoscopic Procedures Performed</td>
<td>71</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Total Endoscopic Diagnostic Yield</td>
<td>43.7% (31/71)</td>
<td>57.9% (33/57)</td>
<td>0.112</td>
</tr>
<tr>
<td>EGD</td>
<td>37.0% (10/27)</td>
<td>70.8% (17/24)</td>
<td>0.017*</td>
</tr>
<tr>
<td>Push Enteroscopy</td>
<td>62.5% (10/16)</td>
<td>55.6% (10/18)</td>
<td>0.689</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>39.3% (11/28)</td>
<td>40.0% (6/15)</td>
<td>0.965</td>
</tr>
</tbody>
</table>

Non-Endoscopic Diagnostic Yield

<table>
<thead>
<tr>
<th>Variable</th>
<th>Heartmate II (n=46)</th>
<th>Heartware (n=44)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tagged RBC</td>
<td>33.3% (1/3)</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>IR Angiography</td>
<td>0.0% (0/2)</td>
<td>100% (1/1)</td>
<td>-</td>
</tr>
</tbody>
</table>
## Abstracts

### Bleeding Site Location

<table>
<thead>
<tr>
<th>Variable</th>
<th>Heartmate II (n = 46)</th>
<th>Heartware (n = 44)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Number of Bleeding Incidences</strong></td>
<td>n = 44 bleeding incidences</td>
<td>n = 41 bleeding incidences</td>
<td>-</td>
</tr>
<tr>
<td>Esophagus</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td><strong>Stomach</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fundus</td>
<td>3</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Body</td>
<td>4</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>Antrum</td>
<td>5</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>Pyloric Channel</td>
<td>1</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td><strong>Small Bowel</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duodenum</td>
<td>8</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>proximal (D1 - first portion)</td>
<td>2</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>mid (D2 - second portion)</td>
<td>2</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>mid (D3 - third portion)</td>
<td>1</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>distal (D4 - fourth portion)</td>
<td>3</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Jejunum</td>
<td>2</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Proximal</td>
<td>1</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Mid-jejunum</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Distal jejunum</td>
<td>1</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Terminal ileum</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td><strong>Large Bowel</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cecum</td>
<td>1</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Ascending colon</td>
<td>2</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Hepatic flexure</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Transverse colon</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Descending colon</td>
<td>3</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Sigmoid colon</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Rectum</td>
<td>4</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

### Bleeding Lesion Etiology

<table>
<thead>
<tr>
<th>Variable</th>
<th>Heartmate II (n = 33 bleeding etiologies)</th>
<th>Heartware (n = 35 bleeding etiologies)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagitis</td>
<td>0.0%</td>
<td>0.0%</td>
<td>-</td>
</tr>
<tr>
<td>Hemorrhagic gastritis</td>
<td>3.0%</td>
<td>11.4%</td>
<td>0.187</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>9.1%</td>
<td>2.9%</td>
<td>0.281</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>0.0%</td>
<td>2.9%</td>
<td>-</td>
</tr>
<tr>
<td>Gastro-duodenal polyt</td>
<td>6.3%</td>
<td>8.6%</td>
<td>0.696</td>
</tr>
<tr>
<td>AVM/angiodyplasia/ectasia</td>
<td>45.5%</td>
<td>62.9%</td>
<td>0.153</td>
</tr>
<tr>
<td>Divaclofy's lesion</td>
<td>0.0%</td>
<td>0.0%</td>
<td>-</td>
</tr>
<tr>
<td>Polyp</td>
<td>9.1%</td>
<td>8.6%</td>
<td>0.943</td>
</tr>
<tr>
<td>Diverticular</td>
<td>3.0%</td>
<td>0.0%</td>
<td>-</td>
</tr>
<tr>
<td>Colonic ulcer</td>
<td>3.0%</td>
<td>0.0%</td>
<td>-</td>
</tr>
<tr>
<td>Ischemic colitis</td>
<td>3.0%</td>
<td>0.0%</td>
<td>-</td>
</tr>
<tr>
<td>Infectious colitis</td>
<td>9.1%</td>
<td>0.0%</td>
<td>-</td>
</tr>
<tr>
<td>Infectious colitis</td>
<td>9.1%</td>
<td>0.0%</td>
<td>-</td>
</tr>
<tr>
<td>Rectal ulcer</td>
<td>3.0%</td>
<td>0.0%</td>
<td>-</td>
</tr>
<tr>
<td>Internal hemorrhoids</td>
<td>6.1%</td>
<td>0.0%</td>
<td>-</td>
</tr>
</tbody>
</table>

### Endoscopic Intervention

<table>
<thead>
<tr>
<th>Total Number of Interventions Performed</th>
<th>n = 80 interventions</th>
<th>n = 63 interventions</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EPI</strong></td>
<td>2.5%</td>
<td>4.8%</td>
<td>0.460</td>
</tr>
<tr>
<td><strong>Clip</strong></td>
<td>8.8%</td>
<td>4.8%</td>
<td>0.355</td>
</tr>
<tr>
<td><strong>APC</strong></td>
<td>17.5%</td>
<td>36.5%</td>
<td>0.010*</td>
</tr>
<tr>
<td><strong>Bipolar Cautery</strong></td>
<td>8.8%</td>
<td>4.8%</td>
<td>0.355</td>
</tr>
<tr>
<td><strong>Bipsoy</strong></td>
<td>3.8%</td>
<td>1.6%</td>
<td>0.433</td>
</tr>
<tr>
<td><strong>Snare</strong></td>
<td>2.5%</td>
<td>4.8%</td>
<td>0.460</td>
</tr>
<tr>
<td><strong>None</strong></td>
<td>55.6%</td>
<td>42.9%</td>
<td>0.133</td>
</tr>
</tbody>
</table>

### Other Interventions

<table>
<thead>
<tr>
<th>Variable</th>
<th>n = 80 interventions</th>
<th>n = 63 interventions</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR embolization</td>
<td>0</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Octreotide Given</td>
<td>26.10%</td>
<td>29.50%</td>
<td>0.720</td>
</tr>
<tr>
<td>Given PRBCs</td>
<td>67.40%</td>
<td>63.60%</td>
<td>0.706</td>
</tr>
<tr>
<td>Units of PRBCs Given</td>
<td>4.1 ± 3.3</td>
<td>3.4 ± 2.8</td>
<td>0.347</td>
</tr>
<tr>
<td>Platelets Given</td>
<td>2.27%</td>
<td>4.54%</td>
<td>0.554</td>
</tr>
</tbody>
</table>

Values reported as either mean ± standard deviation for normally distributed data, median for non-normally distributed data, or %. p-Values for continuous variables are from either a t-test without assuming equal variances or Mann-Whitney U test; p-values from categorical variables are from Pearson chi-squared test. Outliers were excluded if greater than three quartiles from the mean.

1median (range)
2per echocardiogram report at time of first GI bleed
3mean ± standard deviation
*Patients may have bled from more than one location
* Patients may have more than one bleeding etiology
GIB: gastrointestinal bleeding; GI: gastrointestinal; LVAD: left ventricle assist device; FORT: fecal occult blood test; EGD: esophagogastroduodenoscopy; RBC: red blood cell; IR: interventional radiology; EPI: epinephrine; APC: argon plasma coagulation; PRBCs: packed red blood cells
*statistically significant with alpha level ≤ 0.05
## Abstract B01 Table 2 Baseline characteristics of heartmate II and heartware recipients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Heartmate II (n = 101)</th>
<th>Heartware (n = 101)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>60.4 ± 12</td>
<td>55.15 ± 14.5</td>
<td>0.006*</td>
</tr>
<tr>
<td>Sex</td>
<td>83.20%</td>
<td>71%</td>
<td>0.030*</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>47.5%</td>
<td>48.5%</td>
<td>0.887</td>
</tr>
<tr>
<td>Black/African American</td>
<td>37.6%</td>
<td>43.6%</td>
<td>0.386</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>8.9%</td>
<td>6.9%</td>
<td>0.599</td>
</tr>
<tr>
<td>Asian</td>
<td>3.0%</td>
<td>0.0%</td>
<td>-</td>
</tr>
<tr>
<td>Native American</td>
<td>2.0%</td>
<td>0.0%</td>
<td>-</td>
</tr>
<tr>
<td>Other</td>
<td>1.0%</td>
<td>1.0%</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Device Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Device Therapy Goal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bridge to Transplant</td>
<td>24.7%</td>
<td>58.4%</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Destination therapy</td>
<td>75.3%</td>
<td>41.6%</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Reduced Right Ventricular Systolic Function¹</td>
<td>52.5%</td>
<td>70.3%</td>
<td>0.009*</td>
</tr>
<tr>
<td>Hx of GI Bleeding Prior to LVAD</td>
<td>5.0%</td>
<td>1.0%</td>
<td>0.097</td>
</tr>
<tr>
<td>Hx of GI Bleeding Post LVAD</td>
<td>45.5%</td>
<td>43.6%</td>
<td>0.778</td>
</tr>
<tr>
<td>LVAD Therapy Days²</td>
<td>688 (13-3750)</td>
<td>493 (7-3164)</td>
<td>0.131</td>
</tr>
<tr>
<td><strong>Laboratory Results</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine (baseline)³</td>
<td>1.3 (0.6-3.0)</td>
<td>1.2 (0.5-2.2)</td>
<td>0.008*</td>
</tr>
<tr>
<td>Hemoglobin (baseline)³</td>
<td>11.0 (8.0-15.4)</td>
<td>10.7 (8.1-14.1)</td>
<td>0.425</td>
</tr>
<tr>
<td>Platelets (baseline)³</td>
<td>213 (106-480)</td>
<td>250 (84-590)</td>
<td>0.003*</td>
</tr>
<tr>
<td>Lactate dehydrogenase (LDH)</td>
<td>339 (158-1639)</td>
<td>242 (113-1291)</td>
<td>0.001*</td>
</tr>
<tr>
<td>International normalized ration (INR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sub-therapeutic</td>
<td>34.7%</td>
<td>31.7%</td>
<td>0.655</td>
</tr>
<tr>
<td>Therapeutic</td>
<td>48.5%</td>
<td>45.5%</td>
<td>0.670</td>
</tr>
<tr>
<td>Supratherapeutic</td>
<td>16.8%</td>
<td>22.7%</td>
<td>0.294</td>
</tr>
<tr>
<td><strong>LVAD Settings</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Speed (rpm)¹</td>
<td>9315 ± 346</td>
<td>2798 ± 221</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Aortic Valve²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open</td>
<td>30.3%</td>
<td>26.8%</td>
<td>0.589</td>
</tr>
<tr>
<td>Intermittently Open</td>
<td>21.2%</td>
<td>33.0%</td>
<td>0.064</td>
</tr>
<tr>
<td>Closed</td>
<td>48.5%</td>
<td>41.2%</td>
<td>0.306</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taking Acid Reducing Agent</td>
<td>79.2%</td>
<td>81.2%</td>
<td>0.724</td>
</tr>
<tr>
<td>Taking PPI</td>
<td>71.3%</td>
<td>84.2%</td>
<td>0.048*</td>
</tr>
<tr>
<td>Taking ACE/ARB</td>
<td>40.6%</td>
<td>30.7%</td>
<td>0.008*</td>
</tr>
<tr>
<td>Taking Omega-3</td>
<td>6.9%</td>
<td>4.0%</td>
<td>0.352</td>
</tr>
<tr>
<td>Taking Aspirin 81mg</td>
<td>90.1% (91/101)</td>
<td>90.1% (91/101)</td>
<td>1.000</td>
</tr>
<tr>
<td>Taking Aspirin 325mg</td>
<td>73.6% (67/91)</td>
<td>14.3% (13/91)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Taking Clopidogrel</td>
<td>9.0%</td>
<td>0.0%</td>
<td>0.002*</td>
</tr>
<tr>
<td>Taking Dipyridamole</td>
<td>4.0%</td>
<td>11.8%</td>
<td>0.040*</td>
</tr>
</tbody>
</table>

Values reported as either mean ± standard deviation for normally distributed data, median for non-normally distributed data, or %. p-Values for continuous variables are from either a t-test without assuming equal variances or Mann-Whitney U test; p-values from categorical variables are from Pearson chi-squared test. Outliers were excluded if greater than three quantiles from the mean.

¹mean ± standard deviation
²median (range)
³p-value for categorical variables
⁴p-value for continuous variables
GI: gastrointestinal; LVAD: left ventricle assist device; RPM: revolutions per minute; PPI: proton pump inhibitor; ACE/ARB: angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker

*statistically significant with alpha level ≤ 0.05
endoscopic reports, therapeutic interventions, home medications, and echocardiogram reports was collected. Univariate analysis was performed using t-tests, Mann-Whitney U, and Pearson chi-squared tests.

**Results** A total of 101 HMII and 101 Heartware patients were included in this study. There was no difference in the number of first time GIB events between the HMII and Heartware recipients (45.5% vs. 43.6%; p=0.778). HMII patients were younger than Heartware patients (60.4 vs 55.2 years; p=0.006). No differences were found in race, gender, and number of therapy days between devices (table 1). The HMII GIB group had higher median therapy days (1017 vs. 668; p=0.049) and no difference in median days to first bleeding event (200 vs.156; p=0.743). The incidence of first time GIB events per total patient LVAD year was 0.184 and 0.219 for HMII and Heartware recipients, respectively. Melena was the most common presenting sign among GIB groups. Among all endoscopic procedures performed there were no endoscopic yield differences between devices (43.7% vs. 57.9%; p=0.112). EGD had a higher yield among the Heartware GIB group (70.8% vs. 37.0%; p=0.017). Bleeding lesions were most frequent in the small bowel among HMII and in the stomach among Heartware GIB groups. Arteriovenous malformations were the predominant etiology in both groups (table 2).

**Conclusion** This study is the largest single-center comparison of first time GIB among HMII and Heartware recipients. There was no difference in bleeding occurrence between HMII and Heartware patients despite lower LVAD speeds among Heartware recipients. Small bowel and gastric arteriovenous malformations were the most common etiology among the two groups. Our study shows that the majority of upper GIB lesions among both devices can be localized with EGD. Based on our findings in this univariate analysis, one device is not superior to the other in regards to GIB occurrence. Multivariate analysis are underway to confirm these findings.

**Abstracts**

**C01 OVEREXPRESSION OF LONG NON-CODING RNA H19 REGULATED THE METHIONINE METABOLISM IN ALCOHOLIC LIVER DISEASE**

Zhihong Yang, Praveen Kusumanchi, Suthat Liangpunsakul. Department of Medicine, Indiana University, IN

**Objective** Long non-coding RNA (lncRNA) H19 is a maternally expressed and paternally imprinted gene, which is mainly expressed in embryonic liver but diminished in adult liver. Intriguingly, H19 is reactivated in chronic liver diseases, implicating an important regulatory role in hepatic function. This study aims at elucidating the novel function of H19 in ethanol disrupted hepatic methionine homeostasis.

**Methods** Pharmacologic and Genetic Murine Models, IHC/IF, FIB-SEM, Western Blot Results: We are able to follow Cathartocytosis with IHC/IF using the monoclonal antibody Das-1, which identifies an as-yet-identified oncofetal antigen that is expressed during metaplastic and oncogenic transformation of several epithelial cell types. Using the exquisite, three-dimensional detail afforded by focused ion beam scanning electron microscopy (FIB-SEM), we show that the excrated vesicles are enveloped by another membrane, which fuses with the apical membrane, releasing the jettisoned vesicles intact. We believe this outer membrane is the remnant of senescent autophagosome/somatetosome as we are able to block Cathartocytosis in murine models pharmacologically with hydroxychloroquine and genetically in mice null for GNPtA, an enzyme essential for lysosomal hydrolase trafficking.

**Conclusions** The fact that mAb Das-1 both annotates this process and is a highly sensitive and specific marker for premalignant and malignant cellular transformation of several human epithelial types throughout the Gastrointestinal tract suggests that Cathartocytosis is used in premalignant and malignant cellular transformation to access an oncofetal cell state otherwise unavailable to mature differentiated cells.

**Endometriosis**

Jeffrey W Brown, Koushik K Das, Spencer G Willet, Megan D Radyk, Joseph Burdilff, Jason C Mills. Washington University School of Medicine, MO

**Objective** Endometriosis affects reproductive organs and is characterized by the presence of endometrial tissue outside the uterine cavity. Endometriosis affects 10% of women of reproductive age and is one of the leading causes of infertility. The pathogenesis of endometriosis is not fully understood, but several factors, including endocrine disruption, immune response, and genetic factors, have been implicated. Endometriosis may be associated with an increased risk of endometrial carcinoma.

**Methods** Endometriosis was diagnosed in women with subfertility who were referred for an infertility evaluation. Women with endometriosis were compared to age-matched women without endometriosis. Women were enrolled at a university hospital in New York City. Endometriosis was diagnosed by laparoscopy and confirmed by histology. Women with endometriosis were compared to age-matched women without endometriosis. Women were enrolled at a university hospital in New York City. Analysis was performed using Chi-square analysis. The study was approved by the institutional review board.

**Results** Women with endometriosis were more likely to have a history of pelvic inflammatory disease (38% vs 23%, p=0.03), dysmenorrhea (62% vs 38%, p=0.001), and infertility (87% vs 53%, p=0.001). Women with endometriosis had a significantly higher prevalence of endometrial polyps (42% vs 2% p=0.001) and endometrial hyperplasia (28% vs 3%, p=0.001). Women with endometriosis were more likely to have a history of miscarriage (58% vs 29%, p=0.001). Women with endometriosis had a significantly higher prevalence of endometrial polyps (42% vs 2% p=0.001) and endometrial hyperplasia (28% vs 3%, p=0.001).

**Conclusions** Women with endometriosis are at risk for endometrial cancer. Women with endometriosis have a higher prevalence of endometrial polyps and endometrial hyperplasia compared to controls. These findings suggest a need for closer surveillance of women with endometriosis.
Conclusions These results unveiled a novel H19/PTBP1/BHMT feedforward amplifying signaling pathway to exacerbate the development of alcoholic liver disease.

Geriatrics

**CO4**

**ALGINATE OLIGOSACCHARIDE ALLEVIATES D-GLUCOSE-INDUCED CARDIAC AGING IN MICE VIA REGULATING THE SIRT1/PGC-1α SIGNALING PATHWAY**

Wenqing Feng, Jiayna Liu, Jie Mou, Meiping Feng, Shun Wang, Huashi Guan, Yongguan Mao. 1The Affiliated Hospital of Qingdao University, China; 2The Affiliated Hospital of Qingdao University, China; 3School of Medicine and Pharmacy, University of Qingdao, China

Objective Aging is an independent risk factor for the development of age-related cardiovascular disease. Age related mitochondrial dysfunction induce oxidative stress then eventually lead to cardiac dysfunction in aging mice. Alginoglicosaccharide (AOS), which is produced by depolymerizing alginate, has been proved to possess many biological properties. The present study was undertaken to investigate whether AOS could be used as an anti-aging drug to prevent cardiac aging.

Method D-glucose (D-gal)-induced C57BL/6J aging mice were established by subcutaneous injection of D-gal (150 mg/kg-1·d-1) for 8 weeks. AOS (50, 100 and 150 mg·kg-1·d-1) were administrated intragastrically for the last 4 weeks. Echocardiography was performed to assess the cardiac function of mice. Protein expression of p53, p21, sirtuin 1 (SIRT1), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and NADPH oxidase subunits were analyzed by Western blot. Mitochondrial ultrastructure was determined by transmission electron microscopy. Mitochondrial membrane potential (MMP) and reactive oxygen species (ROS) were examined by JC-1 and dihydroethidium (DHE) staining.

Results In this study, we found that AOS significantly prevented the cardiac dysfunction of the aging mice. AOS inhibited D-gal-induced upregulation of aging-related marker protein p53 and p21 in a dose-dependent manner. Furthermore, AOS treatment increased the expression of SIRT1 and PGC-1α, and improved the mitochondrial ultrastructure and mitochondrial membrane potential (MMP). In addition, AOS significantly ameliorates D-gal-induced ROS production and NADPH oxidase activity.

Conclusion Taken together, our results provide in vivo evidence that AOS alleviates D-gal-induced cardiac aging in C57BL/6J mice by improving mitochondrial function and inhibiting oxidative stress through the SIRT1/PGC-1α signaling pathway.

Hematology and Oncology

**A05**

**TARGETING CENTRAL BIOMARKERS TO POTENTIATE ACUPUNCTURE ANALGESIA IN SICKLE CELL DISEASE**

Ying Wang, Jianxun Lei, Kalpna Gupta. Vascular Biology Center, Division of Hematology, Oncology and Transplantation, Department of Medicine, University of Minnesota, MN

Objective Pain management in sickle cell disease (SCD) remains a challenge. Long-term treatment with opioids have side-effects such as addiction, tolerance and opioid-induced hyperalgesia and new approaches are needed. Non-pharmacological strategies, such as acupuncture, reduced pain in majority (80%) of SCD patients (Lu K et al., Clin J Pain 2014). We observed that electroacupuncture (EA) in free-moving transgenic mice with SCD decreased hyperalgesia in approximately 80%. However, analgesic responses were variable and ranged from high (200% increase in nociceptive threshold) to moderate- (100% increase in threshold) and non-responders (<100% increase in threshold) (Wang Y et al., Sci Rep 2016). Importantly, the level of analgesia was negatively correlated with levels of specific inflammatory mediators in the spinal cord including substance P (SP), a proinflammatory vasoactive neuropeptide showing an elevated level in both sickle patients and mice, and spinal p38 mitogen activated protein kinase (p38 MAPK), a critical mediator of chronic pain. We propose that these elevated mediators contribute to the poor EA analgesia in moderate- and non-responders. We hypothesized that the combined treatment of EA and inhibition of SP reduced p38 MAPK phosphorylation (p-p38 MAPK) would enhance EA analgesia in poorly-responding sickle mice.

Methods Only HbSS-BERK sickle mice that were defined as moderate- and non-responders were used. Male and female BERK mice, 5–7 months old, were treated with the SP receptor (NK1R) antagonist, netupitant, (10 mg/kg, i.p., daily), or EA (acupoint GB30, every 3rd day until day 12, frequency: 4 or 10 Hz, pulse width: 100 µs, duration: 30 min), or both. Hyperalgesia to mechanical and thermal stimuli, and deep tissue was measured using von Frey filaments, the Hargreaves test, the cold plate and grip force, respectively. Protein expression of p38 MAPK and p-p38 MAPK in the lumbar spinal cord was quantified using western blot, and p-p38 MAPK expression in spinal dorsal horn was examined using immunohistochemical staining and confocal microscopy.

Results Co-treatment with EA and netupitant in moderate- and non-responders reduced hyperalgesia beginning on day 3, and gradually enhanced the effect through day 9 and/or 12, as previously described (Wang Y et al., Blood 2018 132:1064). Notably, administration of EA or netupitant alone did not reduce hyperalgesia. Importantly, co-treatment with EA and netupitant resulted in reduced levels of p-p38 MAPK in the spinal cord and a lowered co-expression with spinal nuclei (reduced translocation of p-p38 MAPK in the nuclei of spinal dorsal horn) as compared to moderate- and non-responders treated with either EA or netupitant alone. These results suggest a pivotal role of SP in maintaining the chronic pain in SCD via spinal p38 MAPK signaling, which may hinder the effect of EA in poor responders.

Conclusion Robust activation of spinal p38 MAPK is correlated with sustained central sensitization and inflammatory milieu resulting from the inflammatory and algic mediator such as SP. The diminished nuclear translocation of p-p38 MAPK in spinal dorsal horn also suggests the reduced transcriptional activation. Sustained high levels of key mediators such as SP may underlie the poor acupuncture analgesia in SCD and could be predictive for acupuncture’s efficacy. Strategies using acupuncture with mechanism-based targets of central sensitization may be beneficial in treating pain and reducing opioid use in SCD.
Objective Medulloblastoma (MB) is the most common malignant pediatric tumor of the central nervous system (CNS) and a leading cause of childhood related morbidity and mortality. It is divided into four primary subgroups, i.e. SHH (sonic hedgehog), WNT (wingless), and non-SHH/WNT groups 3 and 4. The most frequent cytogenetic abnormality in medulloblastoma, i.e. i17q, distinguishes the non-SHH/WNT subgroups, which concurrently carry the highest incidence and mortality due to age-based restrictions on available therapeutic interventions. Haploinsufficiency of 17p13.3 is reported in up to 50% of non-SHH/WNT medulloblastoma cases and has been correlated with poor prognosis. At the terminal end of this locus is miR-1253, which is exclusively expressed in the brain and an important regulator of bone morphogenic proteins that play a critical role in cerebellar development. Recently, two oncogenic targets of miR-1253, i.e. TGIF2 and ALX4, were identified in SHH medulloblastoma; and miR-1253 was identified as a tumor suppressor gene in non-small cell lung cancer (NSCLC). Based upon these observations, we hypothesized that miR-1253 may be a tumor suppressor gene that undergoes epigenetic silencing in pediatric non-SHH/WNT medulloblastoma.

Methods We started by studying the expression of miR-1253 in ex vivo tumor samples using a combination of in silico and in vitro techniques. To explore genetic silencing mechanisms in cancer, we undertook a detailed methylation analysis of miR-1253 in tumor samples. We then explored the anti-tumorigenic properties of miR-1253 in vitro by studying tumor cell proliferation, migration, invasion, and colony formation using 2 well-established MB cell lines, DAOY and HDMB03. We further complemented these studies with a biochemical analysis of apoptosis and stemness in HDMB03 cells. We concluded our study by identifying a putative oncogenic target of miR-1253.

Results We first discovered expression deregulation of miR-1253 in 24 clinical samples and 7 medulloblastoma cell lines. We then learned that miR-1253 silencing is accomplished via hypermethylation; expectedly, de-methylation of miR-1253 using 5-AzaC, resulted in rapid recovery of expression with a subsequent decline in MB cell proliferation. Aside from an effect on cell proliferation, miR-1253 overexpression led to a reduction in colony formation, migration and invasive potential of MB tumor cell lines. Moreover, miR-1253 restoration was concomitant with activation of apoptotic pathways and a reduction in stemness markers. Using high throughput RNA sequencing analysis and luciferase reporter assay, we further identified a putative oncogenic target of miR-1253, i.e. CDK6.

Conclusions Taken together, these data suggest that miR-1253 possesses tumor suppressor qualities, i.e. 1) loss of expression via epigenetic silencing, 2) negative trophic effects on tumor cell growth, migration, and stemness and 3) downregulation of proteins with cell proliferative properties. This would be the first time such an effect has been attributed to miR-1253 in the context of medulloblastoma.
cell disorder (proteinuria: OR 0.6, P = 0.3; CKD: OR 0.8, P = 0.5). We were unable to replicate the association of APOA1 rs11216132 with hemoglobinuria in this cohort.

Conclusion In summary, we selected ELMO1 and APOA1 as potential candidate genes based on our bioinformatic approach and our studies in SCD mice. We were then able to replicate the association of ELMO1 rs10951509 with kidney disease and identify a tag-SNP in APOA1 associated with hemoglobinuria in SCD patients. Future studies investigating these candidate genes in African Americans and in those with SCD may improve our understanding of the molecular pathways and serve as targets for future research in SCD and African American-related CKD.

B21 EXPRESSION OF THE INTEGRIN ALPHA6 BETA4 IN SEROUS OVARIAN NEOPLASMS
Rachel I. Stewart, Dawa W Piecoro, Teresa Knifley, Kathleen L O’Connor. University of Kentucky, KY
10.1136/jim-2019-midwestern2019.76

Objective The integrin α6β4 is a receptor for laminins that plays an important role in the adhesion of cells to the extracellular matrix. This integrin contributes to carcinoma progression by promoting cell survival, proliferation, invasion, and metastasis. Recent studies have demonstrated that the integrin α6β4 is important in ovarian cancer where it may promote carcinoma cell adhesion to the peritoneal mesothelium. In this study, we sought to characterize expression of the integrin α6β4 in patient-derived ovarian serous neoplasms.

Method We analyzed integrin α6β4 expression in 30 ovarian serous tumors and in 3 benign ovaries using immunohistochemistry for the integrin β4 subunit, which is indicative of expression of the integrin. The cases studied ranged from serous borderline tumors to high grade serous adenocarcinomas. Staining was scored using the Allred method as has been previously described. In addition, we queried publicly available gene expression datasets to investigate the relationship between integrin β4 (ITGB4) gene expression and patient outcomes. Progression-free survival analysis was performed using public microarray data (N = 1,104) and patients were censored at the follow-up threshold (60 months).

Results Integrin α6β4 expression was found in the majority of serous tumors examined (29/30), and a high level of expression (Allred Score ≥ 7) was identified in 50% of the tumors examined. Using publicly available gene expression datasets, we found that elevated expression of ITGB4 is associated with reduced progression-free survival in patients with serous ovarian cancer (HR = 1.25; P = 0.0085).

Conclusion Integrin α6β4 is expressed in the majority of ovarian serous tumors where it may contribute to carcinoma progression. Elevated expression of ITGB4 is associated with reduced progression-free survival in patients with serous ovarian cancer and represents an important target for future studies.

C30 THE EFFECT OF RED BLOOD CELL TRANSFUSION ON FATIGABILITY IN HOSPITALIZED PATIENTS WITH ANEMIA
Michelle Prochaska, Riilwan Babajide, Sarah Bradbury, Daniel Jesuthasan, David Meltzer. University of Chicago Pritzker School of Medicine, IL
10.1136/jim-2019-midwestern2019.78

Objective Inflammatory breast cancer (IBC) is the most aggressive form of breast cancer and is difficult to diagnose and treat. By studying the physiology and pathology that makes inflammatory breast cancer unique we aim to discover therapeutic targets and diagnostic criterion to improve the outcome for patients. The role of reactive oxygen species (ROS) in cancer has been a growing area of research in recent years. We hypothesized that Inflammatory Breast Cancer cells express ROS in order to modulate cellular biochemical pathways, which in turn is regulated by various aquaporins.

Method Using immunohistochemistry to illustrate the upregulation of ROS we will test both cells and tissue to illustrate levels in IBC compared to normal breast tissue. DCFDA Cellular ROS Assay Kit (ab113851) is used to detect levels of ROS using both immunohistochemistry and flow cytometry. Western blotting is used to identify some possible regulators of ROS utilizing control and IBC cells. Cells: 1) Primary human mammary epithelial cell (HMEC) from Cell Applications (San Diego, CA), 2) Inflammatory breast cancer cells SUM149PT, SUM190PT from Asterand (Detroit, MI).

Results The immunohistochemical staining of normal breast tissue versus inflammatory breast tissue illustrates increased hue saturation density of ROS in inflammatory breast tissue when compared to normal breast tissue. Similar results can be seen while measuring ROS in cells SUM149PT and SUM190PT using flow cytometry. Through western blotting we find that several enzymes that regulate ROS are modulated in IBC to increase ROS: AQP3, SOD1, VDAC, and COX IV.

Conclusion The results suggest that hydrogen peroxide is elevated in patients with inflammatory breast cancer implicating ROS species as a possible therapeutic target. ROS has historically been dismissed as an unwanted byproduct that leads directly to cell death, however, it has become clear that ROS plays a larger role in cellular signaling. ROS generators and scavengers play a balancing role in driving the proliferative state of the cell. ROS is a new possible target for screening different cancers. Additionally, it becomes clear that cellular regulation across membranes is important and may be a direct result of aquaporin regulation in inflammatory breast cancer.

B30 AQUAPORINS AND REACTIVE OXYGEN SPECIES IN INFLAMMATORY BREAST CANCER
Anand Saripalli, Salah D Dajani, Miroslava Repak, Neelam Sharma-Walia. Rosalind Franklin University, IL
10.1136/jim-2019-midwestern2019.77

Objective Inflammatory breast cancer (IBC) is the most aggressive form of breast cancer and is difficult to diagnose and treat. By studying the physiology and pathology that makes inflammatory breast cancer unique we aim to discover therapeutic targets and diagnostic criterion to improve the outcome for patients. The role of reactive oxygen species (ROS) in cancer has been a growing area of research in recent years. We hypothesized that Inflammatory Breast Cancer cells express ROS in order to modulate cellular biochemical pathways, which in turn is regulated by various aquaporins.

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on patients’ fatigue in the context of their activity, a measure known as fatigability, may be a more accurate measure of the benefit of transfusion than fatigue alone. To date there are no data on the effect of transfusion on fatigability. The objective of this study was to determine whether transfusion during hospitalization improves fatigability 30 days post-discharge.

**Method**
From June 2017-January 2018 hospitalized general medicine patients with a hemoglobin (Hb)<10g/dL were approached for an inpatient interview and a phone interview 30-days post-discharge. Fatigability was measured using the Pittsburgh Fatigability Scale (PFS). PFS scores range from 0–50, with higher scores indicating greater fatigability (more fatigue at any activity level). Patients were categorized into four groups based on their inpatient fatigability level (high or low) and Hb (<8 g/dL or ≥8 g/dL). A fatigability change score was calculated by subtracting PFS scores 30-days post-discharge from inpatient PFS scores. Clinical and demographic data were obtained from hospital administrative data. Independent sample t-tests were used to compare changes in fatigability within each of the four groups between patients who received a transfusion and those who did not.

**Results**
140 patients completed both the inpatient and post-discharge interview. There were no baseline differences between those who were transfused and those who were not [age 53 vs. 53; p=0.94], (female 67% vs. 59%; p=0.39), (African-American 74% vs. 69%; p=0.76), (Charlson Comorbidity Index, p=0.59), (median inpatient PFS 32 vs. 32; p=0.97]). For patients with high inpatient fatigability (PFS>32) and a Hb<8 g/dL, transfusion was associated with improvement in fatigability 30 days after hospital discharge, compared to patients not transfused (14.8 vs 2.2, p=0.02). The effect of transfusion was not statistically significant in any other group.

**Conclusion**
Transfusion is associated with improvements in fatigability after hospital discharge for patients with high inpatient fatigability and low Hb. This suggests that for highly fatigued hospitalized patients with anemia, transfusion may both reduce fatigue and increase activity.

### Infectious Disease

**A03**

**BIOFILM PRODUCTION IN CLOSTRIDIODES (CLOSTRIDIUM) DIFFICILE EPIDEMIC STRAIN DH/NAP1/106**

Abdullahi Abdi, Aakash Balaji, Egon A Ozer, Larry K Kociolek, Northwestern University Feinberg School of Medicine, IL

**Objective**
C. difficile infection (CDI) is the most common healthcare-associated infection in the US, causing approximately 500,000 infections and 29,000 deaths in adults annually. CDI recurrence is common, complicating more than 20% of CDIs. Among children with CDI at our children’s hospital, we previously identified restriction endonuclease analysis (REA) group DH as the predominant REA group. Since then, ribotype 106 (which corresponds to REA group DH and NAP11 by PFGE) has been identified as the most common strain causing CDI in US adults. We subsequently performed a comparative genomics analysis to generate hypotheses for why REA group DH has emerged as the most common US strain type. By whole genome sequencing (WGS) of our pediatric CDI isolates, we found that all DH strains (and 13% of our non-DH strains) harbor a gene that shares more than 85% sequence identity with a LPxTG-domain containing collagen-binding surface protein (CBSP) gene found in Enterococcus species; this family of proteins is associated with enterococcal biofilm formation. We hypothesized that presence of this gene in C. difficile is associated with more effective biofilm formation.

**Method**
C. difficile isolates were accessed from our Lurie Children’s Hospital biobank of clinical pediatric CDI isolates that have previously undergone both REA typing and WGS. Using the LPxTG-CBSP gene allele from a DH strain as a reference, we identified C. difficile strains that contain this gene (with at least 85% sequence identity to the C. difficile reference allele) by BLAST analysis. We selected 29 genetically distinct C. difficile strains for biofilm assays: 10 DH strains that contain LPxTG-CBSP gene; 9 non-DH strains that contain the LPxTG-CBSP gene; and 10 non-DH strains that lack the LPxTG-CBSP gene. In vitro analysis of biofilm formation was performed on 24-well polystyrene plates. Overnight cultures in supplemented brain heart infusion broth (BHIS) were transferred into 24-well plates containing fresh BHIS. After 72h of anaerobic growth, supernatants were discarded, plates were washed with PBS, stained with crystal violet, and the stained biofilms were extracted with an acetone-alcohol solution. Absorbance was measured at 595 nm (OD595) to characterize relative biofilm abundance.

**C43**

**NUCLEOLIN’ ROLE IN ANGIogenesis/LYMPHANGIOgenesis IN INFLAMMATory BREAST CANCER (IBC)**

Samantha Russell, Mira Repak, Neelam Sharma-Walia. Rosalind Franklin University, IL

**10.1136/jim-2019-midwestern2019.79**

Inflammatory breast cancer (IBC) is an aggressive form of cancer that is usually identified by red swollen breast tissue due to blocked lymph nodes that affect between 1 and 5 percent of the US population and is generally identified at stage three and four. Based on the aggressive nature of IBC, angiogenic factors play a significant role in the metastasis and tumor growth of inflammatory breast cancer. Our preliminary studies showed that IBC cell lines (SUM149PT and SUM190PT) expressed a higher level of nucleolin as compared to control human mammary epithelial cells (HMECs). Nucleolin is a nucleolar protein involved in cell proliferation and angiogenesis in many cancers. Based on our preliminary results and previous reports on the functionality of nucleolin in aggressive cancers, we hypothesize that nucleolin regulates the expression and secretion of angiogenic factors like vascular endothelial growth factor (VEGF). High levels of pro-angiogenic factors, in turn, drive the progression of the formation of new blood vessels and making tumors accessible to other parts of the body. By using enzyme-linked immunosorbent assay (ELISA), Western blot and immunofluorescence assay, we screened for various angiogenic factors and the possible role nucleolin is playing in the regulation of angiogenesis and lymphangiogenesis. Our studies will help in understanding the molecular pathways and functions of nucleolin in the IBC progression and strive for possible therapeutic targets.
Results Strain-specific biofilm production is illustrated in figure 1. Median (interquartile range [IQR]) OD595 of DH and non-DH strains was 6.5 (5.2–7.6) and 2.5 (1.2–8.1), respectively (p=0.08). However, irrespective of REA group, median (IQR) OD595 of strains with and without the LPxTG-CBSP gene (figure 2) was 6.5 (5.2–9.0) and 1.3 (0.9–1.7), respectively (p≤0.0001).

Conclusion We found that DH strains and non-DH strains that contain the LPxTG-CBSP gene produced significantly greater abundance of biofilm than non-DH strains that lack the LPxTG-CBSP gene. Future work will determine whether differential expression of this gene accounts for the distribution of biofilm production among strain containing the LPxTG-CBSP gene, as well as the impact of gene inhibition on biofilm production. In addition, because biofilm production has been postulated to contribute to risk of CDI recurrence, further work is needed to determine strain-specific biofilm production in vivo, as well as its association with CDI recurrence.

Abstract A03 Figure 1 Strain-specific in vitro biofilm production (strains labeled with their REA group and Sequence Type [ST] per multilocus sequence typing). Striped blue bars represent the 10 DH strains, all of which contain the LPxTG-CBSP gene. Striped white bars represent the 9 non-DH strains that contain the LPxTG-CBSP gene. Non-striped white bars represent the 10 non-DH strains that lack the LPxTG-CBSP gene.

Abstract A03 Figure 2 Relative biofilm production among C. difficile strains with and without the LPxTG-CBSP gene (p<0.0001; Wilcoxon rank-sum)

Objective Antibiotic misuse exerts selective pressure towards resistance among bacteria, which has been classified as a global threat to public health. The emergency department (ED) accounts for a substantial proportion of antibiotic prescribing in the US and high rates of inappropriate prescribing are well documented in this setting. There is a paucity of data on effective ED antibiotic stewardship interventions. Skin and soft tissue infections (SSTI) comprise $\sim$3% of all ED visits and have been identified as an important target for improved antibiotic prescribing. The aim of this project is to identify high impact and potentially intervenable factors that influence antibiotic prescribing decisions for SSTIs in the ED.

Method The qualitative phase of this project involved 20 semi-structured interviews with a diverse group of emergency physicians. The interviews were guided by an established framework, Systems Engineering Initiative for Patient Safety. Interviews were coded using an iterative, deductive process. A thematic content analysis was conducted to identify factors that most consistently influenced antibiotic prescribing. These factors were then mapped to proposed stewardship interventions which were then integrated into clinical SSTI vignettes. The vignettes will be administered to a national sample of...
### Abstract A12 Table 1

<table>
<thead>
<tr>
<th>Modifiable Factor</th>
<th>Illustrative Quote</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic Uncertainty</td>
<td>So you’ve got the textbook, right, redness, warmth, venous, tracking, fluctuate or signs of abscess, fever, systemic illness. So that’s kind of the basic level. And then you’ve got the patient in front of you who didn’t read the textbook and could have any mixture of those symptoms or partial symptoms.</td>
<td>Thermal Imaging (cellulitis)</td>
</tr>
<tr>
<td>Patient Expectations</td>
<td>Patients … say, I had an abscess last time and they gave me antibiotics, or I had a cellulitis last time and they think this is another cellulitis, but it’s clearly like a fire ant or something like that so those are challenging to overcome</td>
<td>MRA PCR (abscess)</td>
</tr>
<tr>
<td>Lack of Access to Care</td>
<td>…especially in the patients I see in the emergency department, a lot of them don’t have good access to care and so I’m going to treat them… patients tell me that they wait a long time for an appointment, several weeks. So having them seen in one to two days isn’t always realistic.</td>
<td>Modified patient satisfaction metrics</td>
</tr>
<tr>
<td>Provider Knowledge</td>
<td>I think that typically the diagnostic certainty is in the diagnosis of a skin and soft tissue infection, I don’t find that I come across that too often when I’m not sure if it’s an infection or not.</td>
<td>EHR-integrated Clinical Decision Support</td>
</tr>
<tr>
<td>Fear of Adverse Outcomes</td>
<td>I think probably the biggest [barrier] is the fear of progression to sepsis, you know, sepsis has significant morbidity and mortality, so the bounce back of a patient who you discharged with significant cellulitis came back septic, and you know, diabetic and dies from septic shock or whatever like that. So you certainly worry about that.</td>
<td>Shared Decision Making</td>
</tr>
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### Abstract A23

**IMPROVING SYPHILIS DIAGNOSIS AND TREATMENT IN AN URBAN POPULATION THROUGH ROUTINE EMERGENCY DEPARTMENT SCREENING**


**Objective** With the recent nationwide increase in syphilis, it is imperative to find novel means of reaching at-risk populations for early diagnosis and treatment. Rates of primary and secondary syphilis in Chicago are more than three times the national average. Many urban communities have both high rates of syphilis and frequently utilize the emergency department (ED) as a primary source of medical care. In late 2018, the University of Chicago Medical Center (UCMC) began the preliminary stages of a quality improvement project directing providers to screen ED patients for syphilis regardless of presenting complaint. The objective of this study is to determine the potential utility of ED screening for syphilis as a means of improving rates of diagnosis and treatment in a vulnerable urban population.

**Method** A retrospective chart review was performed of all patients with positive syphilis antibody testing from October through December of 2018, and all patients with positive rapid plasma reagin (RPR, indicating active infection) or treponema pallidum antibody (TPPA, indicating late infection or infection of unknown duration) testing were included as cases. While some early data has been collected, a provider awareness initiative combined with an update to the electronic medical record system with automated ordering reminders in February 2019 is expected to significantly increase the number of patients screened.

**Results** In the last three months of 2018, a total of 727 patients (average of 242 patients per month) were screened for syphilis in the ED. Of these, 61 (8.4%) tested positive for syphilis, 37 (60.1%) of whom had evidence of active infection, and 24 (39.3%) were late or unknown stage. 40.9% of patients testing positive for syphilis had presented with unrelated complaints (symptoms excluding abdominal pain, rash, or genitourinary symptoms). Two (3%) patients testing positive for syphilis were also newly found to be pregnant and were referred for antibiotic treatment in the first trimester.

**Conclusion** Preliminary data suggests that screening of patients for syphilis in the ED regardless of presenting complaint yields high positive rates. ED screening may represent an effective way of combating the syphilis epidemic, particularly in the most vulnerable populations.

### A24

**COMPARATIVE IN-VITRO STUDY OF SUSCEPTIBILITIES OF ERAVACYCLINE, TIGECYCLINE AND MINOCYCLINE AGAINST MULTI-DRUG RESISTANT ACINETOBACTER BAUMANNII**

Udita Chapagain, Monica Stumpf, Najwa Pervin, Vidya Sundareshan. Southern Illinois University School of Medicine, IL. 10.1136/jim-2019-midwestern2019.83

**Objective** To study in vitro susceptibility profile and Minimum Inhibitory Concentration (MIC) of the available tetracycline antibiotics, namely Eravacycline, Minocycline and Tigecycline against Multi Drug Resistant (MDR) Acinetobacter baumannii (A. baumannii)

**Background** MDR A. baumannii is now becoming a commonly encountered pathogen throughout the hospitals in the United States. A. baumannii has been witnessed as a culprit in a myriad of infectious presentations, ranging from wound infection to life threatening sepsis in the intensive care units. It is a usual perpetrator in the nosocomial setting with MDR infections. In 2015, carbapenem resistance in A. baumannii was reported to be 31% in our hospital (Memorial Medical Center). Many of these strains had no other options for treatment.
Abstracts

IN VITRO ACTIVITY OF ERAVACYCLINE AND OTHER TETRACYCLINES ON EXTENDED SPECTRUM BETA-LACTAMASE PRODUCING CLINICAL ISOLATES OF GRAM NEGATIVE ORGANISM

Monica Stumpf, Udita Chapagain, Vidya Sundareshan. Southern Illinois University School of Medicine, IL

10.1136/jim-2019-midwestern2019.84

Abstract A34 Table 1  Tetracycline group of antibiotics susceptibilities for ESBL producing enterobacteriaceae

<table>
<thead>
<tr>
<th>Isolate</th>
<th>Source</th>
<th>Eravacycline (susceptible)</th>
<th>Tigecycline (susceptible)</th>
<th>Minocycline (susceptible)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.125</td>
<td>0.125</td>
<td>1.5</td>
</tr>
<tr>
<td>1</td>
<td>Blood</td>
<td>0.125</td>
<td>1.0</td>
<td>0.094</td>
</tr>
<tr>
<td>2</td>
<td>Blood</td>
<td>0.094</td>
<td>0.094</td>
<td>0.094</td>
</tr>
<tr>
<td>3</td>
<td>Blood</td>
<td>0.25</td>
<td>0.75</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>Blood</td>
<td>0.125</td>
<td>0.125</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>Blood</td>
<td>0.094</td>
<td>0.094</td>
<td>1.5</td>
</tr>
<tr>
<td>6</td>
<td>Blood</td>
<td>0.25</td>
<td>0.5</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>Blood</td>
<td>0.094</td>
<td>0.094</td>
<td>1.5</td>
</tr>
<tr>
<td>8</td>
<td>Blood</td>
<td>0.25</td>
<td>1.0</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>Blood</td>
<td>0.125</td>
<td>0.25</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>Blood</td>
<td>0.19</td>
<td>0.5</td>
<td>4</td>
</tr>
</tbody>
</table>

Objective  The growing rate of antimicrobial resistance warrants the development and investigation of new antimicrobial agents. Eravacycline is a novel fluoroquinolone belonging to the tetracycline class of antimicrobials. Similar to other tetracyclines, it is a potent 30S ribosomal inhibitor (3). As a fully synthetic drug, it differs from other members of the tetracycline family with modifications at the C-7 (fluorine) and C-9 [pyrrolidinoacetamido] positions. In vitro studies have demonstrated broad-spectrum gram-positive, gram-negative, and anaerobic coverage, including strains with acquired tetracycline efflux pumps and ribosomal protection.

Methods 10 clinical isolates of ESBL producing bacteria were tested against Eravacycline, Minocycline, and Tigecycline. E-tests were used to determine MICs according to CLSI standards. Susceptibility was defined by MIC breakpoints of ≤ 1 ug/ml for eravacycline, ≤ 4 ug/ml for Tigecycline, and ≤ 8 ug/ml for Minocycline.

Results Of the 10 isolates studied, all 10 were susceptible to all three antibiotics based on the standard MIC breakpoints for susceptibility as follows: Eravacycline: ≤1 ug/ml, Tigecycline ≤4 ug/ml, Minocycline ≤ 8ug/ml. The MIC range obtained for the three antibiotics in this study is as follows: Eravacycline: 0.016–2ug/ml, Tigecycline: 0.047–12ug/ml, Minocycline: 0.032–16ug/ml. Eravacycline showed relatively lower MIC than Tigecycline and Minocycline in the MDR A. baumannii. Two isolates out of forty were non-susceptible to all three antibiotics. (5%). One was non-susceptible only to Tigecycline. Even in the non-susceptible isolates, the MIC of Eravacycline was relatively lower for its breakpoint compared to Tigecycline and Minocycline respectively for their breakpoints.

Conclusion Most of the isolates tested were susceptible to all three antibiotics of tetracycline family. The main difference being MIC for Eravacycline, which seemed to be comparatively low for its breakpoint as compared to Minocycline and Tigecycline for their respective breakpoints. Based on this study, Eravacycline seems to be a good option for MDR Acinetobacter to be used presumptively and as an aminoglycoside sparing regimen for complicated infections. The high potency and low side effect profile additionally makes it favorable over other drugs of the tetracycline family.

except aminoglycosides which are associated with serious side effects. With a preference for aminoglycoside sparing antibiotics, the limited choices are Tigecycline, Minocycline and Polymyxins. They are associated with significant adverse effects at the high doses required in patients with severe co-morbidities. Eravacycline is a newly developed synthetic fluoroquinolone antibiotic of the Tetracycline family. It differs from the classical tetracycline in being totally synthetic, having modifications at both the C-7 (fluorine) and C-9 [2-(pyrrolidin-1-yl) ethanamido] positions of the tetracyclic core and being minimally affected by tetracycline specific efflux and ribosome protection and inactivation. It is effective for the treatment of complicated intra-abdominal and complicated urinary tract infections. It has shown its activity against the following spectrum of microbes: Carbapenem resistant and multidrug resistant enterobacteriaceae, Carbapenem resistant and MDR A. baumannii, Extended Spectrum Beta Lactamase (ESBL) Producing Enterobacteriaceae, Vancomycin resistant Enterococcus, Methicillin Resistant Staphylococcus aureus (MRSA), Streptococci and Anaerobes. Furthermore, its simpler pharmacokinetics, safety profile and higher serum levels attainable as compared to other drugs of tetracycline family makes it a promising alternative against MDR A. baumannii.

Methods 40 preserved isolates of Multidrug resistant Acinetobacter baumannii at our research laboratory were tested against Eravacycline, Tigecycline and Minocycline and their MIC was determined by E test according to the laid CLSI standards. The results are shown below.

Results Out of the 40 isolates studied, 37 were susceptible to all three drugs tested based on the standard MIC breakpoints for susceptibility as follows: Eravacycline: ≤1 ug/ml, Tigecycline ≤4 ug/ml, Minocycline ≤ 8ug/ml. The MIC range obtained for the three antibiotics in this study is as follows: Eravacycline: 0.016–2ug/ml, Tigecycline: 0.047–12ug/ml, Minocycline: 0.032–16ug/ml. Eravacycline showed relatively lower MIC than Tigecycline and Minocycline in the MDR A. baumannii. Two isolates out of forty were non-susceptible to all three antibiotics. (5%). One was non-susceptible only to Tigecycline. Even in the non-susceptible isolates, the MIC of Eravacycline was relatively low for its breakpoint compared to Tigecycline and Minocycline respectively for their breakpoints.

Conclusion Most of the isolates tested were susceptible to all three antibiotics of tetracycline family. The main difference being MIC for Eravacycline, which seemed to be comparatively lower for its breakpoint as compared to Minocycline and Tigecycline for their respective breakpoints. Based on this study, Eravacycline seems to be a good option for MDR Acinetobacter to be used presumptively and as an aminoglycoside sparing regimen for complicated infections. The high potency and low side effect profile additionally makes it favorable over other drugs of the tetracycline family.
Abstracts

to a future preference of Eravacycline and other members of the tetracycline class of antibiotics in the management multi-drug-resistant infections where appropriate based on its tissue concentration but bacteriostatic activity Further studies on this newer antibiotic are being conducted but this local data information is encouraging.

REFERENCES

PROGNOSTIC VALUE OF INFLAMMATORY MARKERS DURING TREATMENT OF PROSTHETIC JOINT INFECTION

Mohamad A Kalot, Upasna Manchanda, Wissam El Atrouini, Albert Eid. University of Kansas Medical Center, MO

Objectives The role of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in predicting the outcome of prosthetic joint infections (PJI), treated with a 2-stage exchange, has been inconclusive. We evaluated the utility of ESR and CRP and their improvement during treatment in predicting cure at the time of the second stage surgery in adults with PJI treated with a 2-stage approach.

Method We conducted a case-control study of adult patients seen at the University of Kansas Medical Center with PJI for a period of 10 years, treated with a 2-stage exchange. Cases had documented treatment failure defined as (1) one positive culture growing the same original organism; (2) two positive cultures growing a different organism; (3) one positive culture growing a new organism with histopathology showing acute inflammation (>5 WBC/high power field) or (4) gross purulence at re-implantation. Controls were patients who did not meet criteria for treatment failure. Serial ESR and CRP were recorded for patients with treatment success (Group A), and those with treatment failure (Group B).

Results A total of 71 patients were enrolled. The mean age was 55 years; 52% were male. Among our patients, 22.5% were smokers, 28% had diabetes mellitus, 10% were immunosuppressed, and 32% had other co-morbidities (peripheral vascular disease, rheumatoid arthritis, liver disease). The mean time between implant and infection was 1922 days. The indication for treatment failure was osteoarthritis in 64% and post-traumatic causes in 21%. The most common organism isolated was Staphylococcus aureus(34%), followed by coagulase-negative Staphylococcus (30%). Five out of 71 patients (7%) failed treatment. There was no difference in the mean ESR value before treatment between patients in both groups. However, the mean ESR value after treatment was significantly different between the 2 groups (18.9 in Group A and 30.0 in Group B) with a p-value of 0.05. The mean drop in ESR in Group A was 65.5 ± 36.1, compared to 55.2 ± 11.9 in Group B. The percentage drop in ESR in group A was 77%, and was 69% in group B. On the other hand, the percentage mean drop in CRP were the same in both groups (87%). No other predictors of treatment failure were identified.

Conclusion ESR values after treatment might predict treatment failure in patients with PJL.

CHRONIC ACTIVE EBSTEIN-BARR VIRUS-INDUCED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Sirip Dejhanathan, Attaya Suzanamankha. Division of Hematology and Oncology, Department of Internal Medicine, Indiana University School of Medicine, Indianapolis, Indiana

10.1136/jim-2019-midwestern2019.86

Introduction Epstein-Barr virus (EBV) is a ubiquitous herpes virus that estimated to infect over 90% of the world’s population. Primary infections are usually asymptomatic and self-limited. EBV persists in the body in latent state lifelong. Chronic active EBV (CAEBV) infection is a rare condition caused by persistent EBV infection or reactivation of latent EBV leading to severe progressive lymphoproliferative disorders in patients without recognized immunodeficiency. CAEBV infection presentations vary from mononucleosis to life-threatening conditions such as hemophagocytosis, multi-organ failure, disseminated intravascular coagulation, and malignant lymphomas. CAEBV infection diagnosis is based on clinical suspicion of chronic illnesses not attributable to other diseases and abnormal laboratory testing including an unusual pattern of EBV antibodies and/or detection of the EBV genome in affected tissues or peripheral blood. CAEBV was reported more commonly in Asians and among children.

We highlight the diagnosis and treatment dilemma in an adult patient with CAEBV infection who presented with mononucleosis and hepatosplenomegaly who had transient clinical improvement after splenectomy, followed by a fatal course of hemophagocytic lymphohistiocytosis (HLH), multi-organ failure and EBV related lymphoproliferative disorder of the lungs.

Case presentation A 48-year-old Caucasian female presented with persistent fever, progressive jaundice, and shortness of breath for 3 months. Physical examination was significant for fever, jaundice, and hepatosplenomegaly. Laboratory tests were significant for pancytopenia, hyperbilirubinemia, and elevated alkaline phosphatase. The patient underwent splenectomy for diagnostic and therapeutic purposes. Histology of the spleen tissue showed areas of infarction, congestion, and prominent hemophagocytosis. Peripheral blood EBV PCR was 31,000 copies/mL, EBV capsid IgG was 6.8 (positive), EBV nuclear antigen IgG was 7.2 (positive), and EBV IgM was negative. EBV-encoded early small ribonucleic acid (EBER) in situ hybridization performed on a spleen sample demonstrated focal positivity. The patient was therefore diagnosed with CAEBV infection. She had a dramatic clinical improvement within 48 hours after splenectomy with a complete resolution of fever and normalization of blood counts and was discharged to home 5 days after surgery. Within two weeks after discharge, she represented with fever, cytopenia, lung infiltrates, and liver failure. Bone marrow biopsy showed marked hemophagocytosis. Serum lactate dehydrogenase ≤ 6 mg/dL, fibrinogen of 103 mg/dL, ferritin of 1,400 mg/dL, triglyceride of 330 mg/dL, and soluble IL-2 receptor of 25,000. She was diagnosed with HLH and was started on cyclosporine, dexamethasone, and etoposide combination. Repeated EBV PCR titre
showed a further increase in viral copies from 31,000 copies/mL at last admission to 325,000 copies/mL.

Lung biopsy showed clonal B-cells with flow cytometric positivity for CD5, CD19, and surface kappa light chain with lack of CD 20 expression, compatible with EBV related lymphoproliferative disorder. She died 5 days after the start of chemotherapy.

Discussion Adult-onset CAEBV infection is extremely rare and carries a very poor prognosis. Our case covers CAEBV infection manifestations from the initial mononucleosis to HLH and EBV related lymphoma. The diagnosis requires high clinical suspicion and multidisciplinary diagnostic approaches. Treatment options include immunosuppressive agents and systemic chemotherapy. Antivirals have limited efficacy. Best long term outcome was seen with allogeneic transplantation. There is no standard of care in CAEBV infection. Treatment choices need to be individualized based on the severity of the disease, comorbidities, and response. Early diagnosis and treatment are critical for treatment success.

Nephrology

A25 INCREASED HOMOCYSTEINEMIA AND URINE BETAINE EXCRETION IN PATIENTS WITH EARLY AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD)
Hajar Alreefi, Ivan Vuckovic, Song Zhang, Slobodan Macura, Fouad Chebib, Peter Harris, Alfonso Erin, Lilach O Lerman, Vicente Torres, Maria V Irazabal. Mayo Clinic, MN
10.1136/jim-2019-midwestern2019.87

Background Cardiovascular abnormalities are important complications in Autosomal Dominant Polycystic Kidney Disease (ADPKD), and contribute to renal disease progression. Homocysteine (Hcy) mediated endothelial dysfunction (ED) develops early on, preceding hypertension (HTN) and renal function decline, but the underlying mechanisms remain unknown. We hypothesized that abnormalities in Hcy metabolism are responsible for the increased levels, leading to Hcy-induced ED in young normotensive patients with ADPKD.

Methods Plasma and urine Hcy and related metabolites were measured by LC/MS/MS and 1HNMR, and folic acid, vitamin B12, and ADMA by ELISA, in early (18–30 years, eGFR>90 mL/min/1.73m²) normotensive (<130/90 mmHg without medication) patients with ADPKD, and matched controls (n=10 each). Total kidney volume (TKV) and renal blood flow (RBF) were measured by MRI.

Results Blood pressure levels were higher in patients with ADPKD (Mean arterial pressure = 83 vs 93 mmHg p=0.03) compared to controls, and height adjusted TKV was twofold higher (176 vs 366 ml/m p<0.001). Yet, eGFR and RBF were similar between groups (105 vs 111 ml/min/1.73 m² p=0.411 and 977 vs 954 cc/min/1.73 m² p=0.788 respectively). Circulating levels of Hcy and urine excretion of betaine were higher in ADPKD (both p<0.001), as were plasma levels of ADMA (p=0.026). On the other hand, plasma and urine levels of cystathionine (reduced when the transsulfuration pathway is inhibited) and methionine (reduced when the folate dependent pathway is inhibited) were similar between patients with ADPKD and controls (p=0.373 and p=0.172 and p=0.726 and p=0.184 respectively). Plasma folate and vitamin B12 concentrations were also similar (p=0.566 and 0.425 respectively).

In patients with ADPKD, plasma Hcy correlated directly with urine betaine ($R^2=0.456, p=0.032$) and inversely with plasma betaine ($R^2=0.799$ and $p<0.01$). There was a direct correlation between plasma Hcy, and urine betaine with hTKV ($R^2=0.562, p=0.012$ and $R^2=0.444, p=0.035$), but not with eGFR ($R^2=0.105, p=0.361$ and $R^2=0.051, p=0.529$).

Conclusion Early ADPKD presents with elevation in Hcy, likely related to abnormalities in betaine-dependent remethylation associated with increased betaine excretion. These findings provide novel insights into Hcy mediated ED in ADPKD and suggest candidate markers that may be useful to assess vascular and renal disease severity early on.

Abstracts

A36 BETaine INSUFFICIENCY And REDuced betaine DEPENDent REMETHYLIATion ARE ASsOCIATED With HYPERHOMOCYSTEINEIA AND VASCULAR ABNORMALITIES IN EARLY POLYCYSTIC KIDNEY DISEASE
Ali Tug, Ivan Vuckovic, Alexis Adrian, Slobodan Macura, Fouad Chebib, Peter Harris, Alfonso Erin, Lilach O Lerman, Vicente Torres, Maria V Irazabal. Mayo Clinic, MN
10.1136/jim-2019-midwestern2019.88

Background Polycystic kidney disease (PKD) is a group of monogenic disorders that result in renal cyst development and multiple extra renal manifestations, including the heart and vasculature. Vascular abnormalities are the most important non-cystic complication and present even with preserved renal function. However, the underlying mechanisms remain to be fully elucidated. In PKD, elevated plasma levels of the cardiovascular risk factor homocysteine (Hcy) precede renal function decline, but whether abnormalities in Hcy metabolism are responsible for the early increased levels is not clear. We hypothesized that PKD presents with early abnormalities in Hcy metabolism leading to Hcy-induced endothelial dysfunction from early stages of the disease.

Methods We investigated the Hcy metabolic pathway (transsulfuration/remethylation figure 1) in young (4-week-old) PCK and Sprague-Dawley (SD) control rats (n=12 each). Kidneys were harvested, frozen in liquid nitrogen, or preserved in formalin for metabolomics and ex-vivo studies. Twenty-four-hour urine and terminal blood samples were collected for metabolite analysis and chemistries. Plasma folic acid, vitamin B12, and Hcy were determined by ELISA. Hcy pathway metabolites (betaine, dimethylglycine) were determined by 1HNMR. Endothelial Nitric Oxide synthase (eNOS) was assessed by double immunofluorescence staining for CD31/eNOS and capillary index by H&E staining.

Results Serum creatinine and BUN remained unchanged, yet kidney weight/body weight ratio were increased in PCK. eNOS immunoreactivity was lower in PCK vs SD and so was the capillary index. Plasma Hcy and urine excretion of methyl donor betaine were elevated in PCK, and Hcy positively correlated with urine betaine. Plasma betaine was similar between the groups, but its tissue concentration was lower in PCK, which may lead to betaine insufficiency, impaired betaine dependent remethylation, and hyperhomocysteinemia. Contrariwise, tissue glutathione concentration was higher in PCK vs SD, and plasma folate and vitamin B12 were similar, arguing against a defect in the transsulfuration or folate-dependent remethylation pathways.
Conclusion In PKD, early elevation in Hcy is likely related to betaine insufficiency, whereas impaired betaine-dependent remethylation may be responsible for the early elevation of Hcy. Early elevation in Hcy may be important contributors to eNOS down-regulation (consistent with endothelial dysfunction) and decreased capillary density. Our data suggests these may not only be early vascular disease markers, but also play an important pathogenic role in vascular complications associated with PKD, and contribute to renal disease progression.

**Abstract B26**

**CAN VOLUME CALCULATIONS OF EN BLOCK RENAL TRANSPLANTS PREDICT RENAL FUNCTION?**

Martha G Menchacha, Keira Tulla, Manpreet Samra, Ivo Tzvetanov, Suman Setty. University of Illinois, IL

10.1136/jim-2019-midwestern2019.89

Objective Renal transplantation is the mainstay of therapies for relief from end-stage renal disease. In the current milieu,
Abstracts

B32 GREATER PLAINS COLLABORATIVE (GPC): BURDEN OF IMAGING RENAL CYSTS

1Mohamad A Kalot, 1Neda M Husainat, 1Mohammed Al Khatib, 1Kathleen Wilkinson, 2Luna Noureddine, 3Lindsay Cowell, 4Philipp Dahm, 1Reem Mustafa. 1Mohamad A Kalot, 1Nedaa M Husainat, 1Mohammed Al Khatib, 2Kathleen Wilkinson, 3University of Kansas Medical Center, KS; 2University of Texas Southwestern Medical Center, TX; 4University of Iowa, IA; 5University of Minnesota Medical Center, MN

10.1136/jim-2019-midwestern2019.90

MCTRM—GPC Renal Cyst Abstract

Title: Assessing patients’ beliefs and attitudes about renal cysts: A Survey

Introduction Renal cysts are a common incidental finding on cross-sectional radiographic imaging. While most cysts are indolent, individuals with such cysts are frequently monitored for interval growth and potential malignant transformation, which is ultimately rare. To date, no United States based professional society or other organization provides evidence based guidelines to guide the follow-up of patients with incidental cysts. This lack of guidance creates a potential for major variability in

with an acute shortage of organs, the use of pediatric en bloc kidneys has opened up a new possible source of organs. We studied en bloc renal allografts performed at our institution over the last 8 years to perform serial renal volume calculations over the length of the graft, and correlated these measurements with biopsy findings.

Method We studied 27 patients who underwent en block renal transplants at our institution. Renal ultrasounds were obtained at the time of transplant and serial studies were performed. Measurements of renal volume of both kidneys were aggregated and graphed. Renal biopsies performed post-transplant were quantitated for chronic changes in the tubules and interstitium on a scale of 0–3 (interstitial fibrosis and tubular atrophy). The additive IFTA score was compared to the renal volumes.

Results 51 ultrasound studies of renal allografts from 27 patients performed from time 0 to 74 months after transplant were studied. Renal volumes were calculated and trends were studied. Renal volumes increased with time after transplant and peak volumes of 530 cm cubed were observed. Reduction in renal volume was observed at later time points beginning as early as 23 months after transplantation. 20 serial renal biopsies from 6 of these patients were studied (average 3.3 biopsies per patient and performed up to 70 months after transplant) were scored for IFTA and the additive score was plotted against time after transplant (Figure 1). The plots represent statistically integrated data to best represent the trends in renal growth over time and IFTA scores. Increases in IFTA scores (in biopsies) were observed at later time points which correlated well with reduced renal volumes (determined by ultrasound).

Conclusion Renal en bloc allografts develop after transplantation and lead to improved renal function. Chronic damage to the graft from tubular atrophy and interstitial fibrosis (IFTA), caused by the usual suspects-infection, rejection and immunosuppressive drug toxicity, is reflected in reduced renal volume.

Figure legend for figure 1. Serial renal volumes (blue dots) are presented over the life of the en bloc grafts and interstitial fibrosis tubular atrophy (IFTA; pink dots) scores of 5 patients are also presented.

Abstract B32 Table 1 Characteristics of patients with renal cysts

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cysts positive</th>
<th>N=138*</th>
</tr>
</thead>
<tbody>
<tr>
<td>How many renal cysts have you had?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4</td>
<td>2.9</td>
</tr>
<tr>
<td>1-4</td>
<td>90</td>
<td>65.2</td>
</tr>
<tr>
<td>&gt;4</td>
<td>8</td>
<td>5.8</td>
</tr>
<tr>
<td>Unsure</td>
<td>34</td>
<td>24.6</td>
</tr>
<tr>
<td>What is the approximate size of your renal cysts?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 cm</td>
<td>42</td>
<td>30.4</td>
</tr>
<tr>
<td>&gt;3 cm</td>
<td>11</td>
<td>8.0</td>
</tr>
<tr>
<td>Unsure</td>
<td>48</td>
<td>34.8</td>
</tr>
<tr>
<td>Do you have a specific treatment of follow-up plan for your renal cyst?</td>
<td>Yes</td>
<td>40</td>
</tr>
<tr>
<td>No</td>
<td>96</td>
<td>69.6</td>
</tr>
<tr>
<td>No renal cyst</td>
<td>2</td>
<td>1.4</td>
</tr>
<tr>
<td>If you receive specific treatment (N=43), what treatment have you been offered?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repeated imaging</td>
<td>32</td>
<td>23.2</td>
</tr>
<tr>
<td>Surgery</td>
<td>9</td>
<td>6.5</td>
</tr>
<tr>
<td>Would you worry more about the renal cyst(s) if there was not follow-up (N=43)?</td>
<td>Yes</td>
<td>36</td>
</tr>
<tr>
<td>No</td>
<td>96</td>
<td>69.6</td>
</tr>
<tr>
<td>No renal cyst</td>
<td>2</td>
<td>1.4</td>
</tr>
<tr>
<td>Are you satisfied with the management plan (or lack of a management plan) for your renal cyst(s)?</td>
<td>Satisfied</td>
<td>87</td>
</tr>
<tr>
<td>Undecided</td>
<td>2</td>
<td>1.4</td>
</tr>
<tr>
<td>Do you have important questions to ask a doctor about renal cysts?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>35</td>
<td>25.4</td>
</tr>
<tr>
<td>No</td>
<td>96</td>
<td>69.6</td>
</tr>
<tr>
<td>No renal cyst</td>
<td>2</td>
<td>1.4</td>
</tr>
<tr>
<td>Do you agree or disagree with this statement: I feel fully informed about renal cysts and the risk of progression.</td>
<td>Yes</td>
<td>40</td>
</tr>
<tr>
<td>No</td>
<td>48</td>
<td>34.8</td>
</tr>
<tr>
<td>No renal cyst</td>
<td>3</td>
<td>2.2</td>
</tr>
<tr>
<td>In your opinion, what is the risk of progression to cancer for a renal cyst?</td>
<td>High risk</td>
<td>45</td>
</tr>
<tr>
<td>Low risk</td>
<td>47</td>
<td>34.1</td>
</tr>
<tr>
<td>Undecided</td>
<td>43</td>
<td>31.2</td>
</tr>
<tr>
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practice leading to unnecessary testing, patient anxiety, radiation exposure and waste of precious health care resources. We aim to assess patients’ values and preferences (beliefs and attitudes) about renal cysts.

**Methods** We deployed a cross-sectional survey to a random sample of patients who have the diagnosis of renal cysts. This study utilized the Greater Plain Collaborative (GPC) de-identified dataset. GPC is PCORI funded network of 12 leading medical centers in 8 states committed to a shared vision of improving healthcare delivery through ongoing learning, adoption of evidence-based practices, and active research dissemination. This study is a collaborative effort between the University of Kansas Medical Center (KUMC), the University of Texas Southwestern Medical Center (UTSW), University of Minnesota Medical Center, and the University of Iowa (UI). We developed and pilot tested the survey with. We collected data about the demographics, the insurance status, family history and overall health, and characteristics of patients with renal cysts. We performed a binary regression analysis (adjusted for age, gender, family history of cancer and kidney disease, and treatment plan for renal cysts) to determine anxiety predictors in patients with renal cysts. Patients with renal cysts were identified by billing code and self-identification, and the measure of agreement kappa was computed.

**Results** In this paper we present the results of 301 respondents who had agreement on both billing code and self-identification (moderate measure of agreement kappa = 0.52): 138 with renal cysts, and 163 without renal cysts. The mean age was 61 (range 30–82) years. Sixty two percent of the respondent are women and the majority are employed (45%) or retired (32%). Regarding the insurance status, 97% reported having a health insurance, out of which 93% having insurance covering imaging services. While a majority (72%) reported no family history of kidney disease, 5% reported having a family member on dialysis, and 1% had a family history of transplant. The results of the characteristics of patients with renal cysts are described in table 1. In an adjusted regression analysis, patients with a clear treatment plan tend to have no anxiety (OR=0.49, 95% CI [0.22 – 1.11]) and patients with family history of renal disease tend to have anxiety with OR= 1.94, 95% CI [0.76 – 4.94]. Whereas family history of cancer did not predict anxiety with OR=0.54, 95% CI [0.24 – 1.19].

**Conclusion** There is wide variability in patient values regarding renal cysts and their follow-up. While one third of participants with renal cysts expressed concerns about the risk of progression to cancer, others were not worried at all. It appears that patients values was considered when discussing treatment plans for renal cysts. However, less than half feel informed about their renal cysts and the risk of progression. Patients who have a clear plan tend to have no anxiety about their cyst. Guidance on this topic is needed and could help physicians and patients with shared decision making regarding renal cyst management.

**Objective** Cardiotoxic steroids are Na/K-ATPase alpha-1 (NKA α-1) ligands that are increased in volume expanded states such as chronic kidney disease (CKD). We have shown that NKA α-1- Src signaling pathway is essential mediator of cardiotoxic steroid induced inflammation in renal epithelial and immune cells in vitro. As inflammation and oxidative stress play a central role in the onset and progression of renal injury associated with CKD, we performed 5/6th partial nephrectomy (PNx) to induce CKD and study the role of the NKA α-1 and Src kinase in mediating renal inflammation and oxidative stress in vivo. We sought to examine the role of NKA α-1-Src kinase signaling complex in mediating PNx induced renal inflammation and oxidative stress in vivo.

**Methods/Results** First, to examine the role of the NKA α-1 in mediating PNx induced renal inflammation and oxidative stress, age matched male wild type and NKA α-1 mice (25–27 g) were subjected to either 5/6th partial nephrectomy (PNx) or sham surgery. Six weeks post PNx surgery, kidneys of mice were sectioned and stained for 8-Oxo-2-deoxyguanosine (8-OHdG). We found that while PNx induced oxidative stress in the wild type kidneys, kidneys from NKA α-1 mice demonstrated significantly lower levels of DNA oxidation. Similarly, twenty-four hour urine collected from the NKA α-1 mice showed significantly lower excretion levels of 8-OHdG compared to urine collected from wild type controls. Additionally, histological examination demonstrated that NKA α-1 mice had significantly lower inflammation levels represented by less interstitial immune cell accumulation, glomerular hypercellularity, and glomerular immune cell infiltration compared to kidneys from wild type mice. We also found that kidneys from NKA α-1 mice showed less protein cast formation compared to the kidneys from wild type mice. Then, we examined recruitment of CD68 positive immune cells within the kidney. Kidneys from NKA α-1 mice showed less macrophage infiltration compared to kidneys from the wild type controls. In order to examine involvement of Src Kinase signaling role, wild type mice were further divided into two subgroups after the surgery: one group received a specific NKA α-1-Src kinase complex inhibitor, pNaKtide (25 mg/kg i.p.), every other week for a total of 3 injections, and the second group, which serve as the control group, received similar volume of saline. We found that while PNx induced expression of key inflammatory genes (TNF-α, Timp-1, MCP-1, Kim-1 and TGF-β) in renal tissue collected from wild type mice, this effect was significantly attenuated by inhibition of the NKA α-1-Src signaling pathway via pNaKtide.

**Conclusion** These findings suggest that the NKA α-1-Src kinase complex plays central role in regulating the renal inflammatory response in the setting of CKD.

### Abstracts

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*Note: Unless specified otherwise in the question.*
INTRODUCTION

Lactic acidosis is a relatively common clinical presentation in hospitalized patient. It has been well documented in the literatures that Linezolid use, especially in prolonged course, is associated with Type B lactic acidosis. Discontinuation of linezolid is the common treatment, however, in this case, it was not enough.

CASE DESCRIPTION

We present a 50 year old Asian male with past medical history of bilateral above knee amputation after a motor vehicle accident, Wernicke’s Encephalopathy, Congestive heart failure, and a recent scrotal cellulitis taking Linezolid for the past month, who presented after being found altered and hypoglycemic at his nursing facility. Patient was fully alert and oriented and afebrile on arrival to the ED but hypotensive. Pertinent physical exam findings include scrotal edema and erythema with ulcerations, improving from previous admission; as well as a tender abdomen to palpation. His scrotal cellulitis was being treated with linezolid through IV infusion for the past month. Laboratory findings revealed elevated lactate level of 19.36 on admission, pancytopenia, and positive urine culture for Multidrug Resistant Pseudomonas. Patient was fluid resuscitated with 30 ml/kg of normal saline and treated per sepsis guidelines, as well as three doses of rally pack. Thiamine was also given throughout the hospital course, because of his alcohol abuse history. He was diagnosed with Type B lactic acidosis secondary to prolonged linezolid use. After discontinuation of linezolid, his lactic acidosis temporarily improved for 3 days, but eventually trended back to admission level. Rally pack was restarted for 2 days with augmentation of oral B complex- C- folic acid (Nephrocaps) and his lactic acidosis trended down to normal level.

DISCUSSION

Type B lactic acidosis is suspected when systemic impairment in oxygenation could not be identified and it can be caused by variety of conditions including drug induced mitochondrial dysfunction. Linezolid is an oxazolidinone antibiotic that targets bacterial protein synthesis by inhibiting a subunit of bacterial ribosomes, which may also affect human mitochondrial ribosomes and protein synthesis, leading to lactic acidosis.

Mechanism of lactic acidosis in this patient could be dual folds: mitochondrial toxicity and vitamin deficiency. Mammalian mitochondria have similar DNA and RNA as Prokaryotes. Evidence suggests Linezolid binds to the domain V of bacterial 23S rRNA which is equivalent to the 16S mammalian mitochondrial subunit. Some literature postulated that linezolid could potentially bind to the 16S subunit. Others suggest linezolid results in decreased activity of the mitochondrial respiratory complex IV. Both hypotheses are based on the assumption that bacteria and human mitochondria are structurally similar. Regardless of the mechanism, mitochondrial toxicity was observed at concentrations similar to the minimal inhibitory concentration.

Although niacin deficiency induced lactic acidosis was never reported in the literature, we hypothesize that niacin deficiency played a role in this patient's lactic acidosis. Niacin serves as a coenzyme involved with many types of oxidation reactions where alcohols are converted to ketones or aldehydes. Since patient was abusing alcohol, niacin deficiency is likely. Niacin is a cofactor in NADP production and is vital for electron transport chain (ETC) function, since it is involved in the first enzyme complex of the ETC. Dysfunction of ETC leads to a state of anaerobic metabolism and lactic acid accumulation. Thus, it is possible that both alcohol induced niacin deficiency and linezolid toxicity caused this patient’s lactic acidosis.

Thiamine deficiency is described in many literatures to cause pyruvate accumulation, which is metabolized to lactate, resulting lactic acidosis. However, we do not think this is one of the causes of lactic acidosis in our patient, since he was...
given thiamine throughout the hospital course. Rally pack, which includes several other vitamins such as niacin, was only given on admission and his lactic acidosis seemed to improve initially. However, when the rally pack was stopped the acidosis worsened. Rally pack was restarted and lactic acid level improved again. Such pattern suggests certain vitamins other than thiamine were deficient and proves the therapeutic effect of rally pack in this case.

Neurology/Neurodegeneration

**A06** IN VIVO STABLE ISOTOPE LABELING & QUANTITATIVE MASS SPECTROMETRY IMAGING OF Aß PLAQUE DEPOSITION AND NEURONAL METABOLISM IN HUMAN AD BRAIN


Background Alzheimer’s disease (AD) is a neurodegenerative disorder with clinical manifestations of progressive memory decline and is the most common form of age-related dementia. AD is characterized by the extracellular deposition of amyloid-beta leading to amyloid plaques. Despite recent advances in our understanding of AD there is a critical gap in our knowledge of ‘What is the turnover of plaques at different stages of AD?’ and ‘is hypo-metabolism seen by [18F]FDG-PET due to neuronal hypometabolism?’ We provide the first, direct measurements of AD in a cross-sectional cohort of age-matched non-dementia and AD dementia individuals.

Methods Our approach utilizes in vivo incorporation universally labeled 15N-Spirulina (i.e., SILK) into Aß plaque and neurons human AD and non-AD participants via oral labeling. Participant cohorts enrolled in this study are very mild-to-mild AD dementia (CDR0.5–1), moderate-to-severe AD dementia (CDR2–3), and age-matched controls with pathology (CDR0+) and without pathology (CDR0). Cognitive assessment includes the Montreal Cognitive Assessment (MoCA), AD8, and retrospective CDR, followed by National Institute on Aging- Alzheimer’s Association (NIA-AA) pathological workup upon death. Autopsied brain regions are prepared using established SEM protocols and isotopically imaged by nanoscale secondary ion mass spectrometry (NanoSIMS) in a combined approach we term SILK-SIMS.

Results 1) Tracer incorporation is detectable up to 100 days after oral labeling. 2) Incorporation of tracer into plaques increases with increasing disease severity (cognition) and pathological burden. 3) Neurons become hyper-metabolic with increasing disease severity (cognition) and pathological burden. 4) Plaques in participants with AD pathology, but no cognitive impairment incorporate the same [low] levels of 15N tracer as brain parenchyma in a participant with no AD pathology and no cognitive impairment.

Conclusions Our SILK-SIMS studies will provide invaluable information on plaque dynamics and neuronal health with and without tau aggregation in the normal and diseased brain. These studies will offer many new avenues for investigation into pathological mechanisms of the disease, with implications for therapeutics development.

**A14** VELIPARIB PROTECTS AGAINST NEURODEGENERATION AND PHOSPHOLIPASE A2-MEDIATED NEUROINFLAMMATION IN BINGE ALCOHOL-EXPOSED ADULT RATS

1Dimitrios E Kouzoukas, 1Jennifer A Schreiber, 1Nuzhath F Tajuddin, 1Simon Kaja, 2Hee-Yong Kim, 1Michael A Collins. 1Loyola University Chicago, IL; 2National Institute of Alcoholism and Alcohol Abuse, MD 10.1136/jim-2019-midwestern2019.94

Objective Chronic binge drinking can cause brain damage that impairs memory and cognition. Alcohol binges in adult rats also produce neuronal damage in memory-linked regions, notably, in the hippocampus (HC) and lateral entorhinal cortex (LEnt). Alcohol binges also alter levels of poly (ADP-ribose) polymerase-1 (PARP-1), Ca2+-dependent phospholipase A2 (cPLA2) and Ca2+-independent PLA2 (iPLA2). PARP, a DNA repair protein, paradoxically triggers neuronal necrosis when excessively activated, while cPLA2 and iPLA2 respectively liberate pro-inflammatory w-6 arachidonic acid and pro-survival w-3 docosahexaenoic acid. Similarly, rat HC-Ent slice cultures exposed to alcohol binges incur corresponding changes in PARP-1, cPLA2 and iPLA2. PARP inhibitors suppressed cPLA2 elevations, while exerting neuroprotection. Here we examined whether the brain-penetrable PARP inhibitor, veliparib, provided in vivo neuroprotection and...
suppression of PLA2-mediated neuroinflammation in a recognized adult rat model of binge alcohol-induced neurodamage.

**Method** Adult male rats received Ensure diet containing alcohol (ethanol, 7.1 ± 0.3 g/kg/day), or isocaloric dextrose with or without veliparib, a PARP inhibitor (25 mg/kg/day) by gavage 3x daily for 4 days. Rats were sacrificed on the morning after the final binge treatments. Neurodegeneration in HC and LEnt was assessed in fixed sections using Fluoro-Jade B. Levels of cPLA2 and iPLA2 in HC were quantified by immunoblotting.

**Results** Like many studies using this model, binge alcohol produced neurodegeneration in the dentate gyrus (DG) of the ventral HC (VHC) and in LEnt. Veliparib co-treatment significantly reduced neurodegeneration in the dentate gyrus by 79% and in the LEnt by 66%. In the VHC, binge alcohol significantly increased cPLA2, which veliparib co-treatment completely prevented. Consistent with earlier reports, alcohol binges significantly depleted iPLA2 in HC; however, the depletion was only partially reversed by veliparib. No alcohol-induced changes in cPLA2 or iPLA2 were observed in the dorsal HC (DHC) consistent with the lack of neurodegeneration.

**Conclusion** These pharmacological results provide emerging support for binge alcohol-induced PARP activation in vivo playing a crucial role in the ensuing neurodegeneration and cPLA2 and iPLA2-related neuroinflammation.
EVALUATING THE EFFECT OF TUMOR NECROSIS ON GLYCOLYTIC FLUX AND CELL SURVIVAL IN GLIOBLASTOMA
Evan Noch, Isaiah Yim, Lewis Cantley. Weill Cornell Medicine, NY
10.1136/jim-2019-midwestern2019.95

Objective Glioblastoma continues to rank as one of the most lethal primary human tumors. The degree of necrosis in glioblastoma remains one of the most powerful predictors of poor prognosis, but the relationship between necrosis and poor prognosis is not known. It is unclear whether endogenous tumor necrosis is merely an indicator of an aggressive phenotype or whether tumor necrosis itself propagates the aggressive phenotype. Determining the role of necrosis in mediating the malignant potential of glioblastoma therefore represents an important aspect of therapy.

Methods We describe a model of patient-derived glioblastoma spheroids expressing a genetically encoded fluorescent NADH/NAD+ biosensor. This biosensor reports glycolytic flux and can be imaged with fluorescent microscopy. We imaged spheroids using multiphoton microscopy and differentiated cells by high versus low NADH/NAD+ levels to determine gene expression changes in NADH/NAD+high versus NADH/NAD+low cells. We also created an intracranial glioblastoma patient-derived xenograft model to determine the gene expression changes that facilitate tumor cell survival within the peri-necrotic niche.

Results FACS analysis of dissociated spheroids followed by RT-PCR analysis demonstrated increased expression of genes known to be upregulated in peri-necrotic regions, including procollagen-lysine,2-oxoglutarate 5-dioxygenase 2 (PLOD2), activating transcription factor 5 (ATF5), and protein O-fucosyltransferase 2 (POFUT2). These cells also had increased expression of hypoxia-responsive genes, including vascular endothelial growth factor (VEGF) and junonji domain-containing protein 6 (JMJD6). When imaging these tumors in vivo, we demonstrated that cells with high NADH/NAD+ levels are more likely to survive within the peri-necrotic environment. These findings indicate that increased glycolytic flux and associated gene expression changes facilitate survival from expanding regions of necrosis.

Conclusion This model to study cell survival within the peri-necrotic region will improve awareness of necrosis-mediated growth proliferation and may lead to treatments targeted to tumor necrosis that could improve patient prognosis. Future experiments will focus on biopsy of cellular populations with high versus low NADH/NAD+ levels within the peri-necrotic niche. We will then perform RNAseq and metabolomics analysis to determine the specific genetic and metabolic adaptations that facilitate survival within this bioactive microenvironment.

THE ROLE OF RMTG-MEDIATED COCAINE AVERSION IN ADDICTION
Maya Eid*, Dominika Pullmann, Hao Li, Thomas Jhou. 1Department of Neuroscience, College of Graduate Studies, Charleston, SC; 2MUSC, College of Medicine, Charleston, SC; 3Graduate students, Department of Neuroscience, College of Graduate Studies, Charleston, SC; 4Department of Neuroscience, Charleston, SC
10.1136/jim-2019-midwestern2019.97

Over 90% of Americans have had some exposure to drugs of abuse, but only 15–32% of individuals exposed to the major classes of abused drugs go on to become addicted, with the rest presumably being able to stop on their own. Much basic research has been directed at understanding individual animals who have already progressed into addiction-like behaviors, with relatively less study of what protective factors may help prevent acquisition of drug use in the first place.

Although cocaine’s aversive responses are relatively less widely acknowledged than its rewarding effects, they are experimentally robust. Particularly elegant experiments by Ettenberg and his group have shown that single doses of cocaine produce an initial rewarding phase followed by an aversive crash about 15 later that is sufficient to condition a net aversion to cocaine, that in most (but not all) animals, is strong enough to overcome cocaine’s rewarding effects. In our lab, we investigated behavioral responses to cocaine in rats performing a runway operant task that is particularly suited for assessing the combined rewarding and aversive properties of cocaine. In this task rats traverse a 3-foot long corridor to obtain a single daily dose of cocaine. After 4–7 trials, we found large variations in animals responses to cocaine, where some animals slowed down dramatically (high avoiders) and others remained fast (low avoiders). We found that the
aversive effects of cocaine were and much better predictors of cocaine seeking, than the rewarding effects, where cocaine aversion was protective of drug acquisition on self-administration, but is also highly predictive of reinstatement.

In recent years, our lab and others have demonstrated that cocaine avoidance depends critically on the rostromedial tegmental nucleus (RMTg) and its afferents. The RMTg is a major GABAergic midbrain input to midbrain dopamine (DA) neurons that plays major roles in avoidance. We have thus shown that there are individual differences in RMTg neurons firing rate that correlate with cocaine-conditioned avoidance behavior. Indeed, compared to low cocaine avoiders, high avoider animals have similar RMTg inhibition during the rewarding phase of the drug (5’ post injection), but have significantly higher RMTg firing rates during its aversive phase (15’ post-infusion). To investigate the molecular driver of these differences in the RMTg, we used in vitro electrophysiology and demonstrated that low avoiders have less RMTg firing due to aberrant functioning of the GluR1 subunit of the AMPA receptor. Indeed, when we inhibited this subunit pharmacologically, all animals become low avoiders on the runway task, whereas when we activate this subunit, most animals become high avoiders.

**A35**

**OBESITY INDUCES MESENCHYMAL STEM CELL SENESCENCE AND DYSFUNCTION**

Sabena M Conley, LaTonya J Hickson, Hui Tang, Kyra L Jordan, Abdelrhman M Almoawad, Soo Jin Kim, Xiang-Yang Zhu, Tamar Tchkonia, James L Kirkland, Lilach O Lerman, Mayo Clinic, MN

10.1136/jim-2019-midwestern2019.98

**Objective** Chronic inflammatory conditions like obesity may negatively impact the biological properties and cellular functions underlying the regenerative potential of mesenchymal stem cells (MSC). One of the mechanisms by which obesity can impair MSC function is by inducing cellular senescence, a...
growth-arrest program that also transitions cells to a proinflammatory state. However, the effect of obesity on cellular senescence and the reparative potential of MSC in human patients remain unclear. We tested the hypothesis that obesity induces cellular senescence and decreases functionality in MSC of severely obese patients.

Method
Adipose tissue-derived MSC were harvested from abdominal subcutaneous fat samples collected from morbidly obese (n=20, body mass index (BMI) ≥35 kg/m² with weight-associated comorbidities or ≥40 kg/m²) and age-matched non-obese (n=10, BMI ≤30 kg/m²) patients during bariatric or kidney donation surgeries, respectively. Migration and proliferation assays were used to assess function of MSC at passage 3. Cellular senescence was evaluated by expression of cell cycle arrest (p16 and p21) and senescent-associated secretory phenotype (SASP) (MCP-1, IL-1α, and PAI-1) markers (quantitative PCR), and β-galactosidase (β-gal) activity (flow cytometry).

Results
Among all patients, mean age was 58±8 years and 71% were females. MSC from morbidly obese patients (n=12) exhibited a trend (p=0.08) for lower proliferative capacities than non-obese-MSC (n=5) (figure 1A), suggesting decreased function in obese-MSC, whereas their migration function remained unchanged. Senescence burden manifested in β-gal activity (figure 1B), p16 and p21, as well as SASP marker expression (figure 1C), was significantly elevated in morbidly obese patients MSC.

Conclusion
These findings indicate that severe human obesity induces cellular senescence and proliferative dysfunction in adipose tissue-derived MSC. Thus, obesity-induced cellular injury may limit the efficacy of MSC endogenous cellular repair, and hamper the feasibility of autologous transplantation in obese patients.

Pathophysiology

**C28 ACROANGIODERMATITIS OF MALI IN THE SETTING OF SICKLE CELL DISEASE**
Balaji Jothishankar, Haider Bangash, Farah Abdulla. University of Chicago, IL


**Introduction** Acroangiodermatitis of Mali (AAoM) is a rare benign vasoproliferative disorder that is commonly associated with chronic venous insufficiency and stasis. The clinical appearance varies widely between red-to-plum colored macules, papules, nodules or plaques on the lower extremities, which may become ulcerated. Herein, we discuss a case of AAoM in the setting of sickle cell disease (SCD).

**Case description** A 50-year-old African-American man presented with a two year history of bilateral lower extremity swelling, which progressed to discoloration and painful ulcerations. His past medical history was significant for end stage renal disease requiring hemodialysis, SCD, congestive heart failure, venous stasis, and gout. He was a former smoker, consumed 2–3 alcoholic beverages per week, and denied IV drug use.

Physical exam of the dorsum of the bilateral feet and malleoli showed well defined red to plum colored papules and nodules coalescing into purple plaques with irregularly shaped shallow ulcerations and stellate atrophic ivory colored patches. Extensive changes of atrophie blanche were seen on both feet, with a blue-green crusting around the edges of the lesion (figure 1).

Biopsy of these lesions showed lobular collections of small-dilated vessels in the papillary dermis and larger dilated vessels in the papillary dermis and larger dilated vessels in the papillary dermis and larger dilated vessels in the papillary dermis and larger dilated vessels in the papillary dermis and larger dilated vessels in the papillary dermis and larger dilated vessels in the papillary dermis and larger dilated vessels in the papillary dermis. The clinical manifestations of Acroangiodematitis of Mali. A. Dorsum of the left foot showing a purple plaque with irregularly shaped ulcerations. B. Another view of the left foot showing purple blue papules, irregularly shaped ulcerations and more extensive changes of atrophie blanche. C. A view of the right medial malleolus demonstrating irregularly shaped ulcerations.

Histopathology of Acroangiodematitis of Mali. A. Lobular proliferation of small-dilated vessels in the papillary dermis and larger dilated venules in the reticular dermis. B. Rounded vessels composed of endothelial cells without atypia and surrounding fibrosis. C. Immunohistochemical staining with human herpes virus-8 showing no highlighting of vessels.
venules in the reticular dermis. High magnification shows the rounded vessels were composed of plump endothelial cells without atypia with surrounding mild to moderate fibrosis (figure 2). Immunohistochemical staining with human herpes virus-8 did not highlight the vessels while staining with CD34 highlighted the endothelial cells of the hyperplastic vessels.

Our patient was treated with limb elevation, wound care, and topical steroids but not compression stockings due to pain associated with applying the garments.

**Discussion**

AAoM is a rare vasoproliferative disorder associated with chronic venous insufficiency and stasis. It is referred to as pseudo-Kaposi’s sarcoma because of its clinical and histopathological similarities to Kaposi’s sarcoma. Although the exact pathogenesis is unknown, it is thought to be related to chronic edema, increased hydrostatic pressure, and tissue hypoxia, resulting in an increase in vascular endothelial growth factor (VEGF) induced neovascularization.

The mainstay of therapy for AAoM is compression stockings and limb elevation. A handful of case reports have shown other modalities to help, including topical corticosteroids to suppress neangiogenesis and oral antibiotics to treat occult infections. Surgical treatments such as selective embolization, ligation, and even amputation have also been suggested if there are underlying AV malformations.

Venous insufficiency is common in patients with SCD, which can lead to the tissue hypoxia thought to contribute to AAoM. Therefore, patients who have SCD may be at a higher risk for developing AAoM than the normal population. With no published cases on AAoM and SCD, this case illustrates the potential association between the two.

**REFERENCES**


**Pediatics**

**THE DIGITAL CHICAGO ASTHMA PLAN(DCAPE) FOR EVERYONE: MULTI-DISCIPLINARY COLLABORATION TO CREATE AN INTERACTIVE WEB-BASED ASTHMA ACTION PLAN**

Andrea A Pappalardo, Houshang Darabi, Tom MacAvish, Molly A Martin. University of Illinois at Chicago, IL; Illinois Institute of Technology Institute of Design, IL

Objective Paper asthma action plans have conflicting data to support their effectiveness in managing pediatric asthma. Clinical decision support (CDS) tools may be helpful in chronic disease management. Integrating an asthma action plan as a CDS may help improve distribution, but requires collaborative planning involving medical providers, designers, and programmers to make CDS tools more effective and sustainable in real-world settings.

Method A paper emergency department (ED) discharge tool developed through a multi-center pediatric asthma trial was effective in improving ED adherence to asthma guidelines. At the request of stakeholders, investigators converted this tool...
Abstracts

Pulmonary/Critical Care

A07 SEPSIS DRIVES DAMAGE ASSOCIATED MOLECULAR PATTERN EXPRESSION IN HUMAN BRAIN

1Benjamin H Singer, 2Angela C Bustamante, 3Kristopher Opron, 4Paul Crane, 5C Dirk Keene, Washington, WA 1University of Michigan Medical School, MI 2University of Chicago, IL 3University of Washington, WA 10.1136/jim-2019-midwestern2019.101

Objective Critical illness, especially sepsis, causes both acute and long-term brain dysfunction. Long lasting neuroinflammation has been observed in animal models of sepsis survivorship, but the correspondence between these animal models and the changes experienced by the human brain in sepsis is poorly understood. While a few studies have examined the neuropathology of patients with sepsis, there are no unbiased analyses examining the effect of sepsis on gene expression in the human brain. We hypothesize that sepsis will result in a distinct, pro-inflammatory transcriptomic profile in the human brain.

Method We performed transcriptomic analysis of human parietal cortex tissue from patients who died of sepsis or clear infection. Design students tested the system for a quicker snapshot of health information in the event of an emergency. Design students tested the system’s security and user friendliness. This updated version was then evaluated by three caregivers and 22 CHWs and utilized for one week. The final version includes seven components (see figure 1) comprising of clinical and demographic data and patient and app-related goal settings.

Conclusion We created a mobile system for an asthma management plan that aims to improve communication between caregivers, patients, and providers. This platform requires further study to determine if it can achieve meaningful changes in asthma management. Partnerships between computer scientists, design specialists, and the medical team offer a novel approach to the creation of useful clinical decision support tools.

A08 SINGLE CELL METABOLISM REVEALS THAT A RHODIUM-MEDIATED GLYCOLYTIC BURST DRIVES ENDOTHELIAL CELL CONTRACTIONS

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Objective Human endothelial cells (EC) are highly glycolytic and do not generate significant ATP from oxidative phosphorylation, despite being highly oxygenated (Warburg effect). EC glycolysis is thought to play a role in angiogenesis but its role in acute inflammation is unclear. From a clinical standpoint, systemic inflammation (e.g., septic shock) manifests with features of hyperglycolysis such as hyperglycemia and hyperlactatemia which are clearly correlated with poor outcomes. One key feature of septic shock is EC activation, which can manifest as exuberant cell contractions and lead to organ edema and inflammatory cell infiltration, yet how EC activation relates to hyperglycolysis is unclear. We hypothesize that activated ECs perform actin reorganization, enhancing glycolysis and further powering cell contractions.

Method An electrical cell impedance (ECIS) assay was used to assess the effect of glycolytic inhibition on EC contraction. A fluorescence resonance energy transfer (FRET) probe was used to a digital platform. The resulting digital CHICAGO Asthma Plan for Everyone (dCAPE) was created using user-experience design principles through collaboration with system engineers, design experts, providers, caregivers, and community health workers (CHWs).

Results CHWs and asthma specialists from a large care coordination program funded by the Centers for Medicare and Medicaid collaborated with the UIC Department of Engineering’s system engineers and the Illinois Institute of Technology Institute of Design to create a virtual dCAPE application. This was reviewed by clinicians and CHWs and modifications were made. Students programmed the dCAPE for Android devices by applying principles of system engineering. A comprehensive backend subsystem was employed to allow for full data capture and analysis of how users engage with a system. A CHW dashboard was created for patient monitoring and decision making. Then five caregivers of children with asthma and 12 asthma CHWs reviewed the dCAPE system and provided feedback. Using user-experience design principles, the system was modified to include a goal-directed dashboard and to allow for a quicker snapshot of health information in the event of an emergency. Design students tested the system’s security and user friendliness. This updated version was then evaluated by three caregivers and 22 CHWs and utilized for one week. The final version includes seven components (see figure 1) comprising of clinical and demographic data and patient and app-related goal settings.

Conclusion This unbiased analysis reveals the predominance of markers of tissue damage and inflammation in the brain response to sepsis. DAMP-driven pathways drive persistent neuroinflammation in animal models of sepsis survival. Ongoing neuropathologic analysis includes cell-type specific epigenomics and multiplex immunostaining to further elucidate the source of pro- and anti-inflammatory signals in the brains of patients with sepsis. In addition, we continue mechanistic studies of the role of pathways identified in this analysis in sepsis survivor mice.

This work was supported by the National Institutes of Health: T32HL00774921 (to ACB), R01HL123515 (to TJS), K08HS10154 and UL1TR002240 (to BHS), and U01 AG06781

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Conclusion We created a mobile system for an asthma management plan that aims to improve communication between caregivers, patients, and providers. This platform requires further study to determine if it can achieve meaningful changes in asthma management. Partnerships between computer scientists, design specialists, and the medical team offer a novel approach to the creation of useful clinical decision support tools.

Objective Critical illness, especially sepsis, causes both acute and long-term brain dysfunction. Long lasting neuroinflammation has been observed in animal models of sepsis survivorship, but the correspondence between these animal models and the changes experienced by the human brain in sepsis is poorly understood. While a few studies have examined the neuropathology of patients with sepsis, there are no unbiased analyses examining the effect of sepsis on gene expression in the human brain. We hypothesize that sepsis will result in a distinct, pro-inflammatory transcriptomic profile in the human brain.

Method We performed transcriptomic analysis of human parietal cortex tissue from patients who died of sepsis or clear infection. Data were analyzed using iPathways, comparing sepsis cases to controls. Immunohistochemistry was performed on fixed tissue examining several genes identified through the transcriptomic analysis.

Results 176 genes were differentially expressed (adjusted p<0.05) in sepsis cases compared to controls. Overall, immune and inflammation-related genes were up-regulated in the brains of patients with sepsis. Differentially expressed genes included sets of genes associated with neurotoxic astrocyte activation (CXCL1, HSPB1, GBP2, SerpinA3), complement genes and damage associated molecular patterns (DAMPs S100A8, S100A9, S100A10, HSP70 family, and vascular injury (CHI3L1, CHI3L2). SOCS3, a marker of alternative macrophage activation, is also differentially expressed. Immunohistochemistry confirms that astrocytes are a source of $100A8 and complement factors within the human brain, and that CHI3L2 is expressed in both glia and endothelial cells. p.p1 {margin: 0.0px 0.0px 0.0px 0.0px; font: 12.0px Helvetica} Conclusion This unbiased analysis reveals the predominance of markers of tissue damage and inflammation in the brain response to sepsis. DAMP-driven pathways drive persistent neuroinflammation in animal models of sepsis survival.

Ongoing neuropathologic analysis includes cell-type specific epigenomics and multiplex immunostaining to further elucidate the source of pro- and anti-inflammatory signals in the brains of patients with sepsis. In addition, we continue mechanistic studies of the role of pathways identified in this analysis in sepsis survivor mice.

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to assess lactate production, or glycolysis, at the single cell level, in conjunction with live cell microscopy. A digitonin-based cell membrane permeabilization assay, together with Western blotting, was used to determine the amount of specific proteins in the cytoplasm, unbound from the cytoskeleton. Glycolytic and mitochondrial functions were assessed by bioenergetics measurements (Seahorse).

**Results** Using an in vitro model of EC activation with lysophosphatidic acid (LPA), we first show that inhibition of the glycolytic cascade with 2-deoxyglucose prevents EC contractions, as measured by ECIS. To assess if LPA stimulates lactate production through glycolysis, we chose to use a novel FRET probe, Laconic, which is specific for detecting intracellular lactate concentration through 5 orders of magnitude, and can be imaged at high temporal rates and allows for simultaneous assessment of cell morphology. By imaging Laconic, we confirmed a glycolytic burst by visualizing a rapid rise in lactate during EC stimulation with LPA. Since the homolog gene family, member A/Rho-associated protein kinase-1 (Rhoa/ROCK-1) is downstream of LPA, we next inhibited ROCK-1 with Y-27632 in the presence of LPA and found that the glycolytic burst was suppressed, as were cell contractions. Furthermore, we found that LPA stimulation increases the cytosolic concentration of aldolase A (ALDOA), a glycolytic enzyme, and was reduced with Y-27632. ALDOA is known to bind to the actin cytoskeleton, which is thought to significantly diminish its catalytic activity. That actin reorganization affects cytosolic ALDOA concentration was further confirmed with actin reorganization inhibitors such as cytochalasin, jasplakinolide, and blebbistatin during LPA stimulation. We next showed that the presence of cytosolic ALDOA was sufficient to increase endothelial glycolysis in an ALDOA overexpression system in a Seahorse bioenergetics assay. Finally, inhibition of myosin II by itself lowers glycolysis, suggesting that basal actin reorganization activity contributes to a significant fraction of ATP consumption in ECs.

**Conclusion** Together these results suggest Rhoa/ROCK-1-dependent actin reorganization releases actin-bound ALDOA into the cytoplasm, leading to increased glycolysis, powering EC contractions. This furthermore suggests that glycolysis can be spatially compartmentalized, much like oxidative phosphorylation takes place in mitochondria, and regulated on demand. Thus, hyperglycemia may prime ECs to contract during systemic inflammation, and the Warburg effect may be necessary for ECs to perform actin reorganization.

**Objective** Patients who experience unplanned readmission to the intensive care unit (ICU) have increased hospital lengths of stay, costs, and mortality compared to patients discharged from the ICU but not readmitted. We have previously shown that a machine learning approach to predicting ICU readmission is more accurate than existing risk scores. However, whether a machine learning model is more accurate than clinician intuition for predicting ICU readmission is unknown. Therefore, we aimed to compare the accuracy of clinician intuition to our recently validated machine learning algorithm.

**Method** We conducted a prospective study in the medical ICU of an academic hospital from October 2015 to September 2017. Clinicians (nurses, residents, fellows, attending physicians) were voluntarily surveyed once per day after rounds about the likelihood of ICU readmission for patients being discharged on a 1–10 scale. Survey data was linked with electronic health records to determine readmission outcomes, and only surveys collected within 36 hours of ICU discharge were included. The machine learning model was run on clinical data available at the time of ICU discharge to predict the probability of a future ICU readmission during the same hospitalization. Areas under the receiver operating characteristic curves (AUCs) were calculated and compared between the median clinician intuition score, the machine learning algorithm, and a combined model for predicting ICU readmission.

**Results** A total of 2832 surveys from 937 unique ICU discharges were included, of which 114 patients (12%) were readmitted to the ICU during the hospitalization. The median clinician score was 4 (IQR 2–4). The combined model had the highest AUC for predicting those patients ever readmitted (AUC 0.79 [95% CI 0.74–0.83]), followed by the machine learning model (AUC 0.78 [95% CI 0.74–0.83]), and median clinician intuition (AUC 0.71 [95% CI 0.66–0.75]) (figure 1). Both the combined model and the machine-learning model were more accurate than clinician intuition alone (p<0.01 for both comparisons). AUC results were similar for predicting readmission within 48 hours.

**Conclusion** A machine learning model was more accurate than clinician intuition for predicting ICU readmission. Our results demonstrate that a machine learning model using real-time patient data would provide clinicians with additional information to guide decision-making regarding the timing of ICU discharge. Further research is needed to determine if the use of our machine learning model to target interventions for high risk patients would help improve outcomes for patients transferred out of the ICU.
Abstracts

A11  NON-MUSCLE MYOSIN LIGHT CHAIN KINASE ACTIVITY MEDIATES ENDOTHELIAL CELL PROLIFERATION AND INHIBITS APOPTOSIS IN PULMONARY ARTERIAL HYPERTENSION

Mariam Anis, Rachel Halstrom, Noman Baig, Jeffrey R Jacobson, Dustin R Fraidenberg. University of Illinois at Chicago, Department of Medicine, Chicago, IL, USA. IL

Objective Pulmonary artery endothelial cell (PAEC) hyperproliferation and inhibition of apoptosis occur in response to hypoxia and contribute to the pathology of pulmonary arterial hypertension (PAH). Separately, PAEC proliferation induced by vascular endothelial growth factor (VEGF) is also associated with increased promoter activity and protein expression of non-muscle myosin light chain kinase (nmMLCK), a component of the EC cytoskeleton. Basal activation of Raf family members ERK1/2 and p38 MAPK in human pulmonary artery ECs regulate downstream genes driving proliferation and migration. To further explore signaling pathways relevant to these phenotypic traits, evidence was sought for potential interactions between nmMLCK and ERK. We hypothesize that nmMLCK activity is crucial for PAEC hyperproliferation contributing to the development and progression of PAH.

Methods Human PAEC proliferation was induced with either VEGF (100 ng/ml) treatment or incubation in hypoxic conditions (1% O2) for 72 hours and compared to either VEGF (100 ng/ml) treatment or incubation in control conditions. ML-7 (Tocris), a selective inhibitor of MLCK, was used to evaluate the effects of MLCK activity on VEGF and hypoxia-induced EC proliferation as well as the extracellular signal regulated kinase (ERK) signaling pathway. Cell lysates were used for Western blotting for total and phosphorylated ERK as well as phospho-myosin light chain (p-MLC), a substrate of MLCK, and proliferating cell nuclear antigen (PCNA), a marker of cellular proliferation.

Results VEGF and hypoxic stimulation in PAEC were both associated with increased MLC phosphorylation, consistent with increased MLCK activity. Treatment with the MLCK inhibitor, ML-7 (10 uM), in hypoxic conditions and after VEGF stimulation was associated with a relative decrease in MLC phosphorylation by 64% (p<0.05) and 72.3% (p<0.05) respectively compared to control. ML-7 also resulted in decreased proliferation at baseline as well as after VEGF treatment with decreased cell counts and reduction in the expression of PCNA by 84% and 30.8% (p<0.05) respectively. VEGF and hypoxia-stimulated PAEC are also found to have increased ERK phosphorylation which was blocked by the inhibition of MLCK with ML-7.

Conclusions Our work highlights the importance of MLCK activity in proliferation of PAEC. In both models of hyperproliferation induced by either VEGF or hypoxia, MLCK inhibition was associated with decreased proliferation and inhibition of the ERK signaling pathway. Non-muscle MLCK in PAEC may be an important contributor to endothelial dysfunction recognized in the pathobiology of PAH and may represent a unique future therapeutic target.

A17  NOVEL PHARMACOLOGICAL APPROACH TO TREAT 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 results in multisystem organ failure 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 a knockout of microtubule End Binding (EB) protein 3 in endothelial cells or inhibition of EB3 function by a 7-mer allosteric EB Inhibitory (EBIN) peptide significantly attenuated the effects of cytokine storm on lung microvasculature by reducing edema and lung injury in the experimental model of endotoxemia. Here, we employed rational drug design by nuclear magnetic resonance (NMR) to optimize physicochemical and biochemical properties of EBIN for future clinical studies.

Method EBIN analogs were designed using standard methods for backbone rigidification and non-proteinogenic amino acids. The binding affinity of EBIN analogs was assessed using Saturation Transfer Difference (STD) by NMR approach. The binding interfaces of the compounds to target protein were mapped by heteronuclear single quantum correlation (HSQC) NMR. Furthermore, efficacy of selected compounds was tested in endothelial monolayers and in mice challenged with protease-activated receptor 1 (PAR-1) agonist.

Results We have designed and tested sixty-one compounds, twenty-six of which demonstrate an affinity for EB3 at least two-times greater than EBIN. Furthermore, HSQC-NMR experiments with eleven selected analogs further identified the interactions with the C-terminus of EB3 that are remarkably similar to EBIN. Based on the cell-penetrating properties of these compounds, we advanced six of them for further potency studies using cell-based systems. As compared to EBIN, all six compounds were more potent in inhibiting calcium release from the endoplasmic reticulum (ER) stores in primary human lung microvascular endothelial cells (HLMVECs). Based on in vitro stability in human blood plasma, we selected one lead and two backup compounds. All three compounds showed inhibition of endothelial capillary leakage in mice challenged with IV administration of PAR-1 agonist peptide.

Conclusion Our studies establish a workflow for rational drug design to allosterically modulate EB3 function. Novel drug-like compounds are more stable and potent, showing benefits in treating lung endothelial microvascular hyperpermeability. These results suggest clinical potency of novel compounds in treating vascular leakage and pulmonary edema associated with ARDS.
Objective Influenza A virus (IAV) is a highly contagious respiratory virus that infects up to 40% of the pediatric population each year. Infections can range in severity from mild upper respiratory symptoms to life-threatening lower respiratory tract disease. Healthy children are much more likely to die from IAV infection than are healthy adults. We previously demonstrated that viral clearance does not predict severity of illness in juvenile mice infected with IAV. Instead, excess recruitment to the lungs of macrophages with a distinct inflammatory phenotype and increased activation of the NLRP3 inflammasome is associated with increased lung injury and death in IAV-infected juvenile mice. Therefore, we sought to investigate how the microenvironment of the juvenile lung influences the phenotype of recruited macrophages in IAV infection, and how this may predispose juvenile mice to IAV-induced lung injury.

Method Type II alveolar epithelial cells (AT2s) and bone marrow-derived macrophages (BMDMs) were isolated from juvenile (4 week-old) and adult (10–12 week old) mice. Alveolar epithelial cells from juvenile or adult mice were infected with IAV (A/WSN/33) at a multiplicity of infection (MOI) of 5 for 2 hours. Twenty-four hours post-infection, AT2 supernatant was collected and placed under ultraviolet (UV) light to inactivate the virus. Differentiated BMDMs from juvenile or adult mice were exposed to IAV-infected AT2 supernatant for 24 hours. Cytokine levels in the supernatant were assessed by ELISA and transcription factor activation in the cell lysate was assessed by Western Blot. Cell death was measured using an LDH assay and viral titer was measured using plaque assay.

Results Viral titer and cell death were similar in juvenile and adult BMDMs exposed to juvenile IAV-infected AT2 supernatant and those exposed to adult IAV-infected AT2 supernatant. In contrast to previous reports, viral clearance did not predict severity of illness in IAV-infected juvenile mice infected with IAV. Instead, excess recruitment to the lungs of macrophages with a distinct inflammatory phenotype and increased activation of the NLRP3 inflammasome is associated with increased lung injury and death in IAV-infected juvenile mice. Therefore, we sought to investigate how the microenvironment of the juvenile lung influences the phenotype of recruited macrophages in IAV infection, and how this may predispose juvenile mice to IAV-induced lung injury.

Conclusion In spite of an equal susceptibility to IAV infection, juvenile AT2s have an increased inflammatory response to IAV than adult AT2s. In addition, BMDMs exposed to juvenile IAV-infected AT2 supernatant acquire a more inflammatory phenotype and have increased activation of the NLRP3 inflammasome than BMDMs exposed to adult IAV-infected AT2 supernatant. Our data suggest that the microenvironment of the juvenile lung, driven by juvenile AT2s, may promote excess inflammation in recruited macrophages and exacerbate lung injury in IAV infection.
statistical significance, the ‘hyperthermic, slow resolvers’ had twice the in-hospital mortality rate of ‘hyperthermic, fast resolvers’ (30% vs. 15%). The ‘hyperthermic, slow resolvers’ had the highest levels of the inflammatory cytokines IFN-γ, IL-2, and IL-6, with a positive association between both IL-6 and IL-15 levels on regression (p<0.05). The ‘hyperthermic’ group had the lowest levels of all cytokines measured among the four groups. The ‘hyperthermic, fast resolvers’ had the highest levels of several type 2 cytokines (IL-5, IL-9, IL-13, IL-25, and IL-33). Similarly, 10/32 patients in this group had a documented comorbid type 2 disease (allergic rhinitis, asthma, food allergy, or atop dermatitis), while only 2/30 of the ‘hyperthermic slow resolvers,’ 2/25 normothermic, and 0/14 hypothermic patients had a type 2 comorbidity.

Conclusion We draw two conclusions from these data: first, bacteremic patients have inflammatory cytokine profiles that are reflected in their temperature trajectories: ‘hyperthermic, slow resolvers’ have elevated levels of pro-inflammatory cytokines (and the highest mortality), while ‘hyperthermic’ patients have the lowest inflammatory cytokine levels. Thus, temperature trajectories may be a non-invasive surrogate for inflammatory response and a predictor of outcomes. Second, patients with the best outcomes (‘hyperthermic, fast resolvers’) had the highest levels of type 2 cytokines, and had a high likelihood of having type 2-mediated allergic comorbid diseases; thus, activation of the type 2 immune response may protect these patients from mortality and should be explored for its diagnostic and therapeutic potential to improve care of septic patients.

A27 DEFICIENCY OF AUTOPHAGY REGULATORY PROTEIN, ATG16L1, INCREASE AIRWAY EPITHELIAL SECRETORY MUCINS MUC5AC AND MUC5B

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Rationale Autophagy is a homeostatic process that leads to degradation of long-lived proteins and recycling of amino acids during periods of nutrient deprivation, cell stress, infection, and inflammation. Autophagy is regulated by a series of proteins that orchestrate the maturing autophagosome and subsequent membrane fusion events with lysosomes and endosomes. It is now recognized that these autophagy regulatory proteins (ATG) may be re-purposed for other protein processing functions. Airway mucin proteins are the primary components of mucus and are essential for host defense. However, hypersecretion of mucus during inflammation mediated mucous cell metaplasia can lead to loss of lung function, and increased cough and sputum production in human airway disease. We have previously shown that Th2 type inflammation increases airway epithelial cells in vivo and in vitro respectively. Here, we hypothesized that the autophagy regulatory protein, Atg16L1, is required for airway mucin granule cytoplasmic transport in the airway epithelium.

Methods We used wild type (WT) C57BL/6 mice or mice globally deficient in Atg16L1 mice; Atg16L1hm/hm (hypomorph) and assessed mucin accumulation during Th2 type airway inflammation. Activated secretion was assessed in mice treated with nebulized ATP (100 mM). Epithelial mucin stores were assessed by lung homogenate using western blotting or by airway epithelial immunostaining using lectin UEA-1 for Muc5ac or mouse anti-Muc5b. Mucin expression in lung homogenates was assessed by qPCR. Tracheobronchial epithelial cells were derived from mice (mTEC) and differentiated under air liquid interface (ALI) conditions.

Results Atg16L1hm/hm mice challenged with intranasal IL-33 had increased airway epithelial Muc5ac and Muc5b intracellular levels by airway immunostaining and by western blot of lung homogenates compared to IL-33-challenged WT mice. A similar increase in airway Muc5ac and Muc5b levels was found in Atg16L1hm/hm mice after OVA sensitization and airway challenge. This accumulation of airway mucins was not due to defects in stimulated secretion, as both the Atg16L1hm/hm and WT mice had a reduction 60% reduction in intracellular mucus stores following nebulized ATP. There was a toward increased Muc5ac expression by qPCR in Atg16L1hm/hm mice after both IL-33 or OVA challenge suggesting enhanced mucin production. Finally, isolated airway mTEC had increased airway mucin levels under ALI conditions suggesting that loss of epithelial Atg16L1 leads to accumulation of airway mucins.

Conclusion ATG16L1, is an autophagy protein that regulate formation of the mature autophagosome via LC3 lipidation. Loss of Atg16L1 leads to enhanced mucous cell metaplasia during Th2 type airway inflammation. Our findings provide additional support that autophagy proteins, such as Atg16L1, are broadly used for mucin regulatory pathways, and may have alternative targets other than autophagosome membranes. Thus, Atg16L1 represents an attractive target in airway diseases, such as asthma and COPD, that are associated with increased production and secretion of Muc5ac.
Methods Rat lung microvascular ECs (RLMVECs) were used for biochemical and cell biological assays. HEK293T cells stably overexpressing Ano-1 were generated and used for binding assays with the proteins from mitochondrial inner membrane. Mitochondria-enriched fraction and cytosolic (Cyto) fraction containing other cellular organelles were obtained by centrifugation from RLMVECs. Cyto fraction was further separated by high-speed centrifugation into the soluble fraction (Sol) and the insoluble particulate fraction (Part). Cyto fraction was then used to study the translocation of mitochondrial marker proteins.

Results We first confirmed a specificity of commercially available antibody raised against the peptide corresponding to the sequence of 2nd intracellular loop of Ano-1 using the lysates from RLMVECs with or without Ano1-siRNA and HEK293T cells overexpressing Ano-1. Using this Ano1-specific antibody, subcellular localization of Ano1 was determined by co-immunostaining of Ano1 and a mitochondria-localized protein, the translocase of the outer mitochondrial membrane 20 (TOM20) in RLMVECs. We also confirmed mitochondrial localization of Ano1 by live cell imaging of HEK293T cells expressing GFP-tagged Ano1. The data from these systems showed that Ano1 is localized in both plasma membrane and mitochondria. Furthermore, biochemical assays using protein fractionation from RLMVECs showed Ano1 protein expression in the Mito fraction as well as the Part fraction obtained from the Cyto fraction. Moreover, we found by immunoprecipitation of Ano1 from HEK293T cell stably overexpressing Ano1 that Ano1 interacts with a mitochondrial fusion protein OPA1 which possess a trans-membrane domain at inner mitochondrial membrane (IMM).

Conclusion These results indicate the existence of Ano1 protein in the mitochondria, especially at the IMM, in addition to the plasma membrane. Since OPA1 is the critical regulator for the maintenance of mitochondrial cristae formation and mitochondrial bioenergetics, increased Ano1 and OPA1 interactions may be partly involved in the molecular mechanism underlying the hyperproliferative phenotype of pulmonary artery ECs under PAH.

B02 FTY720 S-PHOSPHONATE SIGNIFICANTLY INHIBITS MRSA INDUCED PERMEABILITY, INFLAMMATION AND EPIGENETIC CHANGES IN LUNG ENDOTHELIUM

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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 further demonstrate that Tys significantly inhibits permeability, inflammation and epigenetic changes in lung endothelium that are induced by mexitilin-resistant Staph aureus bacteria (MRSA), a frequent cause of ARDS in patients.

Method Human pulmonary artery or microvascular endothelial cells (EC) were used for experiments. Immunoprecipitation, CHIP, 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 (1 μM) demonstrated significant barrier protective effects in cultured human lung endothelial cells (EC) after injury by heat-killed MRSA (HK-MRSA), or after exposure to alpha hemolysin toxin, a potent staph aureus product. HK-MRSA induced significant disappearance of VE-Cadherin and actin stress fiber formation within EC, which were reversed by Tys. In addition, HK-MRSA significantly induced activation of Rho and NF-kB, release of IL-6 and IL-8 and phosphorylation of MLC, which was inhibited by Tys. HK-MRSA induced epigenetic changes in lung EC, including methylation of histone H3 lysine 4, which was reversed by Tys. By chromatin immunoprecipitation (CHIP) analysis, HK-MRSA significantly enriched H3K9Ac in the NFAT binding region of the S1PR1 promoter, which was significantly inhibited by Tys treatment.

Conclusion MRSA induces significant barrier disruption, cyto-kine 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 and suggest potential utility in ARDS.

B03 ROLE OF LYSOCARDIOLIPIN ACYLTRANSFERASE IN LUNG EPITHELIAL CELL APOPTOSIS INDUCED BY CIGARETTE SMOKE EXTRACT

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Rationale Chronic Obstructive Pulmonary Disorder (COPD), primarily caused by cigarette smoke, is a leading cause of mortality. Cigarette smoke extract (CSE)-induced oxidative damage of the lungs result in mitochondrial dysfunction and apoptosis of epithelium. Cardiolipin (CL) in the inner mitochondrial membrane plays an important role in mitochondrial function, where its fatty acid profile is regulated by lysocardiolipin acyltransferase (LYCAT). We demonstrated that expression of LYCAT is increased in lungs from idiopathic pulmonary fibrosis patients and bleomycin-challenged mice, and this enhanced LYCAT expression had a protective role in reducing pulmonary fibrosis (Huang et al AJRCCM 2014). Human lungs from smokers also exhibited enhanced LYCAT expression; however, little is known about the role of LYCAT in CSE-induced apoptosis in lung epithelium.

Objective This study investigated the role of LYCAT and CL remodeling in mitochondria to characterize molecular mechanisms in COPD pathogenesis.

Methods LYCAT mRNA and protein levels in lungs from human non-smokers and smokers, and CS exposed mice (6 months) were analyzed using RT-PCR and Western blotting. A LYCAT peptide mimetic, which blocked LYCAT activity in cells, was used in CSE-induced oxidative stress and apoptosis in bronchial Beas2B epithelial cells. The CSE-induced changes in CL fatty acid composition of CL was assessed by Gas Chromatography-Mass Spectroscopy.
Results LYCAT mRNA and protein expression was enhanced in lung tissue from human smokers, and CS exposed mice. Exposure of Beas2B cells to CSE increased LYCAT expression in a time and dose-dependent manner. CSE had no effect on total CL levels; however, the 18:1 fatty acid levels in CL were higher compared to control. CSE enhanced total reactive oxygen species (ROS), mitochondrial ROS and apoptosis of Beas2B cells. Inhibition of LYCAT activity in Beas2B cells with a peptide mimetic (30µM) for 24 hours attenuated CSE-induced mitochondrial ROS and apoptosis.

Conclusions Our study suggests that enhanced LYCAT expression in lungs of human smokers and mice may play a key role in COPD pathogenesis by modulation of CL fatty acid profile, mitochondrial ROS, and mitochondrial function. Thus, targeting LYCAT activity by inhibitors may be a novel therapy for COPD.

B07 INHIBITION OF GROUP V PHOSPHOLIPASE A2 (GvPLA2) PROTECTS LUNG ENDOTHELium FROM M ETHICILLIN-RESISTANT STAPH AUREUS (MRSA) INDUCED PERMEABILITY

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Rationale Methicillin-resistant Staph aureus (MRSA) causes infection which frequently progresses to the Acute Respiratory Distress Syndrome (ARDS), a severe form of acute lung injury in which pulmonary endothelial cell (EC) dysfunction increases permeability and alveolar disruption. Previous studies have revealed that group V phospholipase A₂ (GvPLA₂) plays a critical role in EC permeability induced by endotoxin (LPS) and mechanical stretch. In the current study, we characterize the role of GvPLA₂ in mediating MRSA-induced human lung EC dysfunction.

Methods Confluent cultured human pulmonary artery EC (HPAEC) were incubated with heat-killed MRSA (HK-MRSA) at several time points. Cell lysates and supernatants were collected. Expression of GvPLA₂ was detected by Western blotting, and secreted PLA₂ (sPLA₂) activity assays were performed. To quantify intercellular gaps, the XPerT assay was used. Human lung microvascular endothelial cells (HLMVEC) were seeded on biotinylated gelatin-coated plates and grown to confluence. FITC-avidin was added and images acquired.

Intercellular gap area was then quantified in randomly selected images in HLMVEC after HK-MRSA, with or without the global sPLA₂ inhibitor LY311727. The Electric Cell-substrate Impedance Sensing system (ECIS) was used to measure trans-endothelial resistance (TER) of mouse pulmonary vascular EC isolated by flow cytometry from wild type and PLA2G5 global knockout mice (WT or KO mPVEC). IL-8 levels were assessed by ELISA in HPAEC after transfection with GvPLA₂ plasmid followed by MRSA.

Results GvPLA₂ protein expression increased within 2 hours of HK-MRSA exposure and remained elevated for 24 hours in cell lysates; no secreted GvPLA₂ protein was detected in supernatants. Increased sPLA₂ activity was observed within 15 minutes of HK-MRSA exposure. HK-MRSA increased intercellular gaps in HLMVEC, but the effect was attenuated by LY311727. In TER experiments, HK-MRSA increased permeability in both KO and WT mPVEC. LY311727 attenuated this permeability in WT but not KO mPVEC. LY311727 increased basal TER in both KO and WT mPVEC. Overexpression of GvPLA₂ may increase cytokine release after MRSA.

Conclusion In human lung endothelium, HK-MRSA induces GvPLA₂ expression and activity and increases gap formation and permeability. sPLA₂ inhibition attenuates these effects in human lung EC, but not in GvPLA₂ KO mPVEC. These results suggest an important role for GvPLA₂ in mediating MRSA-induced ARDS and highlight it as a potential therapeutic target.

B08 PRIMARY HUMAN AIRWAY AND ALVEOLAR RESIDENT PHAGOCyTES ARE RESISTANT TO ANThRAX LETHAL TOxin

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Objective Bacillus anthracis is a global concern as a bioterrorism agent. Once spores of this pathogen are inhaled and germinate, they begin producing two toxins: lethal toxin (LT) and edema toxin (ET). LT is a combination of protective antigen (PA) and lethal factor (LF), and induces apoptosis of susceptible cell types. ET is a combination of PA and edema factor (EF), and is an adenylate cyclase. Both toxins are thought to impair human immune cells during the course of anthrax pathogenesis. We have previously described six subsets of airway and alveolar resident phagocytes (AARPs) found in the healthy human lung. Their susceptibility to the effects of LT and ET is unknown, and is investigated in this study.

Method Human AARPs were tested for their surface expression of the known toxin receptors TEM8 and CMG2. Biological activity of these receptors was measured by their binding of dye-labeled PA. Induction of apoptosis was measured by Annexin V staining after incubation with LT.

Results Of the six AARP subsets, 10–20% of Langerin⁺, CD14⁺ BDC1⁺, CD14⁺ BDC1⁺, CD14⁺ BDC1⁺, and CD14⁺ BDC1⁺ cells were positive for TEM8 and CMG2. Less than 5% of alveolar macrophages were positive for both markers. In comparison, 50% of human blood granulocytes were positive for TEM8. All six AARP subsets bound labeled PA in a concentration-dependent manner, and this binding was specific based on competition assays with unlabeled PA. However, none of the AARP subsets were sensitive to LT-induced apoptosis at concentrations as high as 1000 ng/ml. Cell death was also not necrosis-mediated. As expected, ET at the same concentrations did not cause apoptosis.

Conclusion Overall, our studies suggest that while phagocytes in the human airways and alveoli may be exposed to anthrax LT early in the course of infection, they are resistant to its effects. While ET may have other effects on these subsets, it does not induce rapid cell death. This work implies that human AARP subsets are vital in mounting a successful immune response against B. anthracis due to their ability to phagocytose spores and their inherent resistance to LT-induced apoptosis.
Background
Home oxygen therapy, the standard of care for patients with chronic lung disease and hypoxemia, is commonly initiated in the hospital prior to discharge based on pulse oximetry readings. Unfortunately, the need for home oxygen is only reassessed in 35–65% of patients when clinically stable even though as many as 30–50% of patients may not need home oxygen 2–3 months later. In recent years, ‘wellness’ (i.e., non-medical) pulse oximeters have become available for over-the-counter purchase and even for download as smartphone applications (‘apps’). Home pulse oximetry could allow patients prescribed home oxygen therapy to self-titrate their oxygen flow rate, and even discontinue it, according to their individual needs. However, the accuracy of wellness pulse oximeters and smartphone-based pulse oximeter apps has not been evaluated.

Objective
The objective of this study is to evaluate the accuracy of these wellness pulse oximeters in patients with chronic lung disease. Although developed for recreational purposes, if accurate, these devices could facilitate the development of interventions to support the management of home oxygen therapy.

Methods
Patients were recruited from the pulmonary clinic and pulmonary function laboratory. Room air pulse oximetry (SpO2) and heart rate (HR) were measured using a wellness pulse oximeter (Walgreens C20®) and three pulse oximeter apps (iCare®, SHealth® and Pulse oximeter®) in patients with physician-diagnosed chronic lung disease. The pulse oximeter readings taken simultaneously as part of clinical care were used as the reference standard. These were performed using Federal Drug Administration-approved pulse oximeters Welch-Allyn® with Masimo SET® or Nellcor®). Moderate and severe hypoxemia were defined as SpO2 89–94% and <89%, as measured by the reference standard, respectively. Cohen’s kappa was calculated to evaluate the agreement between the different pulse oximeters to identify moderate and severe hypoxemia. Bland-Altman analyses were performed to analyze the mean percent error ([reference standard-measured]/reference standard*100%) and 95% confidence interval (CI) between SpO2 obtained by each pulse oximeter vs. the reference standard. T-tests were used to compare the difference between each pulse oximeter with the reference standard.

Results
The 45 participants with chronic lung disease had a mean (SD) SpO2 of 94 (6.4)% as measured by the reference standard pulse oximeters. Among all 45 participants, moderate hypoxemia (SpO2 89–94%) was found in 12 participants and severe hypoxemia (SpO2<89%) was found in 2 participants. Due to their later addition to the study protocol, the SHealth app and Walgreens C20 pulse oximeter were only used in 35 participants. Among the 35 participants, 8 had moderate hypoxemia and 2 had severe hypoxemia. The mean percent error for the various pulse oximeters ranged from -1.0 to +4.3% (figure 1). The Walgreens C20® was the most accurate device with a mean (SD) error of -1.0% (2.2%). However, only the SHealth® and Walgreens C20® were able to identify moderate hypoxemia in 7 out of 8 participants in which these devices were used. The SHealth® was the only device able to identify severe hypoxemia in 1 of 2 participants in which these devices were used. The iCare of iOS pulse oximeter apps were unable to identify severe hypoxemia.
Conclusion Commercially-available pulse oximeters have variable levels of accuracy. Although the Walgreens C20® had a mean error of <1%, further testing is needed prior to routine deployment in clinical settings as it was unable to detect severe hypoxemia in one participant.

Objective Sedentary behavior and low levels of physical activity are common in patients with chronic obstructive pulmonary disease (COPD) and are associated with increased morbidity and mortality. There is increasing interest in adapting home-based physical activity promotion interventions for patients with COPD to underserved and minority populations. To inform the design of a post-hospital discharge home-based physical activity promotion program, we evaluated daily physical activity in patients with COPD recently discharged from a minority-serving hospital.

Method This was a 12-week prospective cohort study of patients with a physician diagnosis of COPD recently hospitalized (≤12 weeks) for respiratory symptoms. Additional eligibility criteria included physical ability to walk and no medical contraindications to participation, as determined by the patient’s physician. Daily physical activity was recorded using wrist-based and ‘clip-on’ pedometers, and analyzed as mean daily step counts averaged over 7 days. At least 4 days with wearing time >8 hours were required for a valid assessment.

Results Twenty-two patients discharged a mean (standard deviation, SD) of 21(19) days prior to enrollment participated in the study. Participants had a mean (SD) age of 63.8(7.1) years and were predominantly women (68%), African American (90%), and had no more than high school education (72%). Almost half of participants (45%) reported at least one comorbidity associated with chronic pain. The median (interquartile range, IQR) incremental shuttle walk distance was 110(30, 210) meters. PROMIS physical function, ability to participate in social roles and activities, and satisfaction with participation in roles and activities T-scores averaged at least one standard deviation lower than the national mean. The median daily step count (IQR) on the week of enrollment was 3,101(1,144, 5,330) steps. The median change in daily step count (IQR) from the week of enrollment to week 12 was 203(-160, 1,633) steps. Over the 12 weeks of observation, within-person correlation of week-to-week daily step counts was high (R>0.8). Time from hospital discharge to enrollment was only weakly correlated with change in daily physical activity from enrollment to week 12 (R=0.35; figure 1).

Conclusion In predominantly African-American patients with COPD, we observed little improvement in daily physical activity after hospital discharge over a 12-week period. Change in daily physical activity was low even in patients discharged from the hospital >4 weeks prior to enrollment. These results provide evidence of the persistently low level of physical activity after hospital discharge and the need for interventions to promote physical activity.
**B24**

**MYOSIN LIGHT CHAIN KINASE GENETIC VARIATION AND THE RISK OF PRECAPILLARY PULMONARY HYPERTENSION IN SICKLE CELL DISEASE**

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Objective Pulmonary hypertension (PH) affects nearly 10% of adult patients with Sickle Cell Disease (SCD) and is associated with significant morbidity and mortality. Myosin light-chain kinase (MYLK) is a gene known to regulate pulmonary vascular function, being an important component to pulmonary artery smooth muscle contraction. Myosin light-chain kinase activation may likely play a role in key components of PH pathobiology, particularly sustained vasoconstriction and vascular remodeling. More importantly, MYLK genetic variation has been associated with acute lung injury and severe asthma susceptibility in African Americans (AAs). We hypothesized that MYLK genetic variation influences PH risk in patients with SCD.

Methods MYLK SNPs associated with acute lung injury and severe asthma susceptibility in AAs were genotyped in discovery (n=511) and validation (n=270) cohorts of patients with SCD. CRISPR/Cas9 gene editing was performed using novel constructs targeted at the SNP of interest in primary human pulmonary artery smooth muscle cell lines. Proliferation was assessed by cell count.

Results In an additive model adjusted for gender, age and ancestry, rs9840993 (721C>T, p.Pro147Ser) tended to be associated with a lower prevalence of PH in both the discovery (OR 0.36 [95% CI 0.14–0.92], P=0.03) and validation (OR 0.69 [95% CI 0.32–1.47], P=0.33) cohorts. This association was stronger in subjects with precapillary PH in both the discovery (OR 0.3 [95% CI 0.10–0.92], P=0.04) and validation (OR 0.3 [95% CI 0.10–0.84], P=0.02) cohorts. We have begun work using CRISPR/Cas9 gene editing to reproduce the genotype associated with PH in SCD. Insertion of 721C in primary PASMC appears to be associated with increased proliferation as measured by cell count both in normoxia and hypoxia compared to control CRISPR/Cas9 transfection.

Conclusions rs9840993, a functional SNP in the MYLK gene, is associated with the presence of precapillary PH in patients with SCD. The ancestral allele C (147Pro) has been shown to be a risk factor for severe asthma in AAs and our work suggests that it also confers risk in the development of precapillary PH in patients with SCD. Future work will continue to expand the role of this SNP functionally as well as to identify its role as a biomarker among other PH patients of African descent.

**B27**

**REAL-TIME CHARACTERIZATION OF INFLAMMATORY LUNG INJURY**

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Objective The acute respiratory distress syndrome (ARDS) is characterized by the flooding of the interstitial and alveolar space with edema fluid rich in protein and inflammatory cells leading to altered gas exchange and lung mechanics. In the present study we combine data obtained from 2-photon intravital microscopy and measurement of lung mechanics in wild-type and genetically modified mice to better understand the pathologic mechanisms contributing to in vivo inflammatory lung injury.

Method Wild type (WT), group V phospholipase A2 deficient (gVPLA2KO) and endothelial specific integrin beta4 knock out (EC-ITGB4KO) mice were subjected to lung injury via administration of intratracheal LPS (2.5 mg/kg) or heat killed methicillin-resistant S. aureus (hkMRSA). After 18 hours, mice were anesthetized, ventilated and injected with FITC-labeled dextran as well as fluorescent anti-Ly-6 antibody to label circulating neutrophils. Thoracotomy was performed to expose the thorax followed by placement of a suction equipped ‘lung window’ coverslip through which 2-photon intravital microscopy was performed. Interstitial area and neutrophils were quantified. Lung mechanics were measured in a second set of mice from each group using the flexiVent™ (Scireq) animal ventilator.

Results The inspiratory capacity of mice injured with LPS was significantly decreased compared to controls (0.948 ± 0.03 mL vs 0.773 ± 0.03 mL). Interestingly, the inspiratory capacity in both groups increases with body mass up to 25 g before plateauing in control animals and decreasing again in injured animals. Following LPS injury, EC-ITGB4KO mice are protected from decreases in lung compliance compared to WT (0.0316 vs 0.0241 ± 0.001; p=0.02). The ratio of interstitial area to open airspace area as measured by 2-photon microscopy was significantly greater in WT mice treated with hkMRSA vs controls (0.783 ± 0.06 vs 0.601 ± 0.02; p=0.04). This ratio was not increased in gVPLA2KO mice following hkMRSA and was similar to control (0.537 ± 0.03 vs 0.535 ± 0.02). WT mice exhibited increased neutrophils per field following injury (24.6 ± 4.4 vs 7.4 ± 1.5; p<0.01). Animals without gVPLA2KO had less neutrophils at baseline (2.7 ± 1.2) and following MRSA (11.9 ± 1.6). Control animals showed a trend in decreased lung compliance following hkMRSA while gVPLA2KO mice were protected. These results are consistent with previous in vitro and in vivo studies. CONCLUSION: Real-time quantification of lung injury in mice is reproducible and may offer new pathophyslogic insights. Additional study is needed to determine the precise relationship between mouse body weight and lung volume.

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**C06**

**ENDOTHELIAL CELL INTEGRIN BETA4 KNOCKOUT ATTENUATES LPS-INDUCED MURINE ACUTE LUNG INJURY**

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Objective We previously reported the attenuation of murine acute lung injury (ALI) by simvastatin, an HMG CoA-reductase inhibitor, is mediated by the inhibition of integrin beta4 (ITGB4) tyrosine phosphorylation. As statin drugs are recognized to have pleiotropic properties and have not proven to have significant clinical efficacy in lung vascular inflammatory syndromes including acute lung injury (ALI), we hypothesized...
that strategies aimed precisely at inhibiting ITGB4 signaling may prove to be more effective in this context.

**Method** We generated EC-specific ITGB4 knockout (KO) mice by crossing ITGB4 LoxP and Tie2-Cre transgenic animals. These animals were then subject to ALI induced by LPS (1.25 mg/kg i.t., 16 h) prior to assessments of lung injury by bronchoalveolar lavage (BAL) fluid cell counts as well as protein and cytokine levels. Lungs were also harvested and utilized for histologic evaluation. In separate experiments, EC-ITGB4 KO mice were administered LPS to induce ALI with lung mechanics subsequently measured using a flexiVent™ (Screq) small animal ventilator. In all experiments, ITGB4 flox/flox mice were used as controls.

**Results** In our LPS-ALI model, EC-ITGB4 KO mice were found to have significantly decreased total cell counts and protein levels compared to controls (42% and 32% reductions, respectively, p < 0.01 for both). In addition, BAL cytokine levels after LPS were also reduced in EC-ITGB4 KO mice compared to controls, including IL-6, KC and TNFα (by 78%, 64%, and 70%, respectively, p < 0.01 for each). These findings were corroborated by evidence of decreased inflammatory cell infiltration and interstitial edema on lung histology in EC-ITGB4 KO mice. Finally, measurements of lung function after LPS confirmed significantly decreased compliance in control animals compared to EC-ITGB4 KO mice.

**Conclusion** Our findings support a critical role for EC ITGB4 after LPS confirmed significantly decreased compliance in inflammatory cell infiltration and interstitial edema on lung histology (up to 72 h). To explore the role of UCHL1 in RILI, we subjected C57Bl/J6 mice to single dose thoracic irradiation (20 Gy) and measured lung UCHL1 mRNA and protein levels. We next treated wildtype mice with vehicle or LDN-57444 (LDN, 5 mg/kg, IP, 3x/wk), an inhibitor of UCHL1, for 6 wks post-radiation when RILI was assessed by BAL fluid cell and protein measurements. We then investigated the effects of UCHL1 on SphK1 expression levels after silencing and overexpression of EC UCHL1. Separately, EC were treated with P-543, a pharmacologic inhibitor of SphK1, followed by Western blotting to assess effects on basal and radiation-induced UCHL1 expression levels. Finally, control and UCHL1-silenced EC were subjected to radiation (20 Gy) and used for immunoprecipitation with a SphK1 antibody prior to Western blotting for ubiquitin.

**Results** We confirmed a significant upregulation of EC UCHL1 at 1 h that increased and persisted at 72 h after radiation while RILI-challenged mice demonstrated significantly increased UCHL1 mRNA (1 d and 6 wks) and protein levels (6 wks) in whole lung homogenates. Moreover, LDN pretreatment attenuated murine RILI severity as measured by BAL fluid cell counts and protein levels. Notably, SphK1 levels in EC were inversely affected by UCHL1-silencing and overexpression of EC UCHL1. Our findings implicate ITGB4 signaling as a key mediator of inflammatory lung injury that warrants further investigation as a potential novel therapeutic target in patients with ALI.

### C08 ROLE OF UCHL1 IN RADIATION-INDUCED LUNG INJURY MEDIATED BY SPHINGOLIPIDS

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**Objective** We previously reported GADD45a is a novel candidate gene in acute lung injury. Subsequently, we found GADD45a-/- mice express decreased Akt and increased Akt ubiquitination as a consequence of reduced expression of UCHL1 (ubiquitin c-terminal hydrolase L1), a deubiquitinating enzyme. Moreover, we found increased RILI susceptibility of GADD45a-/- mice. Separately, we have reported a critical role for sphingolipids in RILI evidenced by increased RILI susceptibility of sphingosine kinase 1 (SphK1) knockout mice. Evidence for a possible mechanistic link between UCHL1 and sphingolipid signaling in RILI is suggested by the known polyubiquitination of SphK1. We hypothesize that regulation of SphK1 ubiquitination by UCHL1 represents an important mediator of RILI.

**Methods** Initially, we performed Western blots of human lung endothelial cells (EC) subjected to radiation (10 Gy) over time (up to 72 h). To explore the role of UCHL1 in RILI in vivo we subjected C57Bl/J6 mice to single dose thoracic irradiation (20 Gy) and measured lung UCHL1 mRNA and protein levels. We next treated wildtype mice with vehicle or LDN-57444 (LDN, 5 mg/kg, IP, 3x/wk), an inhibitor of UCHL1, for 6 wks post-radiation when RILI was assessed by BAL fluid cell and protein measurements. We then investigated the effects of UCHL1 on SphK1 expression levels after silencing and overexpression of EC UCHL1. Separately, EC were treated with P-543, a pharmacologic inhibitor of SphK1, followed by Western blotting to assess effects on basal and radiation-induced UCHL1 expression levels. Finally, control and UCHL1-silenced EC were subjected to radiation (20 Gy) and used for immunoprecipitation with a SphK1 antibody prior to Western blotting for ubiquitin.

**Conclusion** Our findings support regulation of SphK1 expression after radiation is mediated by UCHL1 and suggest that modulation of UCHL1 effecting downstream sphingolipid signaling may represent a novel therapeutic strategy for patients at risk for RILI.

### Rheumatology/Immunology/Allergy

**A32 HEPATIC INJURY ASSOCIATED WITH REDUCED URINARY EXCRETION AND ALTERED HEPATIC SIGNALING PATHWAYS FOLLOWING CHRONIC LOW DOSE EXPOSURE TO MICROCYSTIN-LR IN A MURINE MODEL OF NON-ALCOHOLIC FATTY LIVER DISEASE**

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**Objective** Cyanotoxins like microcystins (MCs) are secondary metabolites produced by cyanobacteria. These potent hepatotoxins are generated from harmful cyanobacterial blooms which frequently contaminate all forms of open water, including municipal and agricultural water sources, and pose a serious and growing global public health risk. Cyanobacterial blooms not only affect every region of the US but are widespread throughout the world with increasing frequency each year. While current exposure guidelines to these toxins have been extrapolated to humans based on studies performed in healthy animal models, their effect in at-risk populations with a pre-existing liver disease is unknown. We tested the hypothesis that the No Observed Adverse Effect Level (NOAEL) of MCs established in healthy mice would cause demonstrable hepatic injury in a murine model of Non-alcoholic Fatty Liver Disease (NAFLD).

C21 THE ROLE OF NUCLEOLIN IN CELLULAR SIGNALING PATHWAYS FOR PROLIFERATION OF INFLAMMATORY BREAST CANCER (IBC)

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Objective Inflammatory breast cancer (IBC) is a rare type of breast cancer characterized by redness and swelling of the skin around the breast. Diagnosis of IBC can be difficult, prognosis is poor and further research is needed to clearly understand this disease. Our preliminary studies demonstrated higher expression of nucleolin in the IBC cell lines SUM149PT and SUM190PT as compared to control human mammary epithelial cells (HMECs). Nucleolin is a type of protein found to be involved in cell proliferation and cell death in various cancers such as prostate, colon, gastric, and liver. Previous studies showed that nucleolin is linked to several different types of cellular signaling pathways, such as AKT, PI3K, mitogen activated protein kinases (MAPKs) and mammalian target of rapamycin (mTOR) in other cancers. Therefore, we hypothesized that nucleolin might be regulating proliferation and survival pathways in IBC.

Method The results were obtained via the conduction of Western Blots and through the use of the control HMEC cell lines and the experimental SUM149PT and SUM190PT cell lines.

Results The expression and activation of cellular signaling pathways was found to be higher in IBC cell lines SUM149PT and SUM190PT, in comparison to control HMEC cells.

Conclusion By examining the role of nucleolin as a binding partner to cell signaling pathways, we will get a molecular understanding of its function in cell proliferation in inflammatory breast cancer. Understanding the functionality of nucleolin in the signaling pathways of inflammation in breast cancer scenario will provide new avenues of promising therapeutic strategies.

Methods/Results Ten week old male Lepr<sup>db</sup>/J mice and C57BL/6 mice were orally gavaged with 50 μg/kg or 100 μg/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 exposure regimen is 2.5 to 5 times below the published NOAEL levels for MC-LR. During the treatment, we observed a non-statistically significant trend in decreased survival in Lepr<sup>db</sup>/J mice, with control group showing 100% survival whereas the 50μg/kg and 100μg/kg group showed 93% and 85% survival respectively. No deaths were reported with healthy C57BL/6 mice exposed to the same regimen. We observed a significant increase in the ALP levels post treatment in a dose-dependent manner in the MC-LR treated vs vehicle Lepr<sup>db</sup>/J mice as well as significant histopathologic evidence of hepatic injury including severe micro- and macro-vesicular fatty infiltration, ballooned hepatocytes, and decreased Periodic acid-Schiff (PAS) staining. In order to determine the biodistribution of the toxin in healthy vs NAFLD settings, we quantified the MC-LR levels in plasma and urine samples of both C57BL/6 and Lepr<sup>db</sup>/J mice using LC-MS/MS. Interestingly, while we were unable to detect circulating plasma levels of MC-LR in healthy C57BL/6 mice after 24 hours of 100 μg/kg MC-LR administration, Lepr<sup>db</sup>/J mice exhibited measurable (≥0.5 ng/mL) circulating plasma levels of MC-LR even 72 hours after administration. Furthermore Lepr<sup>db</sup>/J mice exhibited urinary excretion of MC-LR which was ≥60 times less than that of healthy C57BL/6 mice (p<0.01). Finally, phosphoproteomic analysis with mass spectrometry-based label-free quantification of TiO<sub>2</sub> enriched liver samples was used to determine potential signaling pathways affected by MC-LR treatment in Lepr<sup>db</sup>/J mice. Here we observed a treatment dependent increase in phosphorylation site abundance of proteins belonging to pathways involved in mRNA splicing, and a decrease in those involved in toll-like receptor activation, cytokine signaling, mitosis, carbohydrate metabolism and cellular adhesion.

Conclusion Our results suggest that levels of MC-LR which are below the NOAEL established in healthy animals results in significant hepatic injury, as well as reduced urinary excretion and significantly altered phosphorylation patterns of key signaling pathways in the livers of NAFLD mice.