Bio-engineering

1 E-CIGARETTE CONTENT ALTERS MITOCHONDRIAL AND BIOPHYSICAL PROPERTIES OF LUNG ENDOTHELIUM
Mounica Bandela, James Lee, Steven Dudek. The University of Illinois at Chicago
10.1136/jim-2022-MW.1

Introduction/Background Cigarette smoking (CS) is the major cause of Chronic Obstructive Pulmonary Disease (COPD). E-cigarettes are considered by some as a safer alternative; however, inhalation of nicotine-containing e-cigarettes can also cause pathophysiologic changes, and ‘vaping’ of some substances has led to severe lung damage. Our group has previously identified the effect of CS or e-cigarettes in lung endothelial apoptosis and mitochondrial dysfunction.

Objective(s) This study seeks to characterize the effects of CS or E-cig in lung endothelial dysfunction.

Methods An important marker of mitochondrial dysfunction is excess mitochondrial ROS (mitoROS), and its production in lung ECs was assessed using MitoSOX reagent. Cytoskeleton rearrangement of ECs upon e-cigarette was assessed by immunofluorescence. Lung EC was exposed to E-cigarette extract (50 μg/ml), resulting in disruption of endothelial permeability assessed by Electric Cell Substrate Impedance (ECIS) and Transwell assay. Atomic Force Microscopy (AFM) was used to probe the biomechanical responses of the manipulated ECs upon e-cigarette challenge.

Results Blocking mitoROS with Mito-TEMPO (10 μM, 3 h), a cell-permeable antioxidant, decreased mitochondrial superoxide production. We next assessed the role of Mito-TEMPO on E-cigarette-induced endothelial permeability. Pretreatment with Mito-TEMPO provided barrier protection upon e-cigarette challenge. These results suggest a key role of mitoROS in e-cigarette-induced endothelial permeability. E-cigarette exposure induces cytoskeleton rearrangement leading to gap formation in lung EC, as well as alters elastic properties of ECs as measured by AFM.

Conclusion This study provides novel mitochondrial and biophysical characterization of the effects of e-cigarette exposure on lung EC and advances our understanding of its pathophysiologic effects.

Cardiology/cardiovascular disease

2 PROCEDURAL OUTCOMES OF THE USE OF A MIXED REALITY HEAD MOUNTED DISPLAY IN THE CARDIAC CATHETERIZATION LABORATORY
1Johnny Chahine, 2Stephen George, 1Jason Bartos, 1Ganesh Raveendran, 1Sergey Gurevich.
1University of Minnesota; 2Regions Hospital
10.1136/jim-2022-MW.2

Introduction/Background Mixed reality (MR) head-mounted displays (HMDs) have been traditionally deployed as a teaching aid or for reference of patient data, but not for real-time live guidance of procedures.

Objective(s) To compare the use of MR-HMDs versus standard displays in the cardiac catheterization laboratory.

Methods There were 294 coronary angiograms (CAs) and right heart catheterizations (RHCs) performed at the University of Minnesota between August 2019 and January 2020 were included in the retrospective observational study. The study was approved by the facility’s Institutional Review Board. The study group (MR-HMD guided) included 62 procedures (33 RHCs, 29 CAs), and the control group (standard display guided) included 232 procedures (164 RHCs, 68 CAs). The study endpoints included procedure time, fluoroscopy time, contrast volume used (50 mL (IQR 40–67), p=0.87) vs. 50 mL (IQR 40–68) vs. 50 mL (IQR 36–67), p=0.87) (figure 1). There was no difference in complications (n=1, 1.6% in the study group vs. n=2, 0.9%, p=0.51).

Conclusion The use of MR-HMD in the cardiac catheterization laboratory is safe and may decrease procedure time.

3 SYSTEMATIC ERROR RESULTING IN A LEAD REVERSAL EPIDEMIC IN THE EMERGENCY ROOM: AN UNDERESTIMATED CONSEQUENCE OF THE GLOBAL PANDEMIC
Mohammad Al Bataineh, Abdallah Mansour, Mary Dohrmann. University of Missouri Columbia
10.1136/jim-2022-MW.3

Introduction/Background Electrocardiogram (ECG) lead reversal is a well-known phenomenon that can involve limb and precordial leads. It can occur due to a reversal of the lead placement site at the patient level or a reversal of the lead connection at the machine, the latter being less common, but leading to wide-ranging and often subtle ECG changes that are difficult to discover. A series of precordial lead reversals originating from a single machine in the emergency room (ER) resulted in unnecessary evaluation and medical costs.

Objective(s) The aim of this retrospective evaluation is to highlight a potential systematic error that could affect multiple patients and to highlight the importance of the interpreter’s meticulous assessment of repeated lead reversals in ECGs.
Methods
Over a period of five weeks, multiple ECGs were found to have V1-V2 lead reversal, resulting in errors in interpretation by the computer software for the ECG machine. The ECGs were traced back to a single machine in the ER. A total of 414 ECGs were affected, 44 of which had an interpretation of ‘septal infarct’ by the confirming physician for the ECG. Individual chart review was undertaken of the 44 patients.

Results
Of the 44 charts reviewed, the lead reversal directly resulted in one emergent coronary angiogram and four admissions with extensive cardiac workup (echocardiograms, stress tests, blood tests). Multiple other patients were referred for further outpatient evaluation. Two independent providers deemed the resultant workup clinically inappropriate if the knowledge of the reversal was present at the time of decision-making. Root-cause analysis was carried out, and it was discovered that the leads of the ER machine were switched at the hub during a routine cleaning session. The misplaced leads at their origin from the ECG machine remained undetected for weeks due to a lack of routine technical monitoring since the global pandemic began in March 2020.

Conclusion
The burden of the global pandemic goes beyond direct physical damage caused by the disease. Systematic errors are more common due to staff shortages and shifting priorities. In this series of lead reversals, the shortage of staff to complete scheduled maintenance of equipment resulted in a costly error. Routine technical rounds and meticulous evaluation of repeated lead reversal patterns in ECGs from the same geographical workspace can help identify such errors and reduce the financial burden of health care.

Effectiveness of the AngioVac System in Removal of Intravascular Masses: A Single Center Experience

Austin Nickell, Phanindra Antharam, Orlin Sergev, Neville Alberto, Dubert Guerrero.

University of North Dakota

10.1136/jim-2022-MW.4

Introduction/Background
Cardiovascular diseases including endocarditis, deep vein thrombosis, and septic emboli remain highly significant diseases, resulting in numerous hospitalizations and deaths each year. In addition to anticoagulation and thrombolytic therapies that are used for acute and chronic management of these conditions, surgical debridement and thrombectomy can also be performed. Despite the wide prevalence of these techniques, critically ill and hemodynamically unstable patients are often not viable candidates for these procedures owing to the stress placed on the body during sternotomy. An alternative to these invasive procedures is the AngioVac system designed by AngioDynamics in Latham, NY. Performed either percutaneously or open, this minimally invasive technique has been shown as an effective replacement for the removal and filtration of acute thrombi or emboli. This single-centered, retrospective study focuses on patient presenting comorbidities and indications for the procedure as well as post-procedural outcomes.

Objective(s)
To explore the clinical indications, efficacy, and safety of AngioVac for thrombectomy and removal of intravascular masses including vegetations of right sided endocarditis.

Methods
A total of 33 patients who underwent an AngioVac procedure at Sanford Health between March 2014 and October 2019 was reviewed. Data were collected on pre-existing comorbidities, indication of procedure, length of hospital stay, and post-operative outcomes.

Results
There were a total of 33 patients (male: 22/33, 67%) with a median age of 47 years (18–82) who underwent an AngioVac procedure at Sanford Health. The most common indications for the procedure were endocarditis (24/33, 73%); intracardiac mass (5/33, 15%); and deep vein thrombosis or pulmonary embolism (2/33, 6%). Post-procedural blood transfusion was required in nearly half (15/33, 45%). Almost all patients (31/33, 94%) required intraoperative vasopressor use. The median length of hospital stay after the procedure was 10 days with interquartile range (IQR) of 18 to 8. Nearly all patients (32/33, 97%) were directed to the ICU following the procedure with an average length of stay of 8 days (IQR = 13–3). The most common complications seen after the procedure were shock requiring vaspressors, (13/33, 39%), pleural effusion (9/33, 27%), and sepsis (4/33, 12%). There was also a single occurrence of 30-day mortality deemed unrelated to the procedure. The success rate seen in the single-centered experience was 85% (28/33).

Conclusion
The AngioVac procedure offered a less invasive option to high risk surgical patients presenting with right sided endocarditis requiring vegetation debulking, intravascular thrombi or cardiac masses.
with significant bubbles. In the setting of an elevated D-dimer without bacteremia, the intracardiac masses were consistent with thrombi. Due to worsening respiratory status despite diuresis, a right heart catheterization was performed which showed high pulmonary pressures and normal wedge pressure (table 1). Based on the pulmonary filling pressures and mean arterial pressure (MAP), her calculated pulmonary vascular resistance (PVR): systemic vascular resistance (SVR) was 0.48. Considering refractory respiratory failure due to right to left shunting as the culprit, the PFO was closed to offload the RV (figure 1). However, her respiratory status continued to worsen and progressed to refractory right heart failure. Eventually she had cardiac arrest and succumbed.

Conclusion PFO closure has applications in several disease processes, notably cryptogenic stroke (as shown in RESPECT, REDUCE, CLOSE and DEFENSE-PFO trials), migraines with aura, decompression sickness, platypnea-orthopnea syndrome and in patients undergoing liver transplantation. This is a rare case of acute right heart failure unmasked by PFO closure. Medications including sildenafil, epoprostenol and nitric oxide are recommended to prevent the increase in RV afterload after PFO closure when the PVR:SVR ratio is > 0.66. In our case, RV offloading was not indicated. Hence, we need to keep in mind that in spite of RV hemodynamics assessment, decompensation may still occur.

Conclusion PFO closure has applications in several disease processes, notably cryptogenic stroke (as shown in RESPECT, REDUCE, CLOSE and DEFENSE-PFO trials), migraines with aura, decompression sickness, platypnea-orthopnea syndrome and in patients undergoing liver transplantation. This is a rare case of acute right heart failure unmasked by PFO closure. Medications including sildenafil, epoprostenol and nitric oxide are recommended to prevent the increase in RV afterload after PFO closure when the PVR:SVR ratio is > 0.66. In our case, RV offloading was not indicated. Hence, we need to keep in mind that in spite of RV hemodynamics assessment, decompensation may still occur.
Abstract 6 Figure 2  Intestinal barrier dysfunction in CPB versus controls

Abstract 6 Figure 3  Short chain fatty acid levels in CPB versus controls
Abstract 6 Figure 4  Intestinal eicosanoids levels in CPB versus controls

Abstract 6 Figure 5  Systemic cytokine levels in CPB versus controls
all intestinal short chain fatty acids, which regulate inflammation and are cardioprotective, seen in figure 3. There was also a shift of intestinal inflammatory lipid mediators, eicosanoids, in the pre and post stool sample that differed from controls, seen in figure 4. We also showed an increase in IL-1, IL-6, and TNF-α in CPB/DHCA piglets compared to controls, seen in figure 5.

Conclusion These results are very similar to previously published data on the shift of the microbiome in pediatric patients with congenital heart disease as well as demonstrating evidence of intestinal barrier dysfunction and reduction of short chain fatty acids, along with an increase in systemic cytokine levels. This is the first known animal model of cardiopulmonary bypass to evaluate change to the intestinal microbiome and barrier dysfunction. Identifying this model as feasible to study changes to the microbiome will set the stage for future studies evaluating interventions to the microbiome and evaluate systemic inflammation through cytokine profiling and flow cytometry of activate immune cells.

MECHANISMS OF THROMBOSIS IN PATIENTS WITH LIPOEDEMA AND LYMPHEDEMA

Sharon Shim, Akinrare Ademoyo, Anu Aggarwal, John Bartholomew, Rohan Bhandari, Robert Burton, Scott Cameron, Matthew Godwin, Suman Gunupalli, Annelise Hamer, Douglas Joseph, Xuefeng Liu, Geoffrey Ouma, Crystal Pascual, Michael Tran. Cleveland Clinic Heart, Vascular and Thoracic Institute

Introduction/Background Lipoedema, an under-diagnosed disorder almost exclusively affecting women, is caused by an abnormal accumulation of subcutaneous fat in the limbs and is routinely mistaken for lymphedema, which is another cause of limb swelling. Given the recent observation that platelet-specific biomarkers are elevated in both conditions, we hypothesized that platelets may be central mediators in both disorders.

Objective(s) Capitalizing upon carefully-phenotyped and enriched data, we retrospectively evaluated thrombotic outcomes in patients treated for lipoedema and lymphedema. We then obtained blood from patients with each disorder and investigated platelet-mediated and non-platelet-mediated thrombotic phenotypes ex vivo.

Methods Data collected over 20 years for patients treated with lymphedema (n=14,958; mean age 66, mean BMI 37.6, 70% female) and a concomitant diagnosis of lipoedema (n=8,493, mean age 71, mean BMI 40.6, 69% female) were evaluated and thrombotic outcomes determined by logistic regression analysis. Washed human platelets were assessed for activation by FACS following exposure to ex vivo to PAR1 agonist (TRAP-6), thromboxane receptor agonist (U46619), P2Y12 receptor agonist (ADP) and GPVI receptor agonist (collagen-related peptide [CRP]). Platelet-deplete plasma was used to determine real-time fibrin and thrombin generation kinetics.

Results In patients with lymphedema, 19% experienced a thrombotic event over the observational period (14.3% myocardial infarction (MI), 4.0% arterial thrombosis, 0.04% stroke, 0.6% deep vein thrombosis [DVT]). In patients with lipo-lymphedema, 33% experienced a thrombotic event over the observational period (22.2% MI, 8.2% arterial thrombosis, 0.3% stroke, 2.3% DVT, 0.01% pulmonary embolism [PE]). Antiplatelet medications in aggregate analysis conferred no protective effect against thrombosis in lymphedema (OR=1.36[0.41–4.58],p=0.62); however, the P2Y12 receptor antagonist, clopidogrel, conferred protection from PE.
In patients with lipo-lymphedema, the P2Y12 antagonist ticagrelor protected against DVT (OR=0.45 [0.21–0.98], p=0.045) and stroke (OR=0.22 [0.07–0.72], p=0.012). In patients taking anticoagulants, warfarin conferred no protection from thrombotic events in either lymphedema or lipo-lymphedema, but Factor Xa inhibitors, apixaban and rivaroxaban, protected against stroke in lymphedema and lipo-lymphedema, while apixaban protected against DVT and arterial thrombosis only in lipo-lymphedema. The direct thrombin inhibitor dabigatran protected against DVT only in lymphedema (OR 0.40 [0.17–0.94], p=0.035). Platelet reactivity (n=8–12 in each group) with a PAR1 agonist was augmented at concentrations 1–20 μM in both lipoedema and lymphedema vs. control, with a thromboxane receptor agonist at concentrations 0.1–10 μM in both lipoedema and lymphedema vs. control, with a P2Y12 receptor agonist at concentrations 0.01–10 μM in both lipoedema and especially in lymphedema vs. control and with a GPVI receptor agonist at 0.05–0.1 μg/mL only in lymphedema vs. control (P<0.01 in each case). Optical clot density by fibrin generation ex vivo was augmented in lipoedema (median 32924 a.u., p=0.0052) and lymphedema (median 32207 a.u., p=0.0053) vs. control (25303 a.u.). Thrombin generation was unaltered in either disease (n=19–23 in each group).

Conclusion Both lymphedema and lipoedema are associated with enhanced platelet reactivity and thrombosis, likely due to the inflammatory nature of these disorders. The clear thrombotic outcomes observed in lymphedema and lipo-lymphedema deserve immediate attention in clinical studies given our data suggesting platelet-mediated and non-platelet-mediated thrombosis. Mechanistic studies are underway to highlight additional interventional targets to abrogate thrombotic risk.

OXALATE DIET INDUCED CHRONIC KIDNEY DISEASE IN DAHL-SALT-SENSITIVE RATS INDUCES UREMIC CARDIOMYOPATHY

Introduction/Background Patients with chronic kidney disease (CKD) often develop a ‘uremic’ cardiomyopathy characterized by diastolic dysfunction, left ventricular hypertrophy, and cardiac remodeling, despite contemporary therapies of neurohormonal blockade. This cardiovascular disease is directly responsible for much of the extremely high morbidity and mortality seen in CKD. Development of physiologically relevant animal models of CKD which reflect this cardiovascular pathology is central to mechanistic studies aimed at combating the cardiovascular disease associated with CKD. Diet induced models of CKD may offer several advantages vs surgical models in terms of clinical relevance and animal welfare. Oxalate is a plant-derived, terminal toxic metabolite that is eliminated through glomerular filtration and renal tubular secretion. Increased dietary oxalate leads to supersaturation, calcium oxalate crystal formation, renal tubular obstruction and eventually CKD. Dahl-salt-sensitive rats (SS) are a common background strain used to study for hypertensive renal disease however characterization of other diet induced CKD models on this background would allow for comparative studies of CKD associated cardiovascular disease within the same strain.

Abstract 7 Figure 2  Mechanisms of thrombosis in patients with lipoedema and lymphedema. Fibrin generation in platelet-deplete plasma from subjects
Objective(s) Our objective was to identify and characterize a clinically relevant diet-induced rodent model of uremic cardiomyopathy. We hypothesized that SS rats fed a high oxalate diet will develop cardiac injury and dysfunction compared to SS rats fed a normal chow diet, thus serving as a novel rodent model to study the cardiovascular pathophysiology of CKD.

Results Ten-week-old male SS rats were fed either 0.2% salt normal chow (SS-NC) or 0.2% salt diet containing 0.67% sodium oxalate (SS-OX) for five weeks (n=6–8 group). SS-OX rats demonstrated increased 24-hour urinary protein excretion (97% vs SS-NC, p < 0.01) as well as significant elevations of plasma Cystatin C (135% vs SS-NC, p < 0.01). Furthermore, oxalate diet induced hypertension (23% increase in systolic blood pressure vs. SS-NC, p < 0.05) and renin-angiotensin-aldosterone system (RAAS) profile (via LC-MS/MS) demonstrated significant (p < 0.05) increases in circulating plasma angiotensin I (128% vs SS-NC) and angiotensin II (56% vs SS-NC) as well as suppression of the steroid aldosterone (-54% vs SS-NC). SS-OX also displayed increased cardiac tissue fibrosis (188% vs. SS-NC, p < 0.05) and cardiac inflammation as quantified by morphometric histological analysis (75% vs. SS-NC, p < 0.0001). We also observed an increased cardiac cell cross sectional area in cardiac tissue, indicating pathological cardiac hypertrophy in SS-OX (181% vs. SS-NC, p < 0.0001). Echocardiography of the SS-OX rats further showed an increased posterior wall thickness (128% vs. SS-NC, p < 0.01), increased septal wall thickness (113% vs. SS-NC, p < 0.05), and increased relative wall thickness, indicating left ventricular hypertrophy (124% vs. SS-NC, p < 0.05).

Conclusion Oxalate diet induces significant RAAS activation and hypertension accompanied by significant cardiac fibrosis, inflammation, left ventricular remodeling and hypertrophy, thus providing a novel diet-induced model to study the cardiovascular complications of CKD.

Abstracts

9 VENTRICULAR TACHYCARDIA IN A NORMAL HEART DURING CARDIAC STRESS TEST: SHOULD WE WATCH OUT FOR AN AT(TAC)K?
Pranav Pillai, Apurv Agarwal, Shengnan Zheng. University of Louisville

10 COVID-19 PATIENTS ON CARDIAC MEDICATION THERAPY AT A HIGHER RISK OF IN-HOSPITAL MYOCARDIAL INFARCTION, CARDIAC ARREST AND DEATH
Apurv Agarwal, Hunter Millet, Dipan Karnali, Marianna Weaver, Viral Desai, Hermann Frieboes, Sally Sülman, University of Louisville

Introduction/Background Ventricular tachycardia (VT) is an abnormal heart rhythm, characterized by wide QRS complexes (> 120 ms) with three or more consecutive beats at a rate faster than 100 beats per minute (bpm). There are different etiologies involved depending on whether it is sustained (lasts > 30 s, or terminated by an active intervention) or non-sustained (lasts for Here, we would like to present one such rare instance with sustained monomorphic VT induced by exercise in an otherwise healthy patient with no cardiac condition, and explore its clinical implications.

Objective(s) Understand the clinical significance of sustained monomorphic VT with no structural heart disease (induced by exercise).

Methods Reviewed electronic medical record to reconstruct the sequence of clinical events. Literature review searching for case reports and abstracts describing similar presentations

Results A 42-year-old male with history of hypertension, hyperlipidemia and gastroesophageal reflux disease presented with complaints of chest pain and dyspnea for the past two months. He has no significant prior cardiac history. Patient’s symptoms had resolved at the time of evaluation, and was scheduled for a radiotracer exercise stress test with Bruce protocol. At 7 minutes of exercise (stage 3 of Bruce protocol), patient had abrupt onset of sustained monomorphic VT on EKG, with his heart rate reaching 163. He immediately endorsed significant nausea, diaphoresis, and dyspnea. Patient appeared pale and was suddenly hypotensive, down to 68/35 mm Hg. Stress test was terminated and patient was sat down immediately. He converted back to normal sinus rhythm about 10 minutes later, prior to receiving other interventions. A coronary angiogram and transthoracic echocardiogram was performed during the same admission with completely normal results. He was discharged home with outpatient follow-up.

Conclusion Approximately 33% of individuals without significant cardiac abnormalities exhibit ventricular ectopy during exercise, usually as occasional uniform premature ventricular complexes (PVCs). However, VT is an extremely rare response to exercise especially in a healthy subject, hence the need to rule out coronary ischemia with angiography. The incidence of exercise-induced VT during stress test was 0.08 – 1.1% with 85% of these patients having some form of structural heart disease (most common being coronary artery disease). Although studies exist involving healthy individuals with exercise-induced VT who were followed for years to observe new symptoms or sudden cardiac death, there is not enough data for exercise-induced VT in younger healthy individuals and that may be a potential focus for research in the future.
independent of the presence or absence of cardiac agents. Risk ratios (RR) were found by unconditional maximum likelihood estimation (Wald). Results were considered significant if p≤0.05.

**Results** A total of 503 patients were reviewed with an average age of 50.1 years, 55.9% were Caucasian, and 54.9% were female (figure 1). Among them, 207 (41.1%) were on cardioprotective medications and further analyzed in our treatment group. Within the treatment group, 54.6% were on statins, 48.3% on beta-blockers, 48.3% on ACEIs/ARBs, and 41.6% were on aspirin. Additionally, the majority of patients (59.2%) were on a combination of ≥2 agents, with only 14% on ACEI/ARB in isolation, 10.1% taking just beta-blockers, 8.2% only on aspirin, and 8.2% on statins alone. The overall in-hospital mortality was 9.4% for all patients, and 16.4% for the treatment group. The RR for mortality was highest at 2.6 for statins (p<0.001, 95% CI: 1.9–3.7), 2.2 for aspirin (p=0.004, 95% CI: 1.4–3.6), 2.1 for beta-blockers (p=0.002, 95% CI: 1.4–3.3), and 2.1 for ACEIs/ARBs (p=0.003, CI: 1.4–3.2). The risk of mortality was also significantly elevated for patients on various drug combinations, as shown in the plot below (figure 2). Of note, older age was independently associated with a higher incidence of mortality (figure 3). The incidence of MI was 6.4% in all patients and 10.1% in the treatment group. Among patients who had MI, 51.3% were on a statin (RR:2.4, p< 0.001, 95% CI: 1.6–3.5). Notably, there was no association between MI and aspirin, beta-blockers, or ACEIs/ARBs. The overall incidence of cardiac arrest was 4.1% and was 6.7% in the treatment group. The highest association was found between cardiac arrest and the use of aspirin with a RR of 2.8 (p=0.005, 95% CI: 1.6–4.9). Similarly the RR for beta-blockers was 2.6, (p=0.004, 95% CI: 1.6–4.3), 2.4 for statins (p=0.004, 95% CI: 1.5–3.8), and 2.3 for ACEIs/ARBs (p=0.016, 95% CI: 1.3–4.0).

**Conclusion** Our study highlights several key points regarding the chronic use of cardioprotective medications in patients infected with COVID-19. Firstly, chronic use of statins was associated with an increased risk of MI and overall mortality, despite their well-documented anti-inflammatory effects. They were also associated with a high risk of cardiac arrest. In contrast, ACEI/ARBs appear to have the lowest risk of cardiac arrest and death and no association with MI. To our
knowledge, this is the first study to compare these agents and their associated risk of developing cardiac complications in those infected with COVID-19 and emphasizes the need for further research.

A TRIAD OF PERICARDITIS, PERICARDIAL EFFUSION AND PLEURAL EFFUSION AS THE PREDOMINANT PRESENTATION OF RHEUMATOID ARTHRITIS

Adam Devine, Michael Aljadah, Rebecca Weiner, Iryna Nemesh, Divyanshu Mohananey.
Medical College of Wisconsin

Introduction/Background Herein, we describe a case of a 67-year-old African American male who presented to the emergency department (ED) with a sharp, pleuritic chest pain and shortness of breath. After several admissions and extensive work up, he was ultimately diagnosed with a persistent pleural effusion, pericardial effusion, and secondary constrictive pericarditis due to Rheumatoid Arthritis (RA). We believe this is the first manuscript that demonstrates this triad of cardiopulmonary manifestations as a predominant presentation of RA in a patient with a prior diagnosis of non-erosive, seropositive RA lacking typical musculoskeletal features. By highlighting immunological disorders such as RA in the differential diagnosis, in the setting of a refractory pericardial effusion and serositis, this case report will address key aspects of the presentation both in the emergency and inpatient settings, review the criteria for a RA diagnosis, and emphasize areas of importance in predominantly cardiopulmonary extra-articular manifestations of a typically musculoskeletal disease.

Objective(s) A 67-year-old man with a significant past medical history for seropositive, non-erosive rheumatoid arthritis (RA), chronic obstructive pulmonary disease, paroxysmal atrial fibrillation, chronic kidney disease (CKD) stage 1, gastroesophageal reflux disease (GERD), esophageal dysmotility, and peptic ulcer disease (PUD) who presented to the ED with sharp, pleuritic chest pain and shortness of breath.

On his first admission, the evaluation for his first episode of chest pain revealed nonspecific ST-T wave changes on 12-lead electrocardiogram (ECG) and nondiagnostic elevations in high sensitivity troponin levels, which were attributed to poor renal clearance from his CKD. An initial transthoracic echocardiogram (TTE) was performed in the ED and was unremarkable. With a history of GERD, antacids were administered with partial improvement of his chest pain. Given the presenting history, unremarkable TTE, and cardiac biomarkers and ECG non-suggestive of ischemia, his chest pain was defined as non-cardiac. Further gastroesophageal workup revealed the etiology of his symptoms, as esophagram displayed esophageal dysmotility, intra-esophageal reflux, and poor clearance on marshmallow challenge. Patient was discharged with conservative GERD management.

He was admitted for the second time three days later for evaluation and management of persistent, sharp pleuritic chest pain, worsened when lying supine, and improved with leaning forward. He denied any recent trauma, cardiothoracic surgeries, radiation exposure, or myocardial infarctions. On examination, he was afebrile and without audible friction rub. ECG showed diffuse ST-elevations in anterior and inferior leads and PR depressions in leads II, III, AVF, V5, and V6, with concern for pericarditis (figure 1a). High-sensitivity troponin levels were elevated, but stable from previous admission. Posterior-anterior (PA) chest x-ray showed a small left sided pleural effusion (figure 2a). Repeat TTE depicted a new small, circumferential pericardial effusion measuring up to 7 mm in depth, without any echocardiographic indications of cardiac tamponade, and normal cardiac function. There was also a 20% respiratory phasic variation in the mitral valve inflow velocity (<25% considered normal). The pericardial effusion was further described on CT Angiogram of the chest with contrast (figure 2b, c). With pericarditis suspected, a detailed work up for the causes of pericarditis was pursued.

Rheumatological origins were then considered, as the c-reactive protein (CRP) was elevated at 7.4 mg/dL and erythrocyte sedimentation rate (ESR) was elevated at 78 mm/hr. There was low suspicion for infectious etiology as he was without leukocytosis and his blood, urine, and sputum cultures returned negative. Uremic pericarditis was ruled out with blood urea nitrogen (BUN) within normal limits. Medical record review revealed a positive rheumatoid factor (RF) of

Abstract 10 Figure 3  Plot showing association of increasing age with worse outcomes (p<0.01 for all outcomes)
Nonsteroidal anti-inflammatory drugs (NSAIDs), which are recommended in combination therapy for idiopathic pericarditis. He was treated with high dose aspirin and colchicine for pericarditis. Nonsteroidal anti-inflammatory drugs (NSAIDs), which are recommended in combination therapy for idiopathic pericarditis, were avoided due to patient’s history of PUD. Notwithstanding, the clinical signs of pericarditis, a pleural effusion, and a pericardial effusion, there remained concern of an underlying rheumatological disease, as the aforementioned cardiopulmonary and infectious workup was unrevealing thus far. As the patient was medically stable on aspirin and colchicine, his predischarge plan included continuing medical management for a four-week period.

In spite of outpatient treatment with colchicine and aspirin, the patient was admitted for a third time five days later for resolving persistent sharp, pleuritic chest pain and unresolving shortness of breath. ECG showed persistent, diffuse ST-elevations in anterior and inferior leads, with resolving PR depressions in leads II, III, AVF, and V6. Patient was also noted to be in atrial fibrillation with rapid ventricular response (figure 1b). TTE revealed small to moderate circumferential stable pericardial effusion, unchanged from prior study, but now notable for increased respiratory phasic variation in mitral valve inflow velocity to 35%, suggesting clinical correlation of constrictive pericarditis. The PA chest x-ray showed progression of the left sided pleural effusion (figure 2). A cardiac MRI demonstrated a clear demarcated circumferential rim of delayed enhancement in the pericardium consistent with pericarditis and free breathing sequences showing respirophasic septal shift (figure 2), consistent with constrictive pericarditis. Based on prior elevation of RF and CCP antibodies, now in the setting of constrictive pericarditis and poly-serositis, refractory to aspirin and colchicine, with elevated CRP and ESR, the impression of inpatient rheumatology team was that the patient’s pericarditis was secondary to new diagnosis of RA. There was no indication to repeat RF or CCP serologies, given his history of highly RA specific, positive high-titers. The patient was then started on prednisone 40 mg daily, in addition to aspirin and colchicine. After only two days, the patient reported significant improvement in symptoms. With clinical improvement on prednisone and a formal diagnosis of RA, pericardiection or pericardiotomy were indicated for consideration in treatment of constrictive pericarditis, but ultimately not pursued.

Unfortunately, the patient was admittedly non-adherent to the prescribed regimen and would again present to the ED with acute hypoxia respiratory failure. On initial evaluation he was afebrile, but now requiring 4L of supplemental oxygen. Arterial Blood Gas would show oxygen saturation of 89.1%, pH of 7.40, PaCO2 of 33 mmHg, and HCO3- of 20. ECG would show no ST-elevations or PR-depressions (figure 1c). CT Angiogram would show significant progression of the known left pleural effusion, with new development of potential areas of loculation and near-complete collapse of the left lower lobe. There was no evidence of interstitial lung disease. Based on these findings, infectious etiologies were thoroughly explored, yet workup with blood, urine, and sputum cultures were negative. Nucleic Acid Amplification Tests (NAAT) for Chlamydia pneumoniae, Legionella pneumoniae, and Mycoplasm pneumoniae were negative. Streptococcus pneumoniae antigen and viral respiratory panel were negative as well. Procalcitonin was within normal limits. A diagnostic and therapeutic thoracentesis with chest tube placement was then pursued, which would remove 1.4L. The pleural exudate would show 10,200 unit/liter WBC (ref: <1000 unit/liter), a LDH of 600 unit/L (ref: <50% serum concentration), glucose of 257 mg/dL (ref: 40–70 mg/dL), pH of 8.0 (ref: 7.6–7.64), and protein of 4.4 g/dL (ref: 1–2 g/dL). His serum total protein was 7.7 g/dL and LDH 2047 unit/L. The exudative effusion would be classified most probably secondary to RA. With infectious rule out, prednisone was restarted, and he would be continued an indefinite course of steroid therapy, with eventual transition to azathioprine, a steroid-sparing agent, in the future.

Methods RA is a systemic inflammatory disease primarily affecting joints. The clinical manifestations of RA are diverse, and depend on the pattern of joint involvement, degree of joint destruction, and level of functional impairment. The clinical diagnosis of RA is based on a composite of characteristic clinical symptoms and diagnostic evaluation. Even though RA is known to be primarily an articular disease, this patient illustrates that the extra articular manifestations pose formidable diagnostic challenges for clinicians and increased mortality for patients.

There are several aspects from a patient’s historical, physical, and laboratory standpoint that promote a clinician’s suspicion for RA, yet typically we follow the diagnostic criteria from the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) for a formal diagnosis for RA. The ACR/EULAR outlines criteria that must be met for diagnosis, the first of which is the presence of synovitis involving three or more joints for at least six weeks in duration. The more joints that are inflamed, especially in symmetric, small joint involvement, the higher likelihood RA is the underlying etiology. In addition to these clinical findings, laboratory assessment via serologies and inflammatory markers also are incorporated in the diagnostic algorithm, specifically: RF, anti-CCP antibody, ESR, and CRP. Lastly, all other etiologies of synovitis should be excluded.

Despite long standing, established guidelines to the diagnosis of RA, there are currently no diagnostic criteria for patients who present with predominant cardiopulmonary symptoms, as manifested in this case. Diagnostic criteria have yet to be fully developed for patients with primarily cardiopulmonary symptoms, suggesting that such predominant presentation may be due to the rarity of the presentation. Only four cases in the literature have reported pericarditis and pericardial effusions as predominant presentations of RA. In all four cases, the patients presented with substernal chest pain. In two of those cases, the patients eventually developed wrist and other joint pain within 3–6 months of the initial cardiac presentation requiring continued treatment. Typically RA manifests with musculoskeletal symptoms, or if not initially, will progress to evolve into an inflammatory arthritis. In
this case, the patient never objectively displayed signs of polyarthritis per physical exam or radiographic workup. Notwithstanding the predominant presentation, there is no evidence to suggest the treatment of RA should differ from typical predominant presentations. Disease modifying anti-rheumatic drugs (DMARDs) are considered first-line in the treatment of RA. Glucocorticoids can be used for symptom control and are often used as a bridge therapy to DMARDs during high disease activity.

Rheumatoid pleural effusions (RPE) typically affect 3–5% of patients with RA. Diagnosis of an RPE can be confirmed in an RA patient with a pleural fluid sample that will characteristically show a low pH (<7.2), low glucose level (<60 mg/dL), negative gram stain and culture of the fluid, and WBC elevated above 3,000 unit/liter. The exudative effusion from this patient exhibited a glucose of 257 mg/dL, pH of 8.0, and WBC count of 10,200 unit/liter. Thorough investigation of exudative etiologies was ruled out via laboratory analysis. Per extensive literature review, there is no other RPE documented to show a pH this alkalotic, alongside glucose and WBC count as elevated. However, for definitive diagnosis of RPE in patients who display no signs of arthritis, as in the case with this patient, a pleural biopsy must be completed. Although the etiology of the exudative effusion was not confirmed, clinical context suggests a high likelihood of an atypical RPE as a consequence of RA. This is supported by the lack of regression with steroids and actual improvement, and that the patient had no relapses after a DMARD was introduced, suggestive of underlying rheumatologic origin, specifically RA.

REFERENCES


Abstract 11 Figure 2 Chest X-Ray showing left-sided pleural effusion (a). CT angiogram of chest with contrast depicting pericardial effusion (b, c). Cardiac MRI demonstrating a clear demarcated circumferential rim of delayed enhancement in the pericardium (d)

SULFONYLUREA INDUCED VENTRICULAR ARRHYTHMIAS

Abdullah Ahmad, 1Majedah Alfuqara, 2Suha Khalaf. 1Englewood Hospital and Medical Center; 2Trinitas Regional Medical Center; 3University of Missouri School of Medicine

Introduction/Background Sulfonureas are widely used second-line medications for type 2 diabetes mellitus (T2DM). Ventricular arrhythmia (VA) is an under-recognized side effect of sulfonureas with an incidence rate of 3.6 per 1000 person/year. VAs range from asymptomatic ectopic ventricular beats to ventricular tachycardia/fibrillation. Resulting in severe hemodynamic compromise and sudden cardiac death (SCD).

Objective(s) A 65-year-old male with T2DM presented to the emergency department (ED) complaining of palpitations and
intermittent dizziness of three days. Initially, his heart rate was 70 bpm and appeared comfortable. Vital signs and basic laboratory evaluation were within the reference range. Blood glucose level was 120 mg/dl. A 12-lead electrocardiogram showed normal sinus rhythm with ventricular bigeminy. In the ED, he developed multiple short bursts of non-sustained monomorphic ventricular tachycardia lasting 10–20 seconds each, concurrent with severe palpitations and dizziness. Hence, admitted to cardiology wards.

A transthoracic echocardiogram was done, and the ejection fraction was (60%), no wall motion abnormalities or valvular pathologies were found. An echocardiogram-dobutamine stress test was negative for reversible ischemia. Electrolytes were within the reference range. He continued to have significant ventricular ectopy (>60% of all beats on day one of admission).

Medications’ review revealed the patient was started on glipizide 5 mg by his primary care physician five days before the presentation. The medication was stopped on admission. Symptoms improved and ventricular ectopy was 30% and < 10% on day two and three respectively. Patient discharged with a wearable 30-day event monitor. On follow-up, he was asymptomatic with < 1% ventricular ectopy.

Methods Sulfonylureas are used as add-on with metformin for initial management of DM. They are widely used for being effective, inexpensive, and tolerated. They work through adenosine triphosphate-sensitive potassium channels (KATP) located in the pancreatic β-cell membrane while extrapancreatic activity is not well defined, especially on arrhythmogenic risk. Ischemic preconditioning (IPC) is a ‘self-protective mechanism that allows the heart to minimize a potentially lethal ischemic insult’, which is mediated by KATP channels. Some Sulfonylureas can diminish or abolish IPC leading to larger infarct size in acute ischemia and delayed afterdepolarization-mediated arrhythmia by increasing intracellular calcium load. Other arrhythmogenic mechanisms includes inhibiting delayed rectifier potassium channel (IKr), which prolongs QT interval, myocardial chloride currents such as the cyclic adenosine monophosphate-activated chloride conductance (ICl, cAMP), or by causing hypoglycemia, which leads to QT prolongation and increase intracellular calcium concentration, which can be synergistically arrhythmogenic leading to VA, torsade de pointes, and SCA.

DM is a leading cause of cardiovascular complications, including VA and SCD. Clinicians should be aware of sulfonylureas side effects. Further retrospective and prospective studies should be done to identify the incidence and extent of VA in patients using sulfonylureas.

REFERENCE

FEMORAL ARTERY PSEUDOANEURYSM MASQUERADING AS CHRONIC ABDOMINAL PAIN
1Samira Shiraj, 2Peyman Naji. 1Essen Health Care; 2Lakewood General Hospital

Abstracts

10.1136/jim-2022-MW.13

Introduction/Background Latrogenic common femoral artery (CFA) pseudoaneurysm is an uncommon but serious complication after left heart catheterization (LHC) via femoral approach. Pseudoaneurysms carry the risk of expansion, bleeding, infection, thrombi formation and distal embolization. Diagnosis can be challenging especially if pseudoaneurysm is not thought about. Different treatment modalities exist with good success rates.

Objective(s) Patient was a 71-year-old female with known history of systemic hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease (CKD), and peripheral arterial disease. She had undergone high-risk coronary artery stenting with Impella support (from left CFA access) two weeks prior to presentation. Final angiography after the closure was unremarkable without evidence of bleeding. Patient was discharged home the next day but was complaining of persistent left groin pain post procedure with gradual worsening. She had been prescribed a course of antibiotics by her primary care physician with suspicion to diverticulitis without much relief and therefore presented to hospital again. Physical exam demonstrated low grade fever and left lower quadrant tenderness without evidence of groin hematoma or bruising. Lab studies showed mild leukocytosis. She was started on broad spectrum antibiotics. A CT abdomen/pelvis without contrast (given her CKD) was low yield and mentioned a possibility of abscess vs hematoma vs pseudoaneurysm without clear differentiation. Arterial duplex study was obtained with no evidence of any pseudoaneurysm. She was treated with broad spectrum antibiotics for another five days with no clinical improvement.

Given her persistent symptoms despite ongoing treatment and low diagnostic yield with multiple non-invasive modalities, decision was made to perform a peripheral angiogram for further evaluation of vascular complications. She was found to have a large 8x3 cm CFA pseudoaneurysm extending above the inguinal ligament to the pelvis. Due to extension above the inguinal ligament and lack of adequate visualization on previous ultrasound, she was not a candidate for ultrasound-based therapies. She was not a candidate for surgical repair either because of her recent high-risk PCI and need for dual antiplatelet therapy.

Therefore, decision was made for endovascular treatment of the pseudoaneurysm using covered stents which was successfully performed.

Methods Femoral artery pseudoaneurysm can happen in about 0.5% of patients after cardiac catheterization. A pseudoaneurysm is a contained cavity that remains in continuity with the artery by a neck and is therefore, pulsatile. Pseudoaneurysms can expand in size and cause pain by compression of adjacent nerves.

Pseudoaneurysms larger than 3 cm generally do not close spontaneously and need to be treated. Ultrasound-based techniques (compression of neck with or without procoagulant solution injection) are the most commonly used methods of treatment. Endovascular treatment with covered stents can be considered when ultrasound techniques are not feasible or fail. Covered stents are usually used to exclude the pseudoaneurysm from the circulation. Surgical repair is generally reserved for cases of infected pseudoaneurysm, significant pain due to local compression, and failure of other methods.

Access site complications remain a significant source of morbidity and mortality after percutaneous cardiac procedures. Physicians should be thoughtful of these complications in their differential diagnoses and should be familiar with different diagnostic and therapeutic steps for their management to prevent further complications.
A RARE CASE OF SYSTEMIC EMBOLISM OF LEFT ATRIAL APPENDAGE CLOT IN THE SETTING OF MITRAL STENOSIS WITHOUT ATRIAL FIBRILLATION

Samira Shiraj, Peyman Naji. Essen Health Care; Lakewood General Hospital

Introduction/Background
Formation and subsequent embolization of clot from left atrial appendage (LAA) is the underlying mechanism responsible for systemic thromboembolism in the setting of atrial fibrillation. We present an unusual case of clot embolization from LAA in the setting of mitral stenosis but without atrial fibrillation (AFib).

Objective(s)
A 67-year-old previously healthy female presented to hospital with sudden onset severe left flank pain. On CT scan of the abdomen she was found to have a segmental wedge-shaped area of nonenhancement in left kidney suggestive of renal infarct. Renal Duplex ultrasound showed normal renal arteries without stenosis or thrombosis. EKG and telemetry were showing sinus rhythm and no evidence of AFib.

Echocardiogram was obtained to investigate source of emboli and showed evidence of rheumatic heart disease. Mitral valve was heavily calcified with mean gradient of 14 mmHg consistent with severe mitral stenosis (MS). There was also mild mitral regurgitation and moderate aortic regurgitation present.

Transesophageal echocardiography (TEE) was performed and confirmed severe MS and also showed evidence of small clot present at the tip of the left atrial appendage. Patient was started on anticoagulation for prevention of further thromboembolism. Flank pain was treated with symptomatic management and pain control and patient was discharged. One month outpatient event monitoring did not show any evidence of atrial fibrillation. A repeat TEE a month later showed resolution of the clot from LAA. Patient then subsequently underwent balloon mitral valvuloplasty for treatment of mitral stenosis with significant improvement of the gradient to about 5 mmHg. After more than two years of follow up, her valvular disease has remained stable. She still has not had any evidence of atrial fibrillation. She has been kept on anticoagulation and has not had any more thromboembolism.

Methods
Systemic thromboembolism (particularly embolic stroke) is a feared complication of atrial fibrillation. Since the atria do not contract during AFib, the stasis of blood in the left atrium leads to clot formation.

The clot specifically forms within the left atrial appendage which is a small cavity with reduced blood flow. Mitral stenosis is also a notorious valvular condition for clot formation. MS causes pressure overload in left atrium and results in atrial remodeling and interstitial fibrosis which can predispose to in situ thrombosis formation. Presence of mitral regurgitation seems to have a protective effect against thrombus formation presumably due to constant washout and reduced stasis in the left atrium (our patient only had mild regurgitation). Combination of mitral stenosis and AFib can increase the risk of stroke by 17-fold. However, presence of LAA clot in the setting of pure MS and without AFib has been described much less frequently in the literature. About 5–10% of patients going for surgery for severe MS have LAA clot but vast majority of these patients have AFib at the same time. Patients such as our patient in whom the first manifestation of MS is with systemic thromboembolism in the absence of AFib are extremely rare. This case highlights the importance of proper management of the underlying condition to prevent long-term complications. It also underlines the importance of being familiar with abnormal cardiac sounds and murmurs which can lead to early diagnosis and proper management of significant underlying cardiac valvular disorders before they become symptomatic.

RESPIRATORY ACIDOSIS: AN UNUSUAL CASE OF TRANSIENT LEFT VENTRICULAR DYSFUNCTION

Alexander Shinn, Max Isaac, Mohammad Al Bataineh, Abdallah Mansour, Mary Dohrmann. University of Missouri Healthcare

Abstract 15 Figure 1–3

RESPIRATORY ACIDOSIS: AN UNUSUAL CASE OF TRANSIENT LEFT VENTRICULAR DYSFUNCTION

Alexander Shinn, Max Isaac, Mohammad Al Bataineh, Abdallah Mansour, Mary Dohrmann. University of Missouri Healthcare

Abstract 15 Figure 1–3
Introduction/Background Respiratory acidosis causing left ventricular dysfunction (LVD) has only been reported in animal studies. This case exemplifies a patient with transient LVD due to respiratory acidosis. 

Objective(s) A 57-year-old man with a history of atrial flutter, hypertension, and chronic obstructive pulmonary disease (COPD) presented to the emergency room with respiratory difficulties. Arterial blood gas showed respiratory acidosis with pH 7.09 and PCO2 135 mm Hg. ECG showed sinus rhythm without significant ST changes, and high-sensitivity troponin was negative. Transthoracic echocardiogram (TTE) showed mild global hypokinesis with a left ventricular ejection fraction (LVEF) of 45%. Hypercapnia and COPD were treated with mechanical ventilation, systemic steroids, and bronchodilators, which led to the resolution of respiratory acidosis. After two weeks, a repeat TTE showed improved LVD with LVEF 55%.

Methods The patient presented with severe respiratory acidosis and LVD. Although the TTE showed below normal LVEF, there were no clinical signs consistent with acute myocardial ischemia or other obvious cause of LVD. Decision was made to reassess the left ventricular function after resolution of respiratory acidosis without initiation of guideline directed medical therapy for heart failure.

This case represents a rare presentation of LVD secondary to respiratory acidosis. The severe acidosis likely caused disruption in calcium channels within the cardiomyocytes, resulting in impaired cardiac contractility. This case underscores the importance of considering unusual causes of acute LVD when there are no clinical signs of ischemia.
emergently to the cardiac catheterization lab to drain the pericardial effusion.

This case is an unusual development of pericardial effusion in a healthy man after receiving his first dose of the COVID-19 vaccine. The case highlights the importance of diagnosing cardiac tamponade with echocardiography and promptly addressing adverse reactions after COVID-19 vaccine administration.

1. **Penbrolizumab Induced Myocarditis: A Rare Fatal Multisystem Immune Related Toxicity**

Abdullah Ahmad, Mahmoud Abdelhadi, Musaab Alfaki, Doo Woong Choi, Jason Lofflers, Sofia Tener, Coral Parikh, Maxwell Janosky, Englewood Hospital and Medical Center

10.1136/jim-2022-MW.17

**Introduction/Background** Immune checkpoint inhibitors (ICPi) such as Pembrolizumab, an anti-programmed cell death-1 (PD-1) antibody, have been used for cancer treatment, which can lead to uncommon fatal side effects including myocarditis. This case aims to recognize the variety of presentations of PD-1 inhibitor induced immune related adverse events (irAEs) and to focus on their management.

**Objective(s)** Patient is an 85-year-old female with a seven-month history of vaginal squamous cell carcinoma. She was treated initially with chemoradiation but had progression of disease requiring initiation of Pembrolizumab. One month after her first dose she presented with one day of myalgias, fatigue, shortness of breath and chest pain. Her examination was unremarkable, but labs were significant for troponin I of 2.5 ng/mL, CK of 6000 U/L, ALT 536, AST 501, positive anti-smooth muscle antibody (1:80 titer) with negative ANA, antimitochondrial antibodies and acute hepatitis panel.

EKG showed ST segment elevations in leads V4-V6 prompting urgent cardiac catheterization, which revealed no significant occlusions. Echocardiogram revealed normal sized cardiac chambers with preserved biventricular systolic function but with basal inferior and inferoseptal akinesis without apical ballooning, not suggestive of Takatsubo cardiomyopathy.

Given the constellation of findings she was assessed as having immunotherapy related myocarditis, myositis and hepatitis. She was started on IV methylprednisolone and had gradual decrease in her CK, AST and ALT. Her troponin I peaked at 1.80 titer with negative ANA, antimitochondrial antibodies and acute hepatitis panel.

Methods Pembrolizumab is an ICPi that inhibits PD-1 activity. This results in T-cell inactivation which augments immune reaction against cancer cells. If this immune reaction affects host cells, this may result in one of several irAEs. While any organ system may be involved, the most common are skin, gastrointestinal, and endocrine systems.

In one cohort study of 623 patients with non-small cell lung cancer treated with ICPis, only 9% developed multisystem irAEs. Most of these patients had two irAEs with pneumonitis-thyroiditis, hepatitis-thyroiditis and dermatitis-pneumonitis being the most common patterns in a median time of 3.25 months. In a case series of 38 cases, the co-occurrence of myocarditis and myositis was documented in 32% of cases. In our case irAEs involved myocarditis, myositis and hepatitis. Previous studies, interestingly, have suggested that multisystem irAEs are associated with improved median progression-free and overall survival.

Physicians should be aware of irAEs as a potential complication of ICPi use given the ever-expanding indications for their use. Rarely multiple systems may be involved at the same time. This variability leads to multiple potential presentations and thus, clinicians should remain vigilant to consider this diagnosis.

**References**


Dermatology

18 BCG Vaccination in Early Childhood and Risk of Allergic Disease: Systematic Review and Meta-Analysis

Keyu Zhao, 2Chao Cao, 2Rechard Hubbard, 1Xinyu Jiang, 1Wei Lin, 3Phoebe Miles, 1Suling Xu, 1Gongyan Zhou, 4Fanfeng Fu. 1Department of Dermatology, The Affiliated Hospital of Medical School, Ningbo University; 2Division of Epidemiology and Public Health, University of Nottingham; 3Division of Humanities and Social Sciences, University of Nottingham, Ningbo; 4The Center of Medical Research, The Affiliated Hospital of Medical School, Ningbo University

10.1136/jim-2022-MW.18

Introduction/Background Several large-scale studies suggest that Bacille Calmette-Guerin (BCG) vaccination in early childhood and hepatitis. Previous studies, interestingly, have suggested that multisystem irAEs are associated with improved median progression-free and overall survival.

Physicians should be aware of irAEs as a potential complication of ICPi use given the ever-expanding indications for their use. Rarely multiple systems may be involved at the same time. This variability leads to multiple potential presentations and thus, clinicians should remain vigilant to consider this diagnosis.

**REFERENCES**


may reduce the risk of atopic diseases, but the findings remain controversial.

**Objective(s)** We aimed to investigate the potential correlation between early childhood BCG vaccination and the risk of developing atopic diseases.

**Methods** Eligible studies published on PubMed, EMBASE, and Cochrane CENTRAL were systematically sourced from 1950 to July 2021. Studies with over 100 participants and focusing on the association between BCG vaccine and atopic diseases including eczema, asthma, and rhinitis were included. Preliminary assessment of methods, interventions, outcomes, and study quality was performed by two independent investigators. Odds ratio (OR) with 95% confidence interval (CI) was calculated. Random effects of the meta-analysis were performed to define pooled estimates of the effects.

**Results** Twenty studies with a total of 222,928 participants were selected. The quantitative analysis revealed that administering BCG vaccine in early childhood reduced the risk of developing asthma significantly (OR 0.77, 95% CI 0.63 to 0.93), indicating a protective efficacy of 23% against asthma development among vaccinated children. However, early administration of BCG vaccine did not significantly reduce the risk of developing eczema (OR 0.94, 95% CI 0.76 to 1.16) and rhinitis (OR 0.99, 95% CI 0.81 to 1.21). Further analysis revealed that the effect of BCG vaccination on asthma prevalence...
Abstract 18 Figure 3  Forest plot of the association between BCG vaccination and asthma. Random effects model forest plot shows ORs and 95% CIs for the association between BCG vaccination and asthma. OR = 0.73, 95% CI 0.58 to 0.92. M-H = Mantel-Haenszel; OR = odds ratio; CI = confidence interval

Abstract 18 Figure 4  Forest plot of the association between BCG vaccination and rhinitis. Random effects model forest plot shows ORs and 95% CIs of the association between BCG vaccination and rhinitis. OR = 0.99, 95% CI 0.81 to 1.21. M-H = Mantel-Haenszel; OR = odds ratio; CI = confidence interval
was significant especially in developed countries (OR 0.73, 95% CI 0.58 to 0.92).

Conclusion BCG vaccination in early childhood is associated with reduced risk of atopic disease, especially in developed countries.

**Abstract 18 Figure 5** Forest plot of the association between BCG vaccination and eczema. Random effects model forest plot shows ORs and 95% CIs for the association between BCG vaccination and eczema. OR = 1.09, 95% CI 0.60 to 1.96. M-H = Mantel-Haenszel; OR = odds ratio; CI = confidence interval

---

**19 EVALUATING THE ROLE OF DIFFERENT TYPES OF LASER THERAPY IN BECKERS NEVUS TREATMENT**

Prabhatchandra Dube, Muhammad Albakaa, Muhsin Aldhalimi, Fatimah Khalaf. University of Toledo; University of Jibril ibn Hayyan; University of Kufa; University of Alkafeel

**Introduction/Background** Becker’s nevus (BN) is a cutaneous hamartoma of benign nature that develops through adolescence and affects mostly young men. The nevus is usually located unilaterally and characterized by hypertrichosis and hyperpigmentation. Despite recent advances in treatment modalities, no effective treatment has been established for BN hyperpigmentation.

**Objective(s)** We sought to assess efficacy and safety of Fractional Erbium: YAG 2940 nm and Q-switched Nd:YAG 1064 nm lasers in the treatment of BN hyperpigmentation.

**Methods** Twenty-three patients with BN were included in a prospective randomized controlled, observer-blinded, split-lesion comparative technique trial. In each patient, two similar square test regions were randomized to either treated with fractional Erbium: YAG 2940 nm laser or with Q-switched Nd: YAG 1064 nm laser. Each patient treated with three sessions at six weeks interval. At six-month follow-up, clearance of hyperpigmentation was assessed by physician global assessment, reflectance spectroscopy, melanin index, patient global assessment, and patient satisfaction.

**Results**

Regions treated with Fractional Erbium YAG 2940 nm laser demonstrated significantly better improvement as compared to ones treated with Q-switched Nd:YAG 1064 nm (P-value=0.001). Adverse effects such as re-pigmentation and hypertrophic scarring were not reported during the follow-up period. Although mild hypopigmentation was observed in some patients, the outcomes were cosmetically acceptable with overall high satisfaction among included patients.

**Conclusion** Our data suggests superior role for the fractional Erbium:YAG (2940 nm) laser in the treatment of BN hyperpigmentation compared to the Q-switched Nd:YAG (1064 nm) laser with both being equally safe and having no reported side effects.

---

**20 PAINFUL SKIN LESIONS IN PATIENT WITH MYELODYSPLASTIC SYNDROME**

Mohammad Al Bataineh, Suha Khalaf, Baraa Saad, Taylor Nelson. University of Missouri Health Care

**Introduction/Background** Although myelodysplastic syndrome (MDS) typically presents with abnormal peripheral blood counts, it can be accompanied with atypical presentations, such as neutrophilic dermatoses (like Sweet’s disease, or pyoderma gangrenosum (PG)). Nodular skin lesions in immunocompromised patients can be secondary to various etiologies. Maintaining a broad differential diagnosis and a low suspicion index for such atypical presentations in immunocompromised patients is crucial for earlier diagnosis, treatment and better outcomes.

**Objective(s)** A 59-year-old female presents complaining of painful skin lesions on her bilateral upper extremities for four...
months (figure 1). Medical history includes MDS treated with Ruloxitinib, cutaneous sarcoidosis (previously on infliximab and chronic antibiotics), and hidradenitis suppurativa. Five months before admission, Ruloxitinib was stopped due to plans for dental extraction.

On presentation, the patient was febrile with a temperature of 40°C, tachycardic with a heart rate of 110 beat/minute, hypotensive (blood pressure 70 mm Hg/40 mm Hg). The examination of the upper extremities revealed several dark, non-blanching and extremely tender skin nodules. Treatment was started with intravenous hydration and empiric broad spectrum antibiotics (Meropenem and Vancomycin) to treat possible septic shock.

Laboratory workup was significant for severe pancytopenia (absolute neutrophil count of 340, hemoglobin of 5.2 g/dl, and platelets of 43 platelets/microL). Lactic acid and cortisol were within normal range. The chest radiograph was also unremarkable. Dermatological consultation was conducted, and a skin biopsy was negative for periodic acid Schiff for fungus (PASF), Fite and Gorgot methenamine silver (GMS) stains. However, given the high suspicion for fungal skin infection and secondary fungemia; the patient was started on daily Amphotericin B liposomal 5 mg/kg and twice-daily voriconazole 200 mg. Nevertheless, lesions continued to involve all extremities, trunk and face. All cultures, including regular and fungal, remained negative. The PCR of the skin lesions was positive for three different species of Pseudochrobactrum. However, it was not considered clinically significant. The patient’s condition continued to deteriorate and required several vaspressors to treat her septic shock. Her mental and respiratory status continued to decline until the patient had to be intubated despite antibiotics and antifungal treatments. Her skin condition evolved into hemorrhagic bullae (figure 2) that broke down to cribriform appearing ulcers (figure 3) which prompted a second skin biopsy, which revealed bullous pyoderma gangrenosum, for which the patient was started on prednisone 60 mg daily. Unfortunately, the patient’s condition was advanced with multiple organ failures. The family decided to stop further life-saving measures and take comfort measures. The patient died shortly after extubation.

Methods Our patient was on Ruloxitinib, a JAK (Janus kinase) inhibitor used to treat MDS and is also used to treat PG. Stopping Ruloxitinib five months before presentation possibly caused a flare up of her PG. The patient’s presentation was concerning for Sweet syndrome, PG or fungal infections. Despite extensive antifungal and antibacterial coverage, she continued to have breakthrough skin lesions, increasing suspicion of non-infectious etiologies. Skin lesions PCR positive for pseudochrobactrum was deemed to have no clinical significance. The pathophysiology that underlies PG is not well understood, but a well-described theory is neutrophil dysfunction. It is a rare inflammatory and ulcerative skin disorder characterized by the accumulation of neutrophils in the skin. Skin biopsies in PG are not usually diagnostic; the diagnosis is mainly based on clinical criteria. For patients with progressively worsening PG, systemic treatment with steroids or more powerful immunosuppressants is indicated.
Abstracts

Educational/outcome research

21 FIELD OF SURGERY INCISION AND ENTRY TECHNIQUE ANALYSIS AMONG ORTHOPEDIC SURGEONS PERFORMING TOTAL KNEE ARTHROPLASTY

1Fahad Qureshi, 2Sum Singh, 3Aanya Ramprasad, 4Daniel Derylo, 5Raza Khan. 1University of Missouri School of Medicine; 2University of Missouri at Kansas City School of Medicine; 3Loyola University; 5AMITA

10.1136/jim-2022-MW.21

Introduction/Background The technique utilized for opening the field of surgery in knee arthroplasties has a few acceptable variations within the realm of reason. Though these have been subcategorized in the literature into numerous categories, for the sake of simplicity, we chose to focus on the medial, central, and lateral approaches. Based on earlier research, we knew that orthopedic surgeons tended to have a strong preference for one of the techniques, based primarily on residency mentor training.

Objective(s) We aimed to investigate whether or not one technique was superior in terms of reducing rates of infection.

Methods We contacted 99 orthopedic surgeons for a brief survey asking their entry preference style over the last 12 months. We allowed supplemental descriptive information regarding clarification of the entry styles as we determined. Graphics were utilized to maximize understanding of our location of entry. We enjoyed a high response rate (89%) n=88 with the results illustrated below. These results were compared with infection rates stratified into above or below the national median infection rate of knee arthroplasties, to enable statistical analyses.

Results In terms of the medial approach, seven surgeons reported this technique with five having a lower than average risk of infection and two with a higher than average risk of infection. In terms of the central approach, 25 surgeons reported this technique with 10 having a lower than average risk of infection and 15 with a higher than average risk of infection. In terms of the lateral approach, 67 surgeons reported this technique with 29 having a lower than average risk of infection and 38 having a higher than average risk of infection.

Conclusion All respondents were able to select their style of surgery within our three categories. We found that there was a significant preference to perform the lateral technique which was statistically significant (p < 0.05). We propose that this may be because there are more right-handed surgeons, and right-handed surgeons may prefer the inherently decreased distance offered by the lateral approach. We observed variation between the infection rates between the three categories, however, these results were not statistically significant. We determine not to reject the null hypothesis regarding the potential of superiority among one of the techniques. Future studies are required to increase power and thereby confirm the results established here.

22 PHARMACY STUDENTS’ ATTITUDE TOWARDS OPIOID ABUSE CRISIS

Noopur Walia. Rosalind Franklin University of Medicine and Science

10.1136/jim-2022-MW.22

Introduction/Background In 2017, the U.S. federal government declared the opioid epidemic a national emergency. 70,630 people died from drug overdose and 10.1 million people misused prescription opioids. The total economic impact of opioid overdose during 2017 was $1,021 billion. Opioid abuse has a direct relationship with age, race, income level, education level, and geographic location. The opioid crisis is a challenge to the U.S. healthcare system requiring close coordination amongst government agencies, community organizations, local health departments, and various healthcare professionals. Several states provide pharmacists the authority to dispense and counsel on naloxone, but most pharmacy schools provide little to no training in opioid management for students as a part of their curriculum.

Objective(s) This study aimed to assess the attitude of pharmacy students towards the opioid abuse crisis.

Methods The study was conducted among pharmacy students enrolled at Rosalind Franklin University of Medicine & Science (RFUMS).

Methods A prospective and anonymous one-time Qualtrics® survey accompanied by an informed consent was distributed to pharmacy students at RFUMS. A total of 162 students (81%) completed the survey out of 200 students enrolled in the College of Pharmacy. The survey consisted of demographic and opinion-based questions and was tested for readability, ambiguity, and reliability by using test-retest and Cronbach’s alpha methods. The collected data was coded, verified for data integrity, and analyzed by utilizing Statistical Package for Social Sciences (SPSS®) program for descriptive methods and Chi-square. The study was approved by the RFUMS institutional review board (IRB).

Results Students’ attitudes varied by demographics, and most students were not prepared to manage opioid abuse situations. There was a significant difference amongst various age groups. Ages 20–22 appeared to be the most unprepared in injecting naloxone and managing an overdose situation. P3 and P4 students were marginally more comfortable with identifying and managing an opioid crisis than P1 and P2 students. Both genders of all age groups and races favored proper training for pharmacy staff. Asian and White students were more familiar with the role of a pharmacist and with managing an opioid crisis as compared to the other race groups. Almost all the students indicated that they were inadequately prepared for managing overdose situations and favored more training and certification. Students who had experienced opioid abuse in their family, friends, and acquaintances were more familiar with the role of a pharmacist.

Conclusion Student opinions differed significantly based on gender, race, pharmacy school year, and age. Most pharmacy
students felt they were not skilled enough to manage overdose situations and administer/counseling naloxone. Further research is needed to explicitly address the appropriate level, timings, and approach of opioid abuse management in the curriculum.

Endocrinology/Metabolism

SEL1L-HRD1 ENDOPLASMIC RETICULUM-ASSOCIATED DEGRADATION IS REQUIRED TO MAINTAIN PANCREATIC ISLET αLPHA CELL MASS AND FUNCTION

Rachel Reinert. University of Michigan

Introduction/Background Professional secretory cells rely on endoplasmic reticulum (ER) homeostasis for efficient protein synthesis and folding. Endoplasmic reticulum-associated degradation (ERAD) is a key protein quality control mechanism that helps maintain ER proteostasis. Two highly conserved proteins comprise the core ERAD machinery: Hrd1, a ubiquitin ligase retrotranslocon that sends misfolded ER proteins for proteasomal degradation, and Sel1L, an adaptor protein required for Hrd1 stability and function. We previously showed that Sel1L-Hrd1 ERAD is required for maintaining cellular identity and insulin production in islet beta cells, thus protecting against diabetes. Islet α cells, which make the counterregulatory hormone glucagon, also have a high burden for protein synthesis – but the mechanisms that define ER proteostasis in α cells have been unexplored.

Objective(s) We sought to define the role of ERAD in islet α cell identity, function, and survival.

Methods To investigate the role of ERAD in islet α cells, we targeted deletion of Sel1L with the Cre-lox system, using mice that express Cre recombinase under the endogenous proglucagon promoter (Sel1L<sup>D</sup>Gcg mice). Glucose metabolism was assessed with oral glucose tolerance testing. Glucagon secretion in vivo was measured after prolonged fasting or administration of insulin to induce hypoglycemia. Islet morphology was evaluated by confocal and electron microscopy. Additionally, we generated a cell culture model using CRISPR-mediated inactivation of Sel1L or Hrd1 in αTC1–6 cells (ΔSel1L and ΔHrd1) and evaluated ER signaling pathways by Western blot.

Results Both male and female Sel1L<sup>D</sup>Gcg mice showed normal growth and glucose homeostasis; however, glucagon secretion in vivo declined with age. This was accompanied by a 43.4% reduction in pancreatic glucagon content and a similar reduction in α cell mass in adult Sel1L<sup>D</sup>Gcg mice. By immunofluorescence, pancreatic islet morphology was normal in Sel1L<sup>D</sup>Gcg mice, though α cells showed increased expression of the ER chaperone BiP and ERAD-associated proteins Os9 and XTP3-B, reflecting disrupted ER homeostasis. By transmission electron microscopy, α cells from Sel1L<sup>D</sup>Gcg mice showed ER dilution, with some cells showing fewer glucagon granules. Both ΔSel1L and ΔHrd1 cell lines showed increased expression of PERK, phosphorylated eIF2α, and IRE1α, in addition to increased Xbp1 splicing, reflecting activation of the unfolded protein response in ERAD-deficient α cells.

Conclusion Collectively, these data demonstrate that Sel1L-Hrd1 ERAD is required for ER proteostasis in α cells, thus serving as a principal mechanism for maintaining a fully functional α cell population. This work provides insights into fundamental processes of islet α cells, which ultimately will help in the pursuit for new therapeutic approaches for management of dysglycemia in diabetes.

METABOLIC AND MOLECULAR RESPONSE TO CALORIE RESTRICTION IS HIGHLY DEPENDENT ON TEMPORAL CONDITIONS

Heidi Pak, Cara Green, Rachel Sanderfoot, Mikaela Koller, Dudley Lamming. University of Wisconsin-Madison

Introduction/Background Calorie restriction (CR), defined as a diet low in calories without malnutrition, robustly prevents or delays age-associated diseases and extends lifespan in organisms including mice. Despite a century of study, the mechanism by which CR promotes health and longevity is still unknown. Current prevailing model of CR is reduced nutrient responsive pathways – insulin signaling and the activity of mTOR Complex 1 (mTORC1), a protein kinase that is a key regulator of metabolism. Genetic and pharmacological inhibition of the mTORC1 signaling pathway extends lifespan, and studies in model organisms suggest an epistatic interaction, suggesting a key role for mTORC1 in the response to CR. However, studies have found that CR and mTORC1 inhibition have distinct effects on the transcriptome and metabolome of tissues, and the interaction of CR and reduced mTORC1 signaling on metabolism, health, and longevity have not been formally investigated in mammals. In fact, due to their very different feeding patterns, it is not even clear that CR-fed animals have a reduction in mTORC1 signaling relative to ad libitum (AL) controls. CR-fed mice consume their entire allotment of food within a period of ~2 hrs, and then fast for the remainder of the day. This is in sharp contrast to the normal food consumption pattern of a mouse, in which 60–80% of calories are typically consumed in several feeding bouts during the dark cycle.

Objective(s) We comprehensively determined the physiological and molecular response to fasting every four hours during a 24-hour-cycle in ad libitum-fed and calorie restricted mice.

Methods We randomized male and female C57BL/6J mice to one of the following diets starting at nine weeks of age: AL (ad libitum) and CR (30% restricted, fed once-a-day in the morning or night). These mice were randomized to eight mice per fasting group within each diet which allowed us to measure physiological and molecular response to fasting duration.

Results We discovered that the most widely conserved effect of CR in mammals – increased insulin sensitivity – is only observed at certain times relative to the last feeding. CR animals have increased insulin sensitivity 16–24 hrs following their last meal, but they exhibited insulin resistance (tested with insulin tolerance test) relative to ad libitum (AL) control mice when tested 4–12 hrs after their last meal. mTORC1 activity is a critical regulator of insulin sensitivity through S6K1 mediated feedback inhibition of insulin receptor substrate. Therefore, we hypothesized that insulin sensitivity may be the result of negative feedback regulation of mTORC1 on insulin action. However, when examining
mTORC1 activity, we found that hepatic and skeletal muscle mTORC1 activity was decreased at the same level in both AL and CR mice only after a four-hour fast. This suggest that mTORC1 activity is highly dependent on fed/fasting conditions, and that mTOR activity is essentially diminished in CR fed animals (as CR mice are fasted for about 22 hrs), while AL fed animals have a consistent level of mTORC1 activity throughout the day (as AL mice are feeding throughout the day). Additionally, this insulin resistance was not reflective of glucose tolerance, which was improved regardless of fasting duration. Interestingly, insulin levels appeared to be dependent on the time of first feeding, suggesting that insulin secretion and/or clearance is heavily dependent on peripheral circadian controls.

Conclusion These results reveal that the length of time that has elapsed between feeding and the time at which it is examined has profound implications not only for metabolic phenotypes, but for understanding and identifying the molecular processes that drive the effects of a CR diet.

25 GENOTYPE-PHENOTYPE CORRELATIONS IN SUBJECTS WITH HNF1B ASSOCIATED DIABETES

Maria Salguero Bermonth, Rochelle Naylor, Louis Philipson, University of Chicago Hospitals

Introduction/Background Heterozygous mutations in the HNF1B gene are a rare cause of monogenic diabetes and affect multiple organs with variable expressivity. Studies have failed to show correlation between genotype and phenotype. Most affected individuals are treated with insulin, and there have been few studies of gene-targeted therapy. It is unclear if diabetes severity and treatment response may be impacted either by genotype or phenotype.

Objective(s) We aimed to assess genotype or phenotype correlations either by genotype or phenotype. diabetes severity and treatment response may be impacted regardless of fasting duration. Interestingly, insulin levels appeared to be dependent on the time of first feeding, suggesting that insulin secretion and/or clearance is heavily dependent on peripheral circadian controls.

Conclusion These results reveal that the length of time that has elapsed between feeding and the time at which it is examined has profound implications not only for metabolic phenotypes, but for understanding and identifying the molecular processes that drive the effects of a CR diet.

26 THE ROLE OF ADIPOCYTE-DERIVED EXTRACELLULAR VESICLES IN DIABETES-ASSOCIATED ENDOTHELIAL DYSFUNCTION

Abeer Mahmoud, Mohamed Ali, Imaduddin Mirza, Francesco Bianco, Chandra Hassan, Mario Masiur, University of Illinois at Chicago

Introduction/Background The development of type 2 diabetes (T2D) is strongly associated with obesity, and both are well-established risk factors for cardiovascular disease. Endothelial dysfunction is an early event in developing vascular complications in obese diabetic (OB-T2D) adults. Therefore, our long-term goal is to identify endothelial dysfunction mechanisms in this population, mainly those related to the multifaceted crosstalk between dysfunctional adipocytes and endothelial cells. Our recent findings revealed that ex vivo cultured human adipose tissues (AT) release extracellular vesicles (EVs) that are efficiently captured by endothelial cells. These EVs are lipid-enclosed structures that carry bioactive cargos and are considered vital mediators of intercellular communication. Adipocyte-derived EVs (adiposomes) mediate signaling between cell types within the AT and circulate in the blood to communicate signals to remote cells and tissues. Altered lipid metabolism and enhanced ceramide synthesis in OB-T2D induce adiposome production. Under hyperglycemia, ceramides could be glycosylated into glycosphingolipids (GSLs), selectively packed in adiposomes to be cleared away from adipocytes.

Objective(s) The purpose of this study is to investigate the role of adiposomes and their GSL cargo in communicating the unhealthy milieu of dysfunctional AT to endothelial cells in OB-T2D. We hypothesize that the AT from OB-T2D patients creates excess GSL-rich adiposomes, which are incorporated into endothelial cells causing alterations in endothelial cell surface properties and function.

Methods To test this hypothesis, AT samples were collected from OB-T2D and non-OB subjects (n=10, each). Nanoparticle analysis and confocal microscopy were used to analyze these adiposomes, and mass spectrometry and Western blotting techniques were used to examine their content. Adiposome uptake, lipid fusion, and changes in endothelial membrane structure and signaling pathways were also assessed following adiposome incubation with microvascular endothelial cells.

Results In comparison to non-obese controls, adiposomes isolated from OB-T2D adipose tissues were more abundant and contained higher amounts of GSLs. When added to cultured endothelial cells, GSL-rich adiposomes tended to accumulate in an endothelial structure known as caveolae. These caveolae cover more than 50% of the endothelial cell surface and serve to concentrate signal transduction molecules such as endothelial nitric oxide synthase (eNOS) and others involved in angiogenesis, transcytosis, and permeability. According to our findings, the phosphorylation of the key caveolar protein caveolin-1 by GSL-rich adiposomes caused caveolar fission from the endothelial cell surface. This effect was mediated via activation of Src kinase, as it was inhibited by the Src kinase inhibitor, PP2. These molecular events were accompanied by reductions in eNOS activation and nitric oxide production, disturbances in endothelial gap junction, and increased endothelial permeability.
Conclusions: We concluded that dysfunctional AT in OB-T2D patients produce excess GSL-loaded adiposomes that fuse with endothelial cells and activate the Src kinase/caveolin-1 pathway resulting in caveolar fission, loss of eNOS activity, and eventually endothelial cell dysfunction.

Introduction/Background: Approximately 70% of Americans are overweight or obese, leading to an increased risk of developing many age-associated diseases, including cancer, cardiovascular disease, Alzheimer’s disease, and diabetes. While many individuals have attempted to lose weight by dieting, long-term success at keeping the weight off is low. As a consequence, overweight and obese individuals have experienced ‘yo-yo dieting’, in which periods of high and low compliances with dietary interventions result in severe fluctuations, or cycling, in bodyweight. Little is known about the long-term consequences of short-term periods of dieting and reduced weight. Low protein diets are associated with improved health and reduced risk of diabetes and death, which can be recapitulated by a 67% restriction of dietary branched-chain amino acids (BCAAs; i.e. leucine, isoleucine and valine). The Lamming lab has previously shown that three weeks of BCAA restriction (BCAA-R) normalized body composition, improved glucose homeostasis and increased energy expenditure in diet-induced obese (DIO) mice. However, it has not been established if there is a persistence of the changes induced by exposure to BCAA-R, nor examined the effects of multiple cycles of BCAA-R exposure.

Objective(s): We investigated the persistent effects of short-term BCAA-R in the context of obesity once the diet was abandoned.

Methods: We investigated the long-term consequences of dieting in a DIO mouse model in which we placed six-week-old C57BL/6J male mice on a high-fat, high-sucrose Western diet (WD). With the use of a modified ‘yo-yo’ dietary schedule that contains long weight gain periods and short weight loss periods, WD is provided over a 12-week period to induce obesity, after which the animals are fed a cycle of BCAA-R over a three-week period and WD again over 12 weeks. During each cycle of dieting, metabolic phenotyping was performed prior to sacrifice and tissue collection.

Results: After a single cycle, short-term BCAA-R improved metabolic health by rapidly normalizing body weight and body composition, improving glucose tolerance and insulin sensitivity, and increasing energy expenditure, which was accompanied by the induction of the energy balance regulating hormone fibroblast growth factor 21 (FGF21), recapitulating previous findings from the Lamming lab. Critically, once cycling back to WD, animals previously fed BCAA-R demonstrated a persistent increase in energy expenditure and decreased lipid droplet size as well as a significantly lowered fasting blood glucose level at a 16-hour fast and slightly improved glucose tolerance.

Conclusion: These findings show that short-term dietary interventions confer lasting effects on metabolic health. This suggests that short-term BCAA restriction could be a translatable strategy for long-term improvements to metabolic health and could potentially reduce the risk of developing age-related diseases.

Introduction/Background: Protein restriction diets have anti-aging properties in addition to its tremendous implications in ameliorating diseases associated with metabolic symptoms, such as obesity and diabetes. We have shown that the restriction of the branch-chained amino acid isoleucine is an integral part of protein restriction’s robust effects. Critically, mice fed a lifelong isoleucine restriction diet from a young age enjoy lifespan extension and delayed onset of frailty parameters. To further characterize the anti-aging benefits isoleucine restriction in a more translational context, this present study begins the dietary intervention in mice at an advanced age.

Objective(s): To further understand the effect of isoleucine restriction in late-life, we begin characterizing aged mice fed a 1/3 isoleucine diet starting at 20 months of age in both males and females.

Methods: At 20 months of age, both male and female C57BL/6J mice were placed on a restricted isoleucine diet (1/3 ile). The animals were monitored for several physiological parameters over three months. Tests for metabolic health were carried out. At the end of the study, mice undergo echocardiogram to evaluate for cardiac conditions.

Results: We were able to fully recapitulate the metabolic benefits of isoleucine restriction previously seen in young mice. While isoleucine restriction increased energy expenditure and improved glycemic control, it also induced a significant remodeling of cardiac function in female aged mice only, reducing stroke volume and increasing heart rate. We are in the process of investigating the signaling pathways that is responsible for this phenomenon, whether this is dependent on the branch-chained amino acids specifically or the isoleucine restriction per se.

Conclusion: These findings show that short-term dietary interventions confer lasting effects on metabolic health. This suggests that short-term BCAA restriction could be a translatable strategy for long-term improvements to metabolic health and could potentially reduce the risk of developing age-related diseases.
on an age x sex interaction, and the implications of these results.

Conclusion The metabolic benefits of isoleucine restriction is robust across age groups and sexes in the C57BL/6J strain.

Abstract 28 Figure 2 Isoleucine restriction induces leanness in aged mice of both sexes. Small animal MRI is used to determine the% body composition of mice before dietary intervention and every 3 weeks. It was observed that both male and female mice fed an isoleucine restriction diet become much leaner than their control counterparts. The effect of a protein restriction diet appears to be lessened in female mice.

Abstract 28 Figure 3 Isoleucine restriction improves glucose tolerance in both male and female aged mice. In a glucose tolerance assay, intraperitoneal injection of glucose was better tolerated in animals fed either an isoleucine restriction diet or a protein restriction diet. The benefits of a protein restriction diet was more significant in females.

Abstract 28 Figure 4 Isoleucine restriction induces cardiac remodeling in aged female mice. In females only, echocardiogram experiments revealed a decrease in cardiac stroke volume which was compensated by an increase in heart rate.

Abstract 28 Figure 5 Isoleucine and protein restriction exhibited distinct modulation of enzymatic phosphorylation pathways. A brief evaluation of whole heart protein phosphorylation downstream of mTORC1 found differences between male mice fed an isoleucine restriction diet and a protein restriction diet.
However, an alteration to cardiac function was observed in aged female mice only. More studies are required to further understand the underlying mechanisms and the implications of these phenomenon.

**29**

**DIETARY ISOLEUCINE RESTRICTION ALTERS METABOLISM TO REVERSE DIET-INDUCED OBESITY IN MICE**

Michaela Trautman, Madelyn Green, Esther Zelenovskiy, Dudley Lamming. University of Wisconsin – Madison

10.1136/jim-2022-MW.29

**Introduction/Background** While calorie restriction (CR) is the gold standard for interventions that prolong mammalian lifespan and healthspan, adhering to reduced calorie diets is difficult for humans. Recent findings by our lab and others have shown that protein restriction (PR) promotes health and longevity in mice and in humans. Our lab has found that the key mediators of these benefits seen on PR are the branched-chain amino acids (BCAAs). Restriction of all three BCAAs, or specific restriction of isoleucine (ile) or to a lesser extent valine (val), promotes metabolic health, fitness, and lifespan in mice.

**Objective(s)** We hypothesized that an ile restricted diet would induce improvements in weight, fat mass, and metabolic health in diet-induced obese male and female mice. We also aimed to characterize when and what changes occur in a separate diet crossover experiment utilizing metabolic chambers.

**Methods** After a four-month exposure to a high fat, obesogenic Western diet, C57B6/J mice were separated onto macro-nutrient and calorie matched diets: amino acid (AA)-defined control (no AAs restricted), AA-defined low BCAA, or an AA-defined low ile diet. A series of metabolic phenotyping experiments were conducted, including glucose and insulin tolerance tests, fasting blood glucose measurements, metabolic chambers, and hepatic lipid quantification.

**Results** The ile restricted diet group displayed significant improvements in body composition, hepatic lipid deposition, and glucose tolerance, and these changes occur quite rapidly. This was also demonstrated in our crossover experiment – metabolic improvements occur within a week of initiating an ile-restricted diet, at least in male mice. Further molecular analyses are currently being conducted.

**Conclusion** While further research is needed to describe the specific mechanisms of ile restriction in detail, and its test its effects in humans, this study demonstrates limiting dietary isoleucine is a promising intervention to improve overall health and potentially lifespan. We are collaborating with researchers in the Wisconsin Primate Center to test ile restriction in non-human primates and hope to enroll humans in a clinical trial in the future.

**30**

**MASS SPECTROMETRY BASED LIPIDOMICS AND FATTY ACIDOMICS – A NEW WINDOW FOR THE BIOMEDICAL SCIENCES AND NUTRITION RESEARCH**

Sugasini Dhavamani. University of Illinois

10.1136/jim-2022-MW.30

**Introduction/Background** Lipidomics is a branch of metabolomics and influence to study the molecular and bioactive lipids in plant, algal and animal foods, cells, tissues and biological fluids. Lipids has numerous classes of metabolites that plays a crucial role in the biomedical science, food science and nutrition for the maintenance of good health. This lipidomic approach also helps to analyses the interactions with other lipids, proteins and metabolites. Lipidomic approaches are driven based on Gas chromatography mass spectrometry, high performance or ultra-performance Liquid chromatography and mass spectrometry. The bottomless knowledge of lipidomic on biomedical science and nutrition research has been expanded substantially.

**Objective(s)** Those approaches are identification of novel bioactive food components, screening of bioactive lipids from
various resources, toxicity, measure the food safety and Quality assurance, Assessment of bioactive function, measure the nutrition levels of triglyceride molecular species, phospholipids, sphingolipids, eicosanoids and exploring the new classes and metabolites of bioactive lipids.

**Methods** Lipid metabolism provokes various bioactive lipids which is mediated for several signaling pathways and act as a vital compound for cell membranes. Any transformation in lipid metabolism leads to alteration of membrane composition, permeability and disruption of signaling network which cause cardiovascular disease, inflammation, neurodegeneration, cancer and metabolic diseases. Hence, Lipidomics analysis considered as an important tool to study the triglyceride molecular species, fatty acidomics and minor lipids like phospholipidomics, glycolipidomics, eicosanomics, Neurolipidomics, Neuroprotectins, resolvins, maresins and cardiolipins.

**Results** Majority of the lipids in the diet, edible fats and vegetable oils are triglycerides, the remaining are cholesterol esters, phospholipids and other minor components such. Vegetable oils are the chief sources of fatty acidomics of saturated fatty acids (SFA), MUFA (omega-9) and unsaturated PUFAs (omega-6 and omega-3) and nutraceuticals. However, the fatty acid composition and nutraceuticals depends on vegetable oil or technology followed during their production or blending or making of structured lipids.

**Conclusion** The current lack of lipidomic data in nutraceuticals, nutritional and clinical studies can be critically evaluated both at a biological pathway, biophysical and technological level. Lipidomics with bioinformatics can also be utilized for the identification of clinical endpoints of a dietary interference and identification of novel biomarkers.

31 THYROID IMMUNE-RELATED ADVERSE EVENTS ARE ASSOCIATED WITH IMPROVED SURVIVAL IN CANCER PATIENTS

Duaa Abdallah, Whitney Goldner, Jake Johnson, Anupam Kotwal. University of Nebraska Medical Center

10.1136/jim-2022-MW.31

**Introduction/Background** Thyroid immune-related adverse events (irAEs) occur frequently after immune checkpoint inhibitor (ICI) cancer therapy, but their risk factors and potential influence on survival need further investigation.

**Objective(s)** Identification and characterization of thyroid irAEs, Analyzing association with overall survival.

**Methods** We performed a retrospective cohort study of adult cancer patients who received ICIs including CTLA-4, PD-1, PD-L1 inhibitors from 12/1/2012- 12/31/2019. Patients who developed thyroid irAEs after excluding surgical or ablative hypothyroidism were analyzed. Survival analysis was performed by Kaplan-Meier curves and Cox-proportional hazards model.

**Results** Thyroid irAEs occurred in 145 (17.4%) of 834 ICI-treated patients (median age 64.9 y, 43.4% females) during median follow-up of 11.6 mo. New-onset thyroid dysfunction occurred in 118 (14.2%), of which 55 presented with thyrotoxicosis (32 progressed to hypothyroidism, 22 returned to euthyroid state, one had Graves’ disease). Worsening of pre-existing autoimmune hypothyroidism (≥50% increase in levothyroxine dose) occurred in 27 (3.2%). Of those with new-onset thyroid dysfunction, 79 (67%) required levothyroxine eventually. Patients with thyroid irAE had similar to age, sex and cancer type as compared to those without but had higher median pre-treatment TSH [2.4 vs. 1.7 mIU/L (p< 0.0001); multivariable OR 2.4 mIU/L of 2 (95% CI 1.3, 3.2; p=0.004)] and higher frequency of autoimmune disease history [26.9% vs. 14.8% (p=0.0009); multivariable OR of 2 (95% CI 1.2, 3.5; p=0.013)]. Thyroid irAEs occurred after a median of 2.4 mo from ICI, most frequently with PD-1/PD-L1 inhibitor, alone or in combination with CTLA-4 inhibitor. Thyroid irAEs were associated with better median overall survival [38.8 (95% CI 26.6, not reached) vs. 18.9 (95% CI 14.2, 24.8) mo; p< 0.0001] which persisted on restricting to patients with new-onset thyroid dysfunction [40.1 (95% CI 26.6, not reached) vs. 18.8 (95% CI 13.6, 24.8); p< 0.0001]. On multivariable analysis, thyroid irAEs had HR for mortality of 0.51 (95% CI 0.37, 0.71; p< 0.0001), which persisted on restricting to new-onset thyroid dysfunction [HR 0.48 (95% CI 0.34, 0.69; p< 0.0001)].

**Conclusion** Thyroid irAEs frequently occur after PD-1/PD-L1 inhibitor therapy, presenting as hypothyroidism or thyrotoxicosis usually progressing to hypothyroidism. Higher TSH even within normal range and autoimmune disease history may be risk factors for thyroid irAE. Improved survival with thyroid irAEs suggests these could be a marker for anti-tumor activity.
IMMUNE CHECKPOINTS AND SUPPRESSOR CELLS AFFECT THYROID CANCER OCCURRENCE AND SEVERITY

Anupam Kotwal, Kemal Hajric, Krysten Vance, Ernesto Martinez, Ana Yuli-Valdes, Michael Hollingsworth, Melissa Holzapfel, Salma Elhag, Oleg Shats, Apar Ganti, Hamid Band, Benjamin Swanson, Whitney Goldner. University of Nebraska Medical Center; University of Nebraska-Lincoln; University of Florida College of Medicine

Introduction/Background As the most common endocrine malignancy in the United States (U.S.), differentiated thyroid cancer (DTC) accounts for 3.8% of all cancers in the U.S., with roughly 10% of cases progressing to distant metastatic DTC, which is associated with a poor five-year survival outcome despite conventional management, including surgery and radioactive iodine ablation. Recently, novel immunotherapies have garnered attention as a viable therapeutic resource for patients with advanced DTC. However, the response to therapy has been variable and unpredictable, which may be associated with an immune suppressive circulating phenotype. Nonetheless, the intra-tumoral immune infiltrate remains to be elucidated, demonstrating a critical need to address the gap in understanding in order to better prognosticate the disease.

Objective(s) To identify and compare tumor-infiltrating immune markers with those present in the adjacent normal thyroid tissue, and collate these immune infiltrates with tumor characteristics.

Methods Twenty-nine adult tissue samples containing tumor and stromal regions were collected from patients with DTC. The samples were analyzed using multiplex immunofluorescence (MxIF) with antibodies against cell-surface molecules CD56, PD-1, PD-L1, FOXP3, CD3, CD8, CD4, CD45, CD68, CD163, INOS, HLA-DR, CD33, and CD19. Seventeen of the specimens were analyzed using HALO and a positive threshold was assigned based on review by a trained researcher.

Results In evaluating the immune profiles, important differences in the immune infiltrates between different stages of the cancer were observed. Generally, immune checkpoints PD-1 and PD-L1 were highly expressed within the tumor, despite variability in lymphocyte infiltration. Tumor from patients with distant metastases demonstrated higher infiltration with immune suppressive cells (T regulatory cells, macrophages and PD-L1 positive cells) as compared to localized tumor indicating their importance as potential predictive biomarkers for the aggressiveness of thyroid cancer.

Conclusion Immune profiling demonstrated significant differences between tumor and adjacent thyroid regions, particularly in terms of PD-1 and PD-L1 expression and lymphocyte infiltration, indicating their role in DTC occurrence. Also, infiltration of T regulatory cells, macrophages and PD-1/PD-L1 positive cells was more in metastatic DTC indicating their...
potential role in aggressive behavior of DTC. Our findings demonstrate the efficacy of MxIF in investigating the tumor microenvironment, which will have major implications in guiding the selection of patients for immunotherapy.

### Abstracts

#### 33 REGULATION OF ADIPOSITY AND METABOLISM THROUGH DIETARY HISTIDINE

Victoria Flores, Cara Green, Dudley Lamming. University of Wisconsin-Madison

10.1136/jim-2022-MW.33

**Introduction/Background** The increasing prevalence of obesity is a serious threat to global health, placing many humans at increased risk of many diseases, including diabetes, cancer, vascular dementia, and Alzheimer’s disease. Age-related changes in body fat distribution and metabolism may be key factors of a vicious cycle that can accelerate the aging process and onset of age-related diseases.

**Objective(s)** 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 leanness and glycemic control in humans. However, the specific dietary components altered in a LP diet that promote metabolic health have not been fully characterized.

**Methods** Preconditioned male C57BL/6J mice by placing them on a Western high-fat diet for 12 weeks starting at six weeks of age, with an additional group of mice placed on a chow diet. Mice consuming the Western diet were switched to one of three amino acid-defined WD diets; WD control, WD low protein, WD low histidine. An additional group of mice fed a chow diet in parallel were switched to an AA-defined Control diet with the same amino acid profile as the WD Control AA diet. We characterize the metabolic response to the different diets by measuring changes in glycemic control, energy expenditure, and other metabolic measures.

**Results** 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; and improving glucose metabolism. 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. We also observed supplementation of histidine to increase adipose and lean mass.

**Conclusion** 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, we find that the variation in dietary histidine levels helps to explain differences in body mass index (BMI) in humans living in Wisconsin. 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 obesity, a serious concern of aging and age-related diseases.

#### 34 A LOW ISOLEUCINE DIET EXTENDS LIFESPAN AND IMPROVES HEALTHSPAN IN A SEX-DEPENDENT MANNER IN A GENETICALLY HETEROGENEOUS MOUSE POPULATION

Cara Green, Michaela Trautman, Reiji Babygina, Yang Yeh, Heidi Pak, Shelly Somsella, Ameliee Bleicher, Grace Novak, Mariah Calabag, Nicole Richardson, Victoria Flores, Deyang Yu, Jesse Wei Fan, Dudley Lamming. University of Wisconsin-Madison

10.1136/jim-2022-MW.34

**Introduction/Background** Low protein-high carbohydrate diets promote improved metabolic health in both rodents and humans and have been shown to increase the lifespan of mice. However, it is becoming apparent that micronutrient composition, such as the amino acid make-up of protein may be equally, if not more important for the metabolic and longevity health benefits of a low protein diet. Previously, the branched chain amino acids (BCAAs; leucine, isoleucine and valine), have been identified as potential drivers of changes to metabolic health with a low protein diet, and increased isoleucine intake is associated with increased BMI in humans. In addition, the vast majority of research on protein restriction (PR) has been completed in male C57BL/6 mice, whereas recent work in the calorie restriction (CR) field has highlighted that sex and genetic background (strain) are crucial factors to consider in nutritional intervention studies.

**Objective(s)** To determine if a low isoleucine diet recapitulates the metabolic and lifespan extending benefits of a low protein diet in a genetically diverse heterogeneous line of male and female mice.

**Methods** We utilized male and female HET3 mice, which are the F2 progeny of (BALB/c × C57BL/6) mothers and (C3H/HeJ × DBA/2J) fathers and provide a heterogeneous yet reproducible genetic background to test the causes of age-related mortality and metabolic response to dietary interventions. Due to the allelic variation they possess, they also more accurately reflect the genetic diversity of humans. We placed mice on one of three diets; a Control diet, a Low Amino Acid diet (Low AA), in which all amino acids were reduced by two thirds, or a Low Isoleucine diet (Low ILE) where only isoleucine was reduced by two thirds. All diets were isocaloric, with carbohydrates substituted as necessary and identical levels of fat. We explored the impacts of these diets on young (starting at nine weeks old) and middle-aged (starting at six months old) mice. We characterized the metabolic, molecular and longevity-related responses to different diets by measuring changes in body weight, food intake, glycemic control, energy expenditure, activity levels, the transcriptome, lipidome and metabolome, frailty and lifespan.

**Results** We found that in young HET3 mice a Low ILE diet, but not a Low AA diet was able to reduce body weight gain in both male and female mice over three months. This was a result of both fat and lean mass loss and despite increased food consumption. Weight loss despite increased calorie intake could be explained by an increase in energy expenditure which was observed in both males and females on a Low ILE diet. Interestingly, only Low ILE was able to improve glucose tolerance in males, but both Low AA and Low ILE improved glucose tolerance in females. Many of these responses were recapitulated when started later in life and were maintained throughout the lifespan of the mice. Multivariate analyses at five months old and 24 months old indicated that the hepatic transcriptome, metabolome and lipidome show distinct age, sex- and diet-related signatures, particularly in the Old Low
ILE male mice. In nearly all groups, a greater number of genes were differentially expressed in the Low ILE group than the Low AA group relative to controls, except in young male mice, where the greatest number of changes was in the Low AA group. At a pathway level there were distinct difference between old Low AA males, which showed an increase in many inflammatory pathways relative to young controls, which were not present in old Low ILE males. In females, there was an increase in BCAA metabolism in old Control females which was not present in Low ILE mice, compared to their young counterparts. Frailty was measured at 16 months of age onwards in the middle-aged intervention group, and in males both the Low AA and Low ILE group has less age-associated frailty over time, whereas females did not show any differences between groups. Interestingly, while healthspan appeared to be improved in the Low AA males, they did not have an increased lifespan, and neither did any female groups. However, in the Low ILE males, there was a 30% increase in median lifespan relative to controls.

Conclusion In mice with a heterogenous background, a low isoleucine diet is a powerful tool to reduce weight gain and improve glycemic control in both males and females. However, in HET3 mice isoleucine restriction robustly reduces frailty and increases lifespan in males only. We have determined that there are both sex and age specific effects of a Low ILE diet on both phenotypic (body weight, food intake, glycemic control, energy expenditure, activity and RER) and molecular (hepatic transcriptome, lipidome and metabolome) signatures. Furthermore, while we expected a low isoleucine diet to recapitulate some of the benefits of a low protein (Low AA) diet, we found that in a heterogeneous population, a low isoleucine outperformed the low protein diet. This may suggest that in a genetically diverse population such as humans, there may be drawbacks to a complete reduction in all AAs, and in fact, specific AA reductions can optimize metabolic health and lifespan, and this is likely to be sex specific. This highlights the importance of robustly testing the effects of dietary interventions in studies that seek to improve metabolic health. This will be key for future initiatives that utilize personalized medicine to treat pathologies associated with metabolic health disorders and aging.

AN UNCOMMON CAUSE OF RECURRENT HYPOGLYCEMIA

1Baraa Saad, 1Mahmoud Mansour, 1Mohammad Al Bataineh, 2Aseel Alkhader, 3Omar Hussein, Sawjanya Naha. 1University of Missouri-Columbia; 2Jordan University of Science and Technology

Introduction/Background Hypoglycemia is commonly seen in patients receiving glucose-lowering agents like sulfonylureas and insulin1 and is defined by a low blood glucose level, usually < 0.50 g/L (2.75 mmol/L) along with symptoms such as diaphoresis, tremors, palpitations, confusion, seizures and coma2. Common etiologies for hypoglycemia apart from iatrogenic insulin include other medications such as sulfonamides, tramadol, topiramate and tyrosine kinase inhibitors, acute alcoholism, critical illness, adrenal insufficiency, hypopituitarism and insulinoma3. Other less common etiologies include genetic disorders such as congenital hyperinsulinism, insulin receptor mutations, inborn errors of metabolism, paraneoplastic and autoimmune syndromes4. Diagnosing the cause of hypoglycemia in patients not on glucose-lowering agents can be challenging for many physicians due to the ambiguity of presentation and unfamiliarity with some of these etiologies. In this case, we present our approach to working up postprandial hypoglycemia in a patient presenting with recurrent episodes of hypoglycemia.

Objective(s) A 56-year-old Caucasian female with a past medical history of COPD, diet-controlled type 2 diabetes mellitus, hypothyroidism and a history of multiple abdominal surgeries including bowel resections, splenectomy, hiatal hernia repair and Nissen fundoplication presented to the emergency department with an episode of hypoglycemia witnessed by her husband while she was waiting for a clinic appointment. Her symptoms included profuse sweating, shakiness, lightheadedness, palpitations and confusion. She checked her blood glucose and found it to be 29 mg/dL. Oral glucose was administered by the clinic staff and her symptoms resolved. The patient reported experiencing hypoglycemic episodes for the past 10 years with progressively increasing frequency. She denied taking any antidiabetic medications. Of note, gastric emptying study performed a year ago showed severe gastroparesis. Physical examination revealed multiple surgical scars on her abdomen. Initial labs showed normal renal and hepatic function. Her most recent A1C was 5.4%. Oral hypoglycemic agent screen was negative. Serum insulin level was 4.22 mcunit/mL (29.30 pmol/L), C-peptide was 0.637 mmol/L (637 nmol/L), with an insulin to C-peptide ratio < 1 which ruled out exogenous insulin use. Eight AM cortisol was 4.76 mcg/dL. Cosyntropin stimulation showed appropriate response as following: 6.38 mcg/dL at baseline, 16.2 mcg/dL at 30 min and 17.4 mcg/dL at 60 min.

A 72-hour-fasting test was performed with no significant hypoglycemia, which excluded insulinoma. At the end of the fast, beta hydroxy butyrate was elevated appropriately at 3.05 mmol/L, insulin was appropriate at 3.77 mcunit/mL (ref range 1–14) and C-peptide was 0.253 mmol/L (ref range 0.23–0.86). Following a mixed meal, blood glucose increased to over 200 mg/dL in two hours and then dropped to 70 mg/dL in five hours.

The patient was diagnosed with postprandial hypoglycemia, and was advised dietary modifications including small meals at frequent intervals, avoidance of high carbohydrate foods and increased consumption of fiber, protein and fat. She was also started on acarbose before each meal.

Methods A multi-step systematic approach is required to determine the cause of hypoglycemia. Postprandial hypoglycemia is a known complication of bariatric surgeries especially Roux-en-Y gastric bypass5, but can rarely be seen with Nissen fundoplication. Dietary modification remains the mainstay of treatment for such patients6,7. Further research is required to evaluate the efficacy of such interventions in postprandial hypoglycemia related to Nissen fundoplication.

REFERENCES


J Investig Med 2022;70:1557–1660
Epidemiology/health outcomes/quality improvement/bio-informatics

36 QUALITY IMPROVEMENT: PATIENT EDUCATION FOR MANAGEMENT OF HYPERTENSION IN PREGNANCY

Morgan Cooley, Kriti Goel, Rose Maxwell, Traci Rackett, Jerome Yaklic. Wright State University Boonshoft School of Medicine

Introduction/Background Patient education is a key factor for managing health conditions such as hypertension in pregnancy; however, variability in patient health literacy presents a challenge for the provider-patient discussion and the types of educational materials used. ACOG recommends providers enhance patient education by using plain non-medical language, taking time to speak slowly, reinforcing key issues in print that contains pictorial information, and requesting feedback to indicate understanding. Current educational materials are limited to brochures and handouts that include lengthy, often technical, information about hypertensive conditions. Providing education about preeclampsia during prenatal care can improve outcomes for women with a hypertension in pregnancy diagnosis. However, the average readability of available preeclampsia materials exceeds the recommended 6th grade reading level for patients. A recent review of available patient education materials for preeclampsia by Lange, et al revealed that most materials included risks for developing preeclampsia as well as signs and symptoms, but other content varied with fewer materials containing information about outcomes and complications. The majority of materials were rated as poor quality in terms of actionable information for patients.

Objective(s) To assess the effectiveness and efficiency of patient education tools for hypertension in pregnancy.

Methods Pre-intervention patient education included discussing the symptoms and management of hypertension in pregnancy. Two education tools were introduced for the intervention. Pregnant women with hypertension completed a questionnaire including questions for objective (Actual) knowledge and self-reported (Perceived) knowledge about hypertension. One group (Pre-I) completed the questionnaire before implementation of the new tools and a different group (Post-I) completed

Abstract 36 Figure 1
Abstract 36 Figure 2  ‘A guide to managing your high blood pressure’ brochure

Abstract 36 Table 1  Patient perceived comprehension ratings

<table>
<thead>
<tr>
<th></th>
<th>Pre-Intervention (n=45)</th>
<th>Post-Intervention (n=45)</th>
<th>Effect of Intervention</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Understanding of Condition</td>
<td>4.2 ± 1.1</td>
<td>4.4 ± 0.9</td>
<td>0.3</td>
<td>&lt;.15</td>
</tr>
<tr>
<td>Ability to Manage Condition</td>
<td>4.2 ± 1.1</td>
<td>4.5 ± 0.8</td>
<td>0.3</td>
<td>&lt;.14</td>
</tr>
<tr>
<td>Empowerment to Manage Condition</td>
<td>4.2 ± 1.2</td>
<td>4.5 ± 0.7</td>
<td>0.3</td>
<td>&lt;.15</td>
</tr>
<tr>
<td>Average Perceived Knowledge Score</td>
<td>4.2 ± 1.0</td>
<td>4.5 ± 0.7</td>
<td>0.3</td>
<td>&lt;.10</td>
</tr>
</tbody>
</table>

Abstract 36 Table 2  Patient objective knowledge

<table>
<thead>
<tr>
<th></th>
<th>Pre-Intervention (n=45)</th>
<th>Post-Intervention (n=45)</th>
<th>Effect of Intervention</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Consequences of Condition</td>
<td>0.9 ± 0.6</td>
<td>0.9 ± 0.6</td>
<td>No change</td>
<td>1.00</td>
</tr>
<tr>
<td>How to Manage Condition</td>
<td>1.5 ± 0.7</td>
<td>2.6 ± 0.8</td>
<td>+1.1</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Symptoms to Report</td>
<td>2.6 ± 0.8</td>
<td>3.1 ± 0.8</td>
<td>+0.5</td>
<td>&lt;.50</td>
</tr>
<tr>
<td>Average Objective Knowledge Score</td>
<td>1.7 ± 1.3</td>
<td>2.2 ± 1.0</td>
<td>+0.5</td>
<td>&lt;.005</td>
</tr>
</tbody>
</table>
Providers were surveyed before and after introducing the tools. Providers reported significant improvement in satisfaction with the tools.

Results

Pre-I women (N=45) rated their Perceived knowledge of hypertension as high (4.2 ± 1.0) but had low Actual knowledge (1.7 ± 1.3) scores. Post-I women (N=45) rated their perceived knowledge higher (4.5 ± 0.7) than the Pre-I group. The Post-I group, while having low scores on Actual knowledge (2.2 ± 1.0), showed significant improvement in objective knowledge compared to the Pre-I group (p<0.001).

*Reproduced with Permission*

Abstract 36 Figure 3 ‘Signs and symptoms’ tear sheet

Abstract 36 Table 3 Provider responses

<table>
<thead>
<tr>
<th>Table 3: Provider Responses</th>
<th>Pre-Intervention (n=16)</th>
<th>Post-Intervention (n=10)</th>
<th>Effect of Intervention</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Education Protocol Rating</td>
<td>2.6 ± 1.1</td>
<td>4.1 ± 0.7</td>
<td>+1.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Patient Comprehension Level</td>
<td>2.5 ± 0.6</td>
<td>3.5 ± 0.5</td>
<td>+1.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Patient Confidence Level</td>
<td>2.7 ± 0.6</td>
<td>3.6 ± 0.5</td>
<td>+0.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Duration of Education (minutes)</td>
<td>17.8 ± 8.5</td>
<td>7.8 ± 4.3</td>
<td>-10.0 minutes</td>
<td>&lt;.002</td>
</tr>
</tbody>
</table>

the questionnaire after implementation. Providers were surveyed before and after introducing the tools.

Abstracts

1590 J Investig Med 2022;70:1557–1660
education after using the new tools (2.6 ± 1.1 vs 4.1 ± 0.7; p < .001). Providers reported improvement in patient comprehension (2.5 ± 0.6 vs 3.5 ± 0.5; p < .001) and confidence (2.7 ± 0.6 vs 3.6 ± 0.5; p < .001) in the Post-I group compared to the Pre-I group. Providers reported a significant decrease in time (minutes) needed for education with new tools (17.8 ± 8.5 vs 7.8 ± 4.3; p < .001).

Conclusion After introducing the new tools, patients had higher actual knowledge scores, providers rated higher scores for patient knowledge, and providers reported needing less time for education.

POLICING THE POLICE: PEER-TO-PEER HIGH COST ANTIBIOTICS STEWARDSHIP PROGRAM DIRECTED TOWARDS INFECTION DISEASE SPECIALISTS

Aishwarya Sharma, Dubert Guerrero, Justin Jones, Emily Perry. 1University of North Dakota; 2Sanford Health

Introduction/Background Optimizing the use of antibiotics is critical to effectively treat infections, protect patients from harms caused by unnecessary antibiotic use, and combat antibiotic resistance. Antibiotic Stewardship Programs (ASPs) can help clinicians improve clinical outcomes and minimize harms by improving antibiotic prescribing. At Sanford Health, infectious disease physicians implement interventions with prospective audit, feedback and preauthorization to improve antibiotics use. However, infectious disease physicians also utilize restricted antibiotics with high acquisition cost such as daptomycin. In 2015, the use of daptomycin was added to our ASP monitoring program by ID providers as a self-regulation stewardship strategy based on six agreed upon criteria.

Objective(s) We aimed to review the acceptance rates of infectious disease specialists peer-review and daptomycin stewardship implications in a community teaching hospital in midwestern United States.

Methods Data was obtained from the ASP and hospital infection prevention and control surveillance databases from program implementation in 2014. The clinical appropriateness of daptomycin prescriptions was established by a team of infectious disease specialists and pharmacists to include the following daptomycin therapy guidelines: Non-pulmonary infections by methicillin resistant Staphylococcus aureus (MRSA); Invasive, non-pulmonary infections caused by vancomycin-resistant Enterococcus sp.; and Vancomycin allergy where a beta-lactam could not be used for appropriate coverage. Data on acceptance rate to ASP recommendations and antibiotics usage based on daptomycin days of therapy per 1000 patient days were compared. Rates of nosocomial infections with MRSA, length of stay (LOS), and 30-day readmission were evaluated to ensure no negative clinical implications with restricting daptomycin use.

Results Since program inception, there were 183 peer interventions sent out. A total of 93 (51%) were accepted and 56 (31%) were rejected. Others were modified or unresolved. The ASP acceptance rates for daptomycin was 51% for the five year period. Daptomycin use remained stable at range 2.38–2.39 DOT/1000. Limiting daptomycin use had no impact on MRSA rates, 30 day readmission rates or LOS over five years. Hospital acquired-MRSA incidence rate ranged from 0.22–0.31 per 1000 patient days, percent 30 day readmission ranged from 10.6–11.8 % while mean LOS were also stable and ranged from 4.7–5.0 days.

Conclusion Infectious diseases specialists utilize restricted and high cost antibiotics. While antimicrobial stewardship programs promote the appropriate use of antimicrobials, improve patient outcomes, reduce microbial resistance, and limit the spread of infections, interventions aimed towards infectious disease [ID] specialists remain limited in the literature. ID specialists serve as innate stewards for antimicrobial recommendations; however, it is not unreasonable to implement a peer-to-peer stewardship or self-regulation of one’s practice in order to ensure that therapy guidelines are being followed for a positive clinical and financial impact. We found that only over half of peer-recommendations are accepted in our institution with a stable usage of daptomycin. There were no negative impacts on MRSA rates, LOS or 30 day readmission rate in limiting daptomycin use.

Abstract 38 Figure 1 Infectious disease specialists’ peer-review daptomycin stewardship recommendation acceptance rates. Of 183 interventions, 93 (51%) were accepted over the 5 year program implementation
Introduction/Background Freshwater harmful algal blooms (HABs) are increasing in number and severity throughout the world. These HABs are chiefly composed of one or more species of cyanobacteria, also known as blue-green algae, such as microcystis. Numerous HAB cyanobacterial species produce toxins (e.g. microcystin) that disrupt ecosystems, impact water and air quality, deter recreation and are harmful to both human and animal health. Exposure to these toxins can occur through ingestion, inhalation or skin contact. Acute health effects of HAB toxins have been well documented, and include symptoms such as nausea, vomiting, abdominal pain and diarrhea, headache, fever, skin rashes, or respiratory related symptoms. While these adverse effects increase with amount and duration or frequency of exposure, susceptibility to HAB toxins may also be increased by the presence of co-morbidities. However, there is a paucity of knowledge related to the health effects of HAB exposure in human populations. 

Objective(s) We sought to determine trends and patterns in diagnostic codes relating to HAB exposures from the Healthcare Cost and Utilization Project’s (HCUP) Nationwide Emergency Department Sample (NEDS).

Methods Data for the analysis was obtained from the HCUP NEDS database. We analyzed years 2016 to 2018 as these represented the years in which complete data was available using the World Health Organization (WHO) International Classification of Diseases-10 (ICD-10) diagnosis codes for HAB exposure (i.e. ICD-10 codes T65.82 and Z77.121). HCUP is the largest collection of hospital care data in the United States, and NEDS respectively is the largest emergency department (ED) database in the U.S. Once the data was obtained, each year was screened for instances in which diagnostic codes relating to HAB exposure were used. For each year’s grouping, statistical analysis was performed to uncover patterns and trends. Each patient occurrence was screened for the most prevalent comorbidities associated with HAB exposures.

Results The HCUP NEDS data related to HAB exposure related admissions to the ED was summarized by year in Table 1. ED admissions were classified by primary ICD-10 diagnostic code, age (range), sex, and most prevalent comorbid conditions by year. Over the three-year period studied, there were 118 reported patient admissions to the ED. Respiratory related illness accounted for the majority of comorbidities and were present in 53% of patients, including 30% as the primary diagnostic code.

Conclusion These data represent one of the first attempts to analyze HAB exposure related illness presenting to Emergency Departments in the United States. Admission to the ED with reported HAB exposure related diagnoses increased significantly over the years studied. The predominance of respiratory related diagnostic codes in these patients suggests greater attention to these conditions in the risk characterization of HAB exposure in the development of evidence-based prevention and treatment strategies. These efforts will take on increased importance as the incidence and prevalence of HABs continues to increase in scale and severity both in the U.S. and throughout the world.

Gastroenterology/clinical nutrition

REVIVIFY® MODULATES HEALTHY GUT MICROBIOMES AND SHORT CHAIN FATTY ACIDS EVALUATED BY AN IN VITRO MODEL OF GUT MICROBIOME STUDY

Abstract 40 Table 1 Yearly breakdown of HAB exposure and related risk factor codes

<table>
<thead>
<tr>
<th>Year</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients (n)</td>
<td>20</td>
<td>21</td>
<td>22</td>
<td>63</td>
</tr>
<tr>
<td>Age (range in years)</td>
<td>11 to 76</td>
<td>13 to 68</td>
<td>3 to 90</td>
<td>1 to 90</td>
</tr>
<tr>
<td>Female (%)</td>
<td>25%</td>
<td>40%</td>
<td>55%</td>
<td></td>
</tr>
<tr>
<td>Most Prevalent Comorbid Diagnostic Code</td>
<td>Respiratory related illness</td>
<td>Respiratory related illness</td>
<td>Respiratory related illness</td>
<td>Respiratory related illness</td>
</tr>
<tr>
<td></td>
<td>24%</td>
<td>20%</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>10%</td>
<td>15%</td>
<td>20%</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>15%</td>
<td>10%</td>
<td>15%</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>10%</td>
<td>15%</td>
<td>20%</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>5%</td>
<td>10%</td>
<td>15%</td>
<td>20%</td>
</tr>
</tbody>
</table>
CYTOCHROME P450 4A IN THE PATHOGENESIS OF ALCOHOL-ASSOCIATED LIVER DISEASE

Zhichong Yang, Nazmul Huda, Jing Ma, Yanchao Jiang, Kristina Perez, Suthat Liangpunsakul. Indiana University

Introduction/Background: Alcohol regulates several pathways involving in lipid metabolism favoring the induction in lipogenesis and inhibition of FA oxidation. The fatty acid ω-hydroxylation, under the regulation of CYP4A genes, converts the saturated, unsaturated, and branched-chain fatty acids to dicarboxylic acids, which are preferentially metabolized by the peroxisome beta-oxidation system to shorter chain fatty acids. These genes are under the regulation of circadian clock.

Objective(s): In this study, we explored the mechanistic link between circadian pathway, the alteration in the ω-hydroxylation genes (CYP4A), and alcohol-associated liver disease (ALD).

Methods: CYP4A10, CYP4A14 mice were used. In some experiments, they were fed with NIAAA-ethanol plus binge model. Mice were sacrificed at nine hours post gavage; liver tissues and plasma were collected (ZT12). Primary hepatocytes were isolated for in vitro experiments. ChIP-seq, RNA-seq, lipidomic, and luciferase assay were performed.

Results: Deficiency of Rev-Erbα promoted lipid accumulation and oxidative stress, which were enhanced by ethanol treatment. Venn diagram indicated the increase in the expression of Cyp4a10 and Cyp4a14 in both Rev-Erbα-/- mice liver and ethanol-fed group. RNA-Seq from the liver collected every six hours over a 24-hour period after the gavage showed a significant increase in both Cyp4a10 and Cyp4a14 at all the time points, with the expression peak shifted in ethanol-fed group. We next explored the ChIP-seq data (GSE67962) and found the possible binding sites of Rev-Erbα on Cyp4a14 promoters. Using ChIP-qPCR and luciferase assay, we found that Rev-Erbα bind and repressed Cyp4a10 and Cyp4a14 promoter activity. To determine the role of CYP4A, we found that Cyp4a14-/- mice protected against alcohol-induced hepatic steatosis. Ethanol-fed mice treated either with Rev-Erbα agonist SR9909 or Cyp4a antagonist HET0016 had significant reduction of Cyp4a10 and Cyp4a14 gene expression and steatosis compared to WT. CYP4A antagonist HET0016 ameliorated lipid accumulation in ethanol-treated Rev-Erbα-/- primary hepatocytes; suggesting that Cyp4a is the downstream target of Rev-Erbα.

Conclusion: Our data suggested the mechanistic link between REV-ERBα and CYP4A in the pathogenesis of ALD. Activation of REV-ERBα or inhibition of CYP4A attenuated hepatic steatosis from alcohol; suggesting their potential roles as the therapeutic targets for ALD.
translational modifications such as citrullination that might play a role in the initiation and/or progression of IBD.

Methods A murine model of infectious (C. rodentium) colitis (CITRO) was used as it closely mimics UC. Tissue samples were evaluated for the presence of Claudin-2, Calprotectin, CD19 (B-cells), Citrulline and Malondialdehyde-Acetaldehyde (MAA) Adduct using antibodies and immunofluorescence. Images were analyzed using Zen 2012 software (Zeiss) and quantified using ImageJ software (National Institutes of Health). Results were expressed as the mean ± standard deviation (SD) pixel density. Serum was also tested for MAA IgG antibody to; Human serum albumin (HSA), HSA-MAA, HSA-Citrulline and HSA-MAA-Citrulline using ELISA.

Results There was a significant increase in MAA (p< 0.03) and citrulline antigen (p< 0.001) in the tissue of mice in the CITRO model compared to controls. Other proteins such as Claudin-2 and Calprotectin antigens were both increased in the CITRO model compared to controls (p< 0.001 and p< 0.0001, respectively). Co-localization data showed significant increases in colocalization between MAA, and calprotectin compared to citrulline and calprotectin. Furthermore, significant increase in colocalization was seen between citrulline and claudin compared to MAA and claudin. CD19 was also increased in the tissue of mice in the CITRO model compared to controls (p< 0.001) and showed colocalization with MAA. In the serum circulating antibodies against MAA was also increased in the CITRO model (p< 0.02). Interestingly, there was also a significant increase in antibodies to MAA-Citrulline in the CITRO model (p< 0.001) compared to controls and to MAA and citrulline alone.

Conclusion These data demonstrate a role for MAA in the initiation/progression of IBD. The association between CD19, MAA and calprotectin suggests calprotectin is a potential protein involved in IBD. Further work to determine MAA addition in IBD disease manifestations is warranted.

43 PENICILLIN ALLERGY IS ASSOCIATED WITH INCREASED RISK OF CLOSTRIDIODES DIFFICILE INFECTION: A NATIONWIDE ANALYSIS

Introduction/Background Clostridioides difficile infection (CDI) is a significant global healthcare burden. In the US, CDI has...
become the most common cause of healthcare-associated infections in hospitals. CDI is usually the result of the unnecessary use of broad-spectrum antibiotics. This use is significantly affected by patients’ history of penicillin allergy.

Objective(s) The objective of this study was to investigate the association between penicillin allergy status and the risk of CDI development.

Methods A retrospective study was conducted utilizing the Nationwide Inpatient Sample database (NIS) for the years 2016 to 2018. Patients with CDI were identified using ICD 10 diagnosis codes A04.7 from all listed primary discharge diagnoses. Patients younger than 18 years of age, admitted for elective reasons, or patients with missing information were excluded. Patients with penicillin allergy were also identified using ICD 10 code Z88.0. We further divided the patient population into two groups, with and without penicillin allergy. Univariate logistic regression analysis was performed.

Abstract 43 Table 1 Patients’ characteristics

<table>
<thead>
<tr>
<th>variable</th>
<th>penicillin allergy</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>gender (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>males</td>
<td>45.47%</td>
<td>0.00</td>
</tr>
<tr>
<td>females</td>
<td>54.53%</td>
<td></td>
</tr>
<tr>
<td>AGE (mean)</td>
<td>59.14</td>
<td>0.00</td>
</tr>
<tr>
<td>LOS (days mean)</td>
<td>5.00</td>
<td>0.00</td>
</tr>
<tr>
<td>RACE (%)</td>
<td>65.71%</td>
<td>0.00</td>
</tr>
<tr>
<td>White</td>
<td>16.36%</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>11.54%</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>2.78%</td>
<td></td>
</tr>
<tr>
<td>Native American</td>
<td>0.64%</td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>2.98%</td>
<td></td>
</tr>
<tr>
<td>Median household income national quartile for patients zip code (%)</td>
<td>31.46%</td>
<td>0.00</td>
</tr>
<tr>
<td>15-44,999</td>
<td></td>
<td></td>
</tr>
<tr>
<td>46.0005-58,999$</td>
<td>26.35%</td>
<td></td>
</tr>
<tr>
<td>59.0005-78,999$</td>
<td>23.30%</td>
<td></td>
</tr>
<tr>
<td>79.0005 or more</td>
<td>18.88%</td>
<td></td>
</tr>
<tr>
<td>Primary Expected Payor (%)</td>
<td>50.33%</td>
<td>0.00</td>
</tr>
<tr>
<td>Medicare</td>
<td>18.86%</td>
<td></td>
</tr>
<tr>
<td>Medicaid</td>
<td>18.86%</td>
<td></td>
</tr>
<tr>
<td>Private including HMC</td>
<td>23.13%</td>
<td></td>
</tr>
<tr>
<td>Self-pay</td>
<td>4.61%</td>
<td></td>
</tr>
<tr>
<td>No change</td>
<td>0.41%</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>2.66%</td>
<td></td>
</tr>
<tr>
<td>Region of hospital (%)</td>
<td>19.45%</td>
<td>0.00</td>
</tr>
<tr>
<td>Northeast</td>
<td>19.45%</td>
<td></td>
</tr>
<tr>
<td>Midwest</td>
<td>19.38%</td>
<td></td>
</tr>
<tr>
<td>South</td>
<td>19.38%</td>
<td></td>
</tr>
<tr>
<td>West</td>
<td>19.38%</td>
<td></td>
</tr>
<tr>
<td>Bedsize of hospital (%)</td>
<td>19.45%</td>
<td>0.00</td>
</tr>
<tr>
<td>Small</td>
<td>19.45%</td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>29.62%</td>
<td></td>
</tr>
<tr>
<td>Large</td>
<td>50.93%</td>
<td></td>
</tr>
<tr>
<td>Census division of hospital (%)</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>New England</td>
<td>5.05%</td>
<td></td>
</tr>
<tr>
<td>Middle Atlantic</td>
<td>14.40%</td>
<td></td>
</tr>
<tr>
<td>East North Central</td>
<td>15.40%</td>
<td></td>
</tr>
<tr>
<td>west North Central</td>
<td>6.39%</td>
<td></td>
</tr>
<tr>
<td>South Atlantic</td>
<td>21.60%</td>
<td></td>
</tr>
<tr>
<td>East South Central</td>
<td>6.79%</td>
<td></td>
</tr>
<tr>
<td>West South Central</td>
<td>10.95%</td>
<td></td>
</tr>
<tr>
<td>Mountain</td>
<td>5.85%</td>
<td></td>
</tr>
<tr>
<td>Pacific</td>
<td>13.57%</td>
<td></td>
</tr>
<tr>
<td>IBD (%)</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>99.18%</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>0.82%</td>
<td></td>
</tr>
<tr>
<td>Stem cell transplant (%)</td>
<td>99.89%</td>
<td>0.01</td>
</tr>
<tr>
<td>Absent</td>
<td>99.90%</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>0.11%</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis (%)</td>
<td>97.17%</td>
<td>0.00</td>
</tr>
<tr>
<td>Absent</td>
<td>97.26%</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>2.83%</td>
<td></td>
</tr>
<tr>
<td>GERD (%)</td>
<td>81.42%</td>
<td>0.00</td>
</tr>
<tr>
<td>Absent</td>
<td>75.96%</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>18.58%</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy (%)</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>99.98%</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>0.02%</td>
<td></td>
</tr>
<tr>
<td>CKD (%)</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>80.98%</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>19.02%</td>
<td></td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>82.85%</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>17.15%</td>
<td></td>
</tr>
</tbody>
</table>

Abstract 43 Table 2 Univariate logistic regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>P value</th>
<th>[95% Conf. Interval]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin allergy</td>
<td>1.27</td>
<td>0.00</td>
<td>1.21</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>8.76</td>
<td>0.00</td>
<td>8.36</td>
</tr>
<tr>
<td>Stem cell transplant</td>
<td>2.87</td>
<td>0.00</td>
<td>2.36</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>2.15</td>
<td>0.00</td>
<td>2.05</td>
</tr>
<tr>
<td>GERD</td>
<td>1.52</td>
<td>0.00</td>
<td>1.48</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>0.46</td>
<td>0.18</td>
<td>0.15</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>1.37</td>
<td>0.00</td>
<td>1.34</td>
</tr>
<tr>
<td>Obesity</td>
<td>0.68</td>
<td>0.00</td>
<td>0.66</td>
</tr>
<tr>
<td>Age</td>
<td>1.02</td>
<td>0.00</td>
<td>1.02</td>
</tr>
<tr>
<td>Gender</td>
<td>1.49</td>
<td>0.00</td>
<td>1.46</td>
</tr>
<tr>
<td>LOS</td>
<td>1.01</td>
<td>0.00</td>
<td>1.01</td>
</tr>
<tr>
<td>Race</td>
<td>0.60</td>
<td>0.54</td>
<td>0.59</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>0.42</td>
<td>0.00</td>
<td>0.38</td>
</tr>
<tr>
<td>Native American</td>
<td>0.75</td>
<td>0.00</td>
<td>0.64</td>
</tr>
<tr>
<td>Other</td>
<td>1.57</td>
<td>0.00</td>
<td>1.56</td>
</tr>
<tr>
<td>Median household income national quartile for patients zip code</td>
<td>0.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>46.0005-58,999$</td>
<td>1.18</td>
<td>0.00</td>
<td>1.14</td>
</tr>
<tr>
<td>59.0005-78,999$</td>
<td>1.20</td>
<td>0.00</td>
<td>1.15</td>
</tr>
<tr>
<td>79.0005 or more</td>
<td>1.26</td>
<td>0.00</td>
<td>1.20</td>
</tr>
<tr>
<td>Census division of hospital</td>
<td>0.85</td>
<td>0.02</td>
<td>0.75</td>
</tr>
<tr>
<td>Middle Atlantic</td>
<td>0.97</td>
<td>0.66</td>
<td>0.86</td>
</tr>
<tr>
<td>West North Central</td>
<td>0.99</td>
<td>0.91</td>
<td>0.88</td>
</tr>
<tr>
<td>South Atlantic</td>
<td>0.11</td>
<td>0.11</td>
<td>0.80</td>
</tr>
<tr>
<td>East South Central</td>
<td>0.93</td>
<td>0.38</td>
<td>0.80</td>
</tr>
<tr>
<td>West South Central</td>
<td>0.83</td>
<td>0.01</td>
<td>0.73</td>
</tr>
<tr>
<td>Mountain</td>
<td>1.00</td>
<td>0.95</td>
<td>0.87</td>
</tr>
<tr>
<td>Pacific</td>
<td>0.75</td>
<td>0.00</td>
<td>0.66</td>
</tr>
<tr>
<td>Region of hospital</td>
<td>1.10</td>
<td>0.01</td>
<td>1.12</td>
</tr>
<tr>
<td>South Atlantic</td>
<td>1.00</td>
<td>0.90</td>
<td>0.93</td>
</tr>
<tr>
<td>West</td>
<td>0.93</td>
<td>0.07</td>
<td>0.86</td>
</tr>
<tr>
<td>Location/teaching status of hospital</td>
<td>1.04</td>
<td>0.21</td>
<td>0.98</td>
</tr>
<tr>
<td>Urban non-teaching</td>
<td>0.78</td>
<td>0.00</td>
<td>0.74</td>
</tr>
<tr>
<td>Bed size of hospital</td>
<td>0.96</td>
<td>0.22</td>
<td>0.91</td>
</tr>
<tr>
<td>Medium</td>
<td>0.94</td>
<td>0.03</td>
<td>0.89</td>
</tr>
<tr>
<td>Large</td>
<td>0.48</td>
<td>0.00</td>
<td>0.46</td>
</tr>
<tr>
<td>Primary Expected Payor (%)</td>
<td>0.66</td>
<td>0.00</td>
<td>0.64</td>
</tr>
<tr>
<td>Private including HMC</td>
<td>0.39</td>
<td>0.00</td>
<td>0.36</td>
</tr>
<tr>
<td>Self-pay</td>
<td>0.44</td>
<td>0.00</td>
<td>0.42</td>
</tr>
<tr>
<td>No change</td>
<td>0.49</td>
<td>0.00</td>
<td>0.46</td>
</tr>
<tr>
<td>Others</td>
<td>0.51</td>
<td>0.00</td>
<td>0.46</td>
</tr>
</tbody>
</table>
between penicillin allergy status and CDI. Multivariate regression analysis was then done while adjusting for presumed confounders and covariates.

**Results**

There were 69,542,949 patients included in this study, 5.3% of them were penicillin allergic. Adults admitted to the hospitals for non-elective reasons and with known penicillin allergy have increased odds of developing CDI by 27% when compared to patients who were not penicillin-allergic, and this relationship was statistically significant (Odds Ratio (OR) of 1.27, 95% confidence interval (CI) [1.21–1.33], P-value of 0.00). When adjusting for other presumed confounders using multivariate logistic regression adjusted OR was 1.13, 95% CI [1.08–1.19], with a P-value of 0.00.

**Conclusion**

This study demonstrates that patients with labeled penicillin allergy status are associated with an increased risk of acquiring CDI. Therefore, it is an essential implement for antimicrobial stewardship to evaluate patients for penicillin allergy before choosing not to prescribe penicillin or other β-lactam antibiotics.

---

**Abstract 43 Table 3**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>P-value</th>
<th>[95% Conf. Interval]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin allergy</td>
<td>1.12</td>
<td>0.00</td>
<td>1.06</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>8.06</td>
<td>0.00</td>
<td>7.54</td>
</tr>
<tr>
<td>Stem cell transplant</td>
<td>2.83</td>
<td>0.00</td>
<td>2.30</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>1.05</td>
<td>0.16</td>
<td>0.98</td>
</tr>
<tr>
<td>GERD</td>
<td>1.27</td>
<td>0.00</td>
<td>1.23</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>1.21</td>
<td>0.00</td>
<td>1.18</td>
</tr>
<tr>
<td>Obesity</td>
<td>0.68</td>
<td>0.00</td>
<td>0.66</td>
</tr>
<tr>
<td>Age</td>
<td>1.01</td>
<td>0.00</td>
<td>1.01</td>
</tr>
<tr>
<td>Gender</td>
<td>1.54</td>
<td>0.00</td>
<td>1.50</td>
</tr>
<tr>
<td>Length of stay</td>
<td>1.01</td>
<td>0.00</td>
<td>1.01</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>0.68</td>
<td>0.00</td>
<td>0.64</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.74</td>
<td>0.00</td>
<td>0.69</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>0.47</td>
<td>0.00</td>
<td>0.42</td>
</tr>
<tr>
<td>Native American</td>
<td>0.95</td>
<td>0.52</td>
<td>0.80</td>
</tr>
<tr>
<td>Median household income national quartile for patients zip code</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>46,000.5-58,999S</td>
<td>1.07</td>
<td>0.00</td>
<td>1.03</td>
</tr>
<tr>
<td>59,000.5-78,999S</td>
<td>1.05</td>
<td>0.02</td>
<td>1.01</td>
</tr>
<tr>
<td>79,000 or more</td>
<td>1.08</td>
<td>0.00</td>
<td>1.03</td>
</tr>
<tr>
<td>Primary Expected Payer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicaid</td>
<td>0.78</td>
<td>0.00</td>
<td>0.74</td>
</tr>
<tr>
<td>Private including HMO</td>
<td>0.91</td>
<td>0.00</td>
<td>0.87</td>
</tr>
<tr>
<td>Self-pay</td>
<td>0.68</td>
<td>0.00</td>
<td>0.62</td>
</tr>
<tr>
<td>No change</td>
<td>0.86</td>
<td>0.30</td>
<td>0.76</td>
</tr>
<tr>
<td>Others</td>
<td>0.74</td>
<td>0.00</td>
<td>0.67</td>
</tr>
</tbody>
</table>

**Abstract 44 Table 1**

<table>
<thead>
<tr>
<th>ICD codes of patients included</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>K85.1 (Biliary acute pancreatitis)</td>
<td>3</td>
</tr>
<tr>
<td>K85.9 (Acute pancreatitis, unspecified)</td>
<td>11</td>
</tr>
<tr>
<td>K86.0 (Alcohol-induced chronic pancreatitis)</td>
<td>4</td>
</tr>
<tr>
<td>K86.1 (Other chronic pancreatitis)</td>
<td>18</td>
</tr>
<tr>
<td>K86.2 (Cyst of pancreas)</td>
<td>3</td>
</tr>
<tr>
<td>K86.8 (Other specified diseases of pancreas)</td>
<td>1</td>
</tr>
<tr>
<td>K86.9 (Disease of pancreas, unspecified)</td>
<td>4</td>
</tr>
<tr>
<td>C25.9 (Malignant neoplasm of pancreas, unspecified)</td>
<td>1</td>
</tr>
</tbody>
</table>
Results Over a five-year period, 45 patients were managed in the outpatient GI clinic under the ICD criteria mentioned above (table 1). Of these, 23 (51.1%) had PERT in their medication chart. Only three out of the 45 (6.67%) patients were tested with fecal elastase, of which one had a positive test and was on PERT, and the other two tested negative and were not on PERT.

Conclusion EPI is frequently an unrecognized entity, and is often underdiagnosed in high risk population despite the potential for development of poor outcomes. Outpatient EPI screening using fecal elastase at an academic outpatient clinic was very low (6.67%) in seemingly high-risk patients, with high rates of inappropriate PERT administration (51.1%). We plan to implement interventions including digital and educational means to improve the quality and value of care to patients at risk of developing EPI.

45 INTESTINAL PERMEABILITY IN CIRRHOSIS VARIES BY GUT SEGMENT
Patricia Bloom, Anna Lok, Vincent Young, Chung Owyang, University of Michigan
10.1136/jim-2022-MW.44

Introduction/Background Several complications of cirrhosis are thought to result from translocation of bacterial products across the intestinal epithelium. However, little is known regarding which gut segment is associated with increased permeability in cirrhosis. Interventions targeting the small intestine differ from those targeting the colon; therefore, isolating the most permeable gut segment(s) in cirrhosis will have considerable therapeutic implications.

Objective(s) We aimed to 1) identify the gut segment with greatest permeability in cirrhosis and 2) identify the gut segment most permeable relative to non-cirrhotic controls.

Methods From October 2020 to November 2021 we obtained duodenal, ileum, and colon tissue biopsies from patients with cirrhosis undergoing routine outpatient screening endoscopies, as well as non-cirrhotic controls. Patients were excluded if they used an antibiotic (including rifaximin) or immunosuppression in the prior four weeks, or had inflammatory bowel disease. Samples were analyzed for intestinal permeability via transepithelial electrical resistance (TEER). Our group had previously collected duodenal TEER from 10 young and healthy controls, without gastrointestinal symptoms.

Results Twenty-four patients with cirrhosis underwent sampling, including 23 duodenum, five ileum, and five colon samples. Fifteen non-cirrhotic controls underwent sampling, including seven duodenum, 10 ileum, and 11 colon samples. Our group had previously collected duodenal TEER from 10 young and healthy controls. Of the patients with cirrhosis, median MELD was eight (range 6 – 15), median Childs Pugh score 5 (range 5–9), 33% had ascites, 75% had varices on endoscopy, and 4% had a history of encephalopathy. In patients with cirrhosis, intestinal permeability varied between gut segments as measured by TEER ($r^2 = 0.20$, $P = 0.03$). Lower TEER signifies greater permeability. The ileum was the most permeable segment (9.4 $\Omega/\text{cm}^2 \pm 2.7$), followed by duodenum (13.0 $\Omega/\text{cm}^2 \pm 3.3$), and colon (14.9 $\Omega/\text{cm}^2 \pm 3.1$; figure 1). We compared intestinal permeability between the 3 groups: cirrhosis, non-cirrhotic controls, and healthy controls. Patients with cirrhosis and non-cirrhotic controls were similar in age (60 vs 64 years) and older than healthy controls (48 years). Patients with cirrhosis had higher Charlson Comorbidity Index than non-cirrhotic controls, driven by liver disease (4.8 vs 2.4). Duodenal TEER was lower in patients with cirrhosis compared to healthy controls (13.0 $\Omega/\text{cm}^2 \pm 3.3$ vs. 23.5 $\Omega/\text{cm}^2 \pm 6.7$; $P < 0.0001$). TEER trended towards lower in cirrhosis compared to non-cirrhosis controls in the duodenum (13.0 $\Omega/\text{cm}^2 \pm 3.3$ vs. 15.1 $\Omega/\text{cm}^2 \pm 3.3$; $P = 0.21$) and the ileum (9.4 $\Omega/\text{cm}^2 \pm 2.7$ vs. 11.2 $\Omega/\text{cm}^2 \pm 2.2$; $P = 0.23$), but did not differ in the colon (14.9 $\Omega/\text{cm}^2 \pm 3.1$ vs. 13.8 $\Omega/\text{cm}^2 \pm 4.1$; $P = 0.56$).

Conclusion Intestinal permeability varies by gut segment in cirrhosis, with greatest permeability in the ileum. These data suggest that patients with cirrhosis have more permeable small bowels but not colons, compared to controls.

46 EVALUATING RISK FACTORS FOR POOR BOWEL PREPARATION IN COLONOSCOPIES FOR CHRONIC DIARRHEA
Mahmoud Mansour, Ravinder Mankoo, Vanessa Kuwajima, University of Missouri Columbia
10.1136/jim-2022-MW.45

Introduction/Background Chronic diarrhea, typically defined as >4 weeks of loose stool or increased stool frequency, can be a source of significant personal distress for patients with the potential for significant morbidity and even mortality. Colonoscopy with mucosal biopsy to identify inflammatory bowel disease, microscopic colitis, or even underlying malignancy, is an essential tool in the work-up of chronic diarrhea. Inadequate bowel preparation can lead to missed diagnosis, increased procedural time, and potentially increased cost to the patient and healthcare system stemming from the need for repeat procedures.

Objective(s) Through this study, we sought to preliminarily determine whether inadequate bowel preparation in patients undergoing colonoscopy for chronic diarrhea was a common occurrence and whether any predictors of inadequate bowel preparation in this patient population were evident.

Methods We performed a retrospective electronic medical record evaluation of patients who underwent diagnostic
Intraabdominal hypertension is a powerful predictor of mortality and poor clinical outcome in patients admitted with severe acute pancreatitis: META ANALYSIS

Mohammad Danwee, 1Rutib Mafhouz, 1Adham Obeidat, 1Fares Ghanem, 4Mahmoud Mannour, 1Chakradhar Reddy, 1East Tennessee State University; 2Brown University/Kent Hospital; 3University of Hawaii; 4University of Missouri Columbia

Introduction/Background Acute pancreatitis (AP) is one of the leading causes of mortality and morbidity with unpredictable clinical outcomes. Several scoring systems have been developed to assess severity and outcome in patients with acute pancreatitis; most of these scoring systems have no physiologic or pathophysiologic basis. Such a limitation led to an interest in measuring intraabdominal pressure (IAP) as a method to predict outcomes in patients with acute pancreatitis. Unlike other prognostic scoring systems, variations in IAP in patients with acute pancreatitis are likely to result from the pathophysiology of the underlying disease process.

Objective(s) Investigate the predictive impact of intra-abdominal hypertension on mortality and clinical outcomes in a patient hospitalized with severe acute pancreatitis.

Methods We conducted a systematic search of the PubMed, EMBASE, and Cochrane databases from inception through November 2021 for studies evaluating the effect of IAH on AP. Relevant data were extracted and analyzed using STATA 17 software. A random-effects model was used for all variables. Publication bias was assessed using Egger’s test.

Results Fourteen studies (four prospective and 10 retrospective) published between 2002 and 2021 investigating 1056 patients were included in our analysis. Mortality (primary outcome) was more likely in patients with IAH with OR 9.08 (CI95% 4.84–17.02) and heterogeneity of (I²=22.49%).

Abstracts

**Table 1** Patient characteristics

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>% Inadequate Prep (B/B)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;60</td>
<td>22/26</td>
<td>0.62</td>
</tr>
<tr>
<td>BMI &gt;30 kg/m²</td>
<td>14 (9/55)</td>
<td>0.52</td>
</tr>
<tr>
<td>Sex: Male</td>
<td>18 (4/22)</td>
<td>0.21</td>
</tr>
<tr>
<td>Female</td>
<td>13 (10/76)</td>
<td></td>
</tr>
<tr>
<td>Prior abdominal surgery</td>
<td>14 (5/9)</td>
<td>0.59</td>
</tr>
<tr>
<td>Neurologic comorbidity</td>
<td>32 (6/19)</td>
<td>0.04</td>
</tr>
<tr>
<td>Medical comorbidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>40 (2/5)</td>
<td>0.16</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9 (1/11)</td>
<td>0.59</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19 (3/16)</td>
<td>0.05</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>31 (5/16)</td>
<td>0.05</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>25 (1/4)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

10.1136/jim-2022-MW.46(1598)
Abstract 47 Figure 1  
Mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>No IAH No event</th>
<th>IAH No event</th>
<th>IAH Event</th>
<th>Odds ratio with 95% CI</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen, 2008</td>
<td>29 1</td>
<td>23 1</td>
<td></td>
<td>1.26 [ 0.07, 21.27]</td>
<td>4.32</td>
</tr>
<tr>
<td>Gupta, 2021</td>
<td>18 2</td>
<td>31 10</td>
<td></td>
<td>2.90 [ 0.57, 14.75]</td>
<td>10.38</td>
</tr>
<tr>
<td>De Weeke, 2005</td>
<td>5 1</td>
<td>13 8</td>
<td></td>
<td>3.08 [ 0.30, 31.33]</td>
<td>6.04</td>
</tr>
<tr>
<td>Goenka, 2020</td>
<td>64 3</td>
<td>63 12</td>
<td></td>
<td>4.06 [ 1.09, 15.09]</td>
<td>13.09</td>
</tr>
<tr>
<td>Al-Bahrani, 2008</td>
<td>6 1</td>
<td>6 5</td>
<td></td>
<td>5.00 [ 0.44, 56.62]</td>
<td>5.61</td>
</tr>
<tr>
<td>Bhandari, 2013</td>
<td>8 0</td>
<td>4 1</td>
<td></td>
<td>5.67 [ 0.19, 169.53]</td>
<td>3.11</td>
</tr>
<tr>
<td>Ke, 2011</td>
<td>22 0</td>
<td>31 5</td>
<td></td>
<td>7.86 [ 0.41, 149.40]</td>
<td>4.02</td>
</tr>
<tr>
<td>Marcos-Neira, 2017</td>
<td>26 1</td>
<td>120 44</td>
<td></td>
<td>9.53 [ 1.26, 72.37]</td>
<td>7.50</td>
</tr>
<tr>
<td>Stojanovic, 2019</td>
<td>37 3</td>
<td>32 28</td>
<td></td>
<td>10.79 [ 3.00, 38.86]</td>
<td>14.08</td>
</tr>
<tr>
<td>Kordia, 2020</td>
<td>17 0</td>
<td>10 8</td>
<td></td>
<td>28.33 [ 1.48, 542.96]</td>
<td>4.00</td>
</tr>
<tr>
<td>Pupelis, 2006</td>
<td>41 0</td>
<td>18 6</td>
<td></td>
<td>29.16 [ 1.56, 545.13]</td>
<td>4.06</td>
</tr>
<tr>
<td>Pupelis, 2002</td>
<td>26 0</td>
<td>7 4</td>
<td></td>
<td>31.80 [ 1.53, 659.57]</td>
<td>3.82</td>
</tr>
<tr>
<td>Verma, 2021</td>
<td>17 0</td>
<td>10 10</td>
<td></td>
<td>35.00 [ 1.85, 660.99]</td>
<td>4.04</td>
</tr>
<tr>
<td>Atken, 2014</td>
<td>178 4</td>
<td>20 16</td>
<td></td>
<td>35.60 [ 10.84, 116.92]</td>
<td>15.32</td>
</tr>
</tbody>
</table>

Overall: Heterogeneity: $\chi^2 = 0.30, I^2 = 22.49\%$, $H^2 = 1.29$
Test of $\theta = 0$: $Q(13) = 14.13, p = 0.36$
Test of $\theta = 0$: $z = 6.87, p = 0.00$

Random-effects REML model
Sorted by: _meta_es

Abstract 47 Figure 2  
Mortality with subgrouping according to ACS patients’ exclusion. ACS: abdominal compartment syndrome
Abstract 47 Figure 3  Mortality with subgrouping according to IAH pressure cut off. IAH: intra-abdominal hypertension

Abstract 47 Figure 4  Multiorgan organ dysfunction syndrome
Multiorgan dysfunction syndrome was more likely in patients with IAH with OR 5.33 (CI95% 1.80–15.74) (I²=29.43%). Individual organ systems were further investigated and showed IAH was associated with increased renal, respiratory, and cardiovascular failure with OR 4 (CI95% 1.26–12.69), 8.06 (CI95% 3.40–19.11), and 52.56 (CI95% 10.07–274.43), respectively. Pancreatic necrosis was also more common in the IAH group with OR 3.62 (CI95% 1.07–12.26); however, other local complications, including infected necrosis and surgical intervention, were not statistically significant between the two groups.

**Conclusion** Patients admitted to the hospital with severe acute pancreatitis have higher odds for mortality, MODS, renal, respiratory, and cardiovascular failure if they developed IAH.
when compared to patients who have normal IAP. Our study reinforces, that development of IAH is a strong predictor of mortality and poor clinical outcome in such a population.

Introduction/Background

Millions of people worldwide suffer from gastroesophageal reflux disease (GERD). Many factors contribute to the development of GERD, but the disorder primarily stems from transient lower esophageal sphincter relaxation which results in acid reflux. As described in the pathophysiology of acid reflux and asthma, esophageal acid is thought to cause bronchoconstriction through three mechanisms one of them is increased vagal tone which can also affect the atrioventricular (AV) node and result in bradycardia. In severe cases AV block.

Objective(s)

The objective of this study was to investigate the effect of GERD on mortality in patients admitted with bradycardia or AV block.

Methods

A retrospective study was conducted utilizing the Nationwide Inpatient Sample database (NIS) for the years 2016 to 2018. Patients with bradycardia or AV block were identified using ICD-10 diagnosis codes R00.1, I44.0, I44.1, I44.2, I44.30, or I44.39 from all listed primary discharge diagnoses. Patients younger than 18 years of age, admitted for elective reasons, or patients with missing information were excluded. Patients with GERD were also identified using ICD 10 code K21, K21.0, or K21.9. We further divided the patient population into two groups, with and without GERD. Univariate logistic regression analysis was performed between GERD and bradycardia/AV block. Multivariate regression analysis was then done while adjusting for presumed confounders.

Results

There were 258,714 patients included in this study, 21.03% of them had GERD. Adults admitted to the hospitals for non-elective reasons and with GERD have 36% decreased odds of mortality compared to patients who did not have GERD, and this relationship was statistically significant (Odds Ratio (OR) of 0.64, 95% confidence interval (CI) [0.53–0.78], P-value of 0.00). When adjusting for other presumed confounders using multivariate logistic regression adjusted OR was 0.58, 95% CI [0.48–0.71], with a P-value of 0.00.

Conclusion

This study demonstrates that GERD decreases the odds of mortality in adult patients admitted to the hospital with bradycardia or AV block. The mechanism for the protective effect is unknown due to the nature of the study being retrospective. There are two possibilities for less mortality; the first is: the role of the H2 blocker and proton pump inhibitors, and the second is: these patients are conditioned with bradycardia due to long-term acid reflux and increased vagal tone as many patients are symptomatic despite therapy. Thus, further cohort studies are needed to assess this relationship.
Abstract 48 Table 2  Univariate logistic regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>P value</th>
<th>[95% Conf. Interval] Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>GERD</td>
<td>0.64</td>
<td>0.00</td>
<td>0.53</td>
<td>0.78</td>
</tr>
<tr>
<td>Age</td>
<td>1.04</td>
<td>0.00</td>
<td>1.03</td>
<td>1.05</td>
</tr>
<tr>
<td>Gender</td>
<td>1.18</td>
<td>0.02</td>
<td>1.02</td>
<td>1.35</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>1.01</td>
<td>0.96</td>
<td>0.81</td>
<td>1.25</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.63</td>
<td>0.01</td>
<td>0.46</td>
<td>0.87</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>1.23</td>
<td>0.30</td>
<td>0.83</td>
<td>1.82</td>
</tr>
<tr>
<td>Native American</td>
<td>1.28</td>
<td>0.58</td>
<td>0.53</td>
<td>3.06</td>
</tr>
<tr>
<td>other</td>
<td>0.92</td>
<td>0.72</td>
<td>0.58</td>
<td>1.46</td>
</tr>
</tbody>
</table>

Medline household income national quartile for patients zip code

- 46,000S-58,999$ 0.98 0.81 1.18
- 59,000S-78,999$ 0.92 0.41 1.12
- 79,000S or more 1.04 0.69 1.28

Census division of hospital

<table>
<thead>
<tr>
<th>Region</th>
<th>Value</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Middle Atlantic</td>
<td>1.19</td>
<td>0.35 1.69</td>
</tr>
<tr>
<td>East North Central</td>
<td>1.11</td>
<td>0.56 1.59</td>
</tr>
<tr>
<td>West North Central</td>
<td>1.27</td>
<td>0.24 1.91</td>
</tr>
<tr>
<td>South Atlantic</td>
<td>0.97</td>
<td>0.86 1.38</td>
</tr>
<tr>
<td>East South Central</td>
<td>1.26</td>
<td>0.26 1.89</td>
</tr>
<tr>
<td>West South Central</td>
<td>1.01</td>
<td>0.96 1.49</td>
</tr>
<tr>
<td>Mountain</td>
<td>0.97</td>
<td>0.90 1.53</td>
</tr>
<tr>
<td>Pacific</td>
<td>1.23</td>
<td>0.27 1.76</td>
</tr>
</tbody>
</table>

Region of hospital

- Midwest 1.02 0.87 1.25
- South Atlantic 0.90 0.29 1.09
- West 1.01 0.92 1.26

Bed size of hospital

- Medium 1.00 1.00 1.24
- Large 1.14 0.21 3.38

Primary Expected Payer

- Medicaid 0.56 0.00 0.83
- Private Including HMO 0.62 0.00 0.79
- Self-pay 0.83 0.55 1.52
- Others 0.59 0.10 1.10

Charlson Comorbidity Index 1.32 0.00 1.29

Abstract 49 Table 1  Patients characteristics

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Cirrhosis</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (% of patients)</td>
<td>70,404 (11.16%)</td>
<td>560,405 (89.84%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>58.65</td>
<td>66.51</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Gender (%)</td>
<td>Males</td>
<td>62.37%</td>
<td>54.30%</td>
</tr>
<tr>
<td>Females</td>
<td>37.63%</td>
<td>45.70%</td>
<td></td>
</tr>
<tr>
<td>Race (%)</td>
<td>White</td>
<td>65.32%</td>
<td>69.48%</td>
</tr>
<tr>
<td></td>
<td>African American</td>
<td>10.63%</td>
<td>14.94%</td>
</tr>
<tr>
<td></td>
<td>Hispanic</td>
<td>17.07%</td>
<td>8.84%</td>
</tr>
<tr>
<td></td>
<td>Asian/Pacific Islander</td>
<td>2.03%</td>
<td>3.60%</td>
</tr>
<tr>
<td></td>
<td>Native American</td>
<td>2.17%</td>
<td>0.69%</td>
</tr>
<tr>
<td>Other</td>
<td>2.79%</td>
<td>2.44%</td>
<td></td>
</tr>
<tr>
<td>Median household income (%)</td>
<td>15-45,999$ 34.06%</td>
<td>29.70%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>46,000S-58,999$ 26.92%</td>
<td>26.41%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>59,000S-78,999$ 22.88%</td>
<td>23.97%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>79,000S or more 16.14%</td>
<td>19.92%</td>
<td></td>
</tr>
<tr>
<td>Hospital size (%)</td>
<td>Small</td>
<td>17.40%</td>
<td>19.37%</td>
</tr>
<tr>
<td></td>
<td>Medium</td>
<td>29.55%</td>
<td>30.98%</td>
</tr>
<tr>
<td></td>
<td>Large</td>
<td>53.05%</td>
<td>49.66%</td>
</tr>
<tr>
<td>Location/teaching status of hospital (%)</td>
<td>Rural</td>
<td>5.83%</td>
<td>7.81%</td>
</tr>
<tr>
<td></td>
<td>Urban non-teaching</td>
<td>23.76%</td>
<td>25.78%</td>
</tr>
<tr>
<td></td>
<td>Urban teaching</td>
<td>70.41%</td>
<td>66.41%</td>
</tr>
<tr>
<td>Region of hospital (%)</td>
<td>Northeast</td>
<td>15.12%</td>
<td>17.55%</td>
</tr>
<tr>
<td></td>
<td>Midwest</td>
<td>19.34%</td>
<td>22.04%</td>
</tr>
<tr>
<td></td>
<td>South</td>
<td>39.31%</td>
<td>39.10%</td>
</tr>
<tr>
<td></td>
<td>West</td>
<td>26.23%</td>
<td>21.31%</td>
</tr>
<tr>
<td>Charlson Comorbidity Index (%)</td>
<td>0</td>
<td>0.07%</td>
<td>10.37%</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>7.64%</td>
<td>27.18%</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>9.33%</td>
<td>19.72%</td>
</tr>
<tr>
<td></td>
<td>&gt;=3</td>
<td>82.97%</td>
<td>42.73%</td>
</tr>
</tbody>
</table>
mortality. Compared to variceal upper gastrointestinal bleeding (VUGIB), non-variceal upper gastrointestinal bleeding (NVUGIB) is much less studied in the literature.

**Objective(s)**

This study aims to evaluate the impact of NVUGIB in hospitalized patients with cirrhosis.

**Methods**

The United States Nationwide Inpatient Sample (NIS) was used to extract hospitalization data of patients admitted between January 1, 2016, to December 31, 2018. Using International Classification of Diseases 10th revision (ICD-10 CM) codes, we identified patients with a primary discharge diagnosis of NVUGIB and a concomitant diagnosis of cirrhosis. The control group included patients with a primary discharge diagnosis of NVUGIB without cirrhosis. Our primary outcome was in-hospital mortality. Our secondary outcomes were length of stay (LOS) and hospital charges. Statistical analyses were performed using STATA 17 (STATA Corp., College Station, TX). Multivariate logistic regression was used to adjust for the relevant variables while determining the impact of cirrhosis on the outcomes of NVUGIB.

**Results**

During the study period, an estimated 630,809 patients were admitted for NVUGIB. Of these patients, 70,404 had cirrhosis (table 1). Compared with patients without cirrhosis, patients with cirrhosis had higher mortality (3.4% vs. 1.8%, P < 0.01). Additionally, compensated cirrhotics had higher mortality than decompensated cirrhotics (3.7% vs. 3% P < 0.04). After adjusting for confounders with multivariate analysis, the presence of cirrhosis independently increased mortality (adjusted odds ratio [AOR] 1.76, 95% confidence interval [CI], 1.57–1.98) (table 2). However, when adjusted for confounders, decompensated cirrhotics did not have a statistically significant difference in mortality rate than compensated cirrhotics (AOR 1.19, 95% CI, 0.97–1.45). Patients with cirrhosis were slightly more likely to receive an endoscopy within the first 24 hours of admission (AOR 1.13, 95% CI, 1.09–1.18). Patients with cirrhosis had higher hospitalization charges (mean increase, 2901 $; P < 0.01). There was no statistically significant difference in LOS between the cirrhotic and non-cirrhotic groups (P = 0.52).

**Conclusion**

Patients with cirrhosis who were admitted with NVUGIB had higher mortality and hospital charges than those without cirrhosis. Cirrhotic patients were more likely to undergo an endoscopy in the first 24 hours of hospitalization. Diagnosis of cirrhosis among hospitalized patients with NVUGIB was associated with a significant healthcare burden and carries higher mortality than in patients without cirrhosis. It is pertinent to appropriately treat GI bleeding in this group of high-risk individuals.

**Genetic and molecular medicine**

**REVIVIFY® GEL ATTENUATES HUMAN BRAIN MICROVASCULAR ENDOTHELIAL CELLS (HBMEC) FROM OXIDATIVE DAMAGE**

Roksana Akter, 1Syeda Azroze, 2Ziauddin Ahmed, 3AHM Ashraf, 4Liaquat Hossain, 1Ahmed Pantho, 1Mohammad Uddin. 1Orion Institute for Translational Medicine; 2Lewis Katz School of Medicine; 3The University of Texas at Austin; 4Advance Pharmaceutical

10.1136/jim-2022-MW.49

**Introduction/Background**

Background: Accumulating data suggests that oxidative stress and mitochondrial damage are involved in the pathogenesis of neurodegenerative disorders.
including Parkinson Disease [PD], Multiple Sclerosis [MS], Alzheimer’s Disease [AD], and many others. Brain uses about 20% of oxygen consumption, thus high producer of reactive oxygen species [ROS]. Also brain cell membrane composed of more unsaturated fatty acids [M UFA and PUFA], thus more prone to lipid auto-oxidation due to ROS. REVIVIFY® Gel, addresses instant reduction of oxidative stress from multi-dimensional pathways and resulted an immediate effect induced by the disease symptoms.

**Objective(s)** The purpose of the study is to evaluate whether REVIVIFY® Gel attenuates human brain microvascular endothelial cells (HBMEC) from oxidative damage.

**Methods** Human brain microvascular endothelial cells (HBMEC) were seeded on 6 well plates in hypoxia condition. Prior to treatment, cells were incubated in serum free media for 24 hours. Cells will be treated with following agents: 1. Superoxide Dismutase only; 2. Prebiotic fiber only; 3. Fruit juice only; 4. superoxide Dismutase + Prebiotic fiber + Fruit juice (Combination); 5. Negative Control: Cell culture media for 48 hours. Enzyme-Linked Immunosorbent Assay: After the 48h incubation, the media were removed from cells were placed in tubes. To evaluate whether REVIVIFY® Gel attenuated human brain microvascular endothelial cells (HBMEC) from oxidative damage. The following biomarkers were evaluated in a hypoxia-induced HBMEC culture media: 1. Malondialdehyde (MDA); 2. 4-Hydroxynonenal, or 4-hydroxy-2-nonenal or 4-HNE or HNE; 3. Protein Carbonyls; and 4. 3-nitrotyrosine by commercially available ELISA Kits as described previously.

**Results** The hypoxia increased the lipid oxidative damaged biomarkers: Malondialdehyde (MDA) and 4-Hydroxynonenal (HNE) in HBMEC. REVIVIFY® Gel significantly attenuated the hypoxia-induced upregulation of MDA and HNE. The protein oxidative damage biomarkers: Protein Carbonyls (PC); and 3-nitrotyrosine were elevated at the hypoxic condition in HBMEC. REVIVIFY® augmented the hypoxia-induced upregulation of Protein Carbonyls and 3-nitrotyrosine in HBMEC.

**Conclusion** REVIVIFY® Gel; Pertaining to PD, it can improve motor activity, muscle stiffness, and overall body response with less exhaustion. For AD, it may improve the memory response, coordination with surrounding atmosphere. As others, it can improve focus, concentration, and alertness, which may be beneficial to people with learning disability, people with autistic problem, people with mental exhaustion, and can benefit to the people who needs study focus, or job associated with high concentration. The pre-biotic soluble corn fiber encompasses the healthy gut-echo-system where the modulation of beneficiary microbes influences various positive neurological effect. The gut-brain bi-directional axis can relate instant neuro-responses. Thus, REVIVIFY® PRO-VITALITY GEL is unique and exert prompt responses towards neuro disease induced symptoms in PD, MS, AD and other conditions.
Mesenchymal stem cells will model KS; B-cells (BCBL-1 and BC-3) will model PEL. Ultimately this will be accomplished by comparing the cell cycle distribution of cells treated with solvent against those inhibited with a PLD2 inhibitor for 24–48 hours.

**Methods**

**Materials** Human B-cells (healthy control), Control (BJAB) – Burkitt Lymphoma Cell, which is KSHV negative and EBV negative. PEL (BCBL-1, BC-3) – KSHV positive and EBV negative cells. Human mesenchymal stem cells (Adherent cells, a model for KS): Uninfected and KSHV (10 DNA copies) infected for 48 hours.

**Methods:** Cells were washed, prepared, fixed with 80% ethanol, and stained with Propidium Iodine/RNase. Samples were then analyzed on FACS analysis and ModFit Lt V3 software. The percent of cells in G0/G1, S, and G2/M phase were calculated.

**Results**

**PEL Model**

<table>
<thead>
<tr>
<th></th>
<th>uninhibited</th>
<th>inhibited</th>
</tr>
</thead>
<tbody>
<tr>
<td>BJAB</td>
<td>G0/G1 .628; S .146; G2 .201</td>
<td>G0/G1 .710; S .145; G2 .139</td>
</tr>
<tr>
<td>BCBL1</td>
<td>G0/G1 .673; S .169; G2 .151</td>
<td>G0/G1 .617; S .271; G2 .109</td>
</tr>
</tbody>
</table>

**KS Model**

<table>
<thead>
<tr>
<th></th>
<th>uninhibited</th>
<th>inhibited</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLD2</td>
<td>G0/G1 .785; S .067; G2 .139</td>
<td>G0/G1 .763; S .04; G2 .063</td>
</tr>
</tbody>
</table>

**Conclusion**

There is statistically significant induction in G0/G1 phase in KSHV infected MSCs upon PLD2 inhibition but not statistically significant induction of G0/G1 in PEL. There are several possible explanations for these findings: 1. MSCs are de novo infected, whereas the PEL-cells are already carrying the viral genome. Studies have shown that PLD2 is important for viral entry into the host cell. The protective effects PLD2 inhibition would have on viral entry are not observed in B-cells as these cells already carry virus. 2. PLD2 is part of the larger family of phospholipase Ds. There is a possibility that PLD1’s redundant function could be sufficient in the absence of PLD2 for cell survival of the PEL cells. 3. The inhibitory procedure was insufficient and/or toxic to the cell lines. Follow-up tests should be done on various cell lines to be sure that there was sufficient PLD2 inhibition in PEL cells. These data, when paired with studies on PLD1, can begin to show a more complete picture on the role of PLD as a potential therapeutic target.

---

### Abstract 51 Figure 3  MSC model results

**52 CHRONIC ILLNESS ALTERS ODDS OF EXPOSURE TO PRESCRIPTION DRUGS WITH EVIDENCE-BASED PHARMACOGENOMIC INFORMATION FOR BLACK AND WHITE PATIENTS**

1Loren Saulsberry, 1Jacob Jameson, 1Keith Danahey, 1M Eileen Dolan, 2Sarah Gollust, 1Robert Gibbons, 1Peter O’Donnell. 1The University of Chicago; 2University of Minnesota

**Introduction/Background** Chronic conditions are the top drivers of morbidity and mortality in the United States. Prescription drugs are a critical foundation in the medical treatment and care management for chronic conditions, which disproportionately affect underrepresented and medically underserved populations. Several of the prescription drugs commonly used to treat prevalent chronic conditions among U.S. adults have associated evidence-based pharmacogenomic (PGx) information to guide prescribing.

**Objective(s)** The objective was to assess the impact of various chronic conditions and race/ethnicity on exposure to drugs with potentially actionable PGx information among adults.

**Methods** We identified adults (18+ years) with chronic conditions (cardiovascular disease, hypertension, high cholesterol, asthma, cancer, and diabetes) in a nationally representative Agency for Healthcare Research and Quality (AHRQ) dataset from 2014–2019 including patient demographics and prescription drug use. PGx drugs were those with potentially actionable information as defined by U.S. Food and Drug Administration (FDA) or Clinical Pharmacogenetics Implementation Consortium (CPIC). With the primary outcome being prescriptions for PGx drugs, we performed logistic regression analyses by chronic condition and adjusted models for race/ethnicity, age, and gender. We then evaluated the variables significantly contributing to PGx drug exposure from these logistic regression analyses, including chronic conditions and race/ethnicity, for interactions potentially impacting PGx drug exposure.
Results In the study population (N=31,955,810 patients) with prescription drug use, 35% reported cardiovascular disease, 25% hypertension, 22% high cholesterol, 11% asthma, 7% cancer (any type), and 6% diabetes. Patients self-reported as 43% non-Hispanic White, 18% non-Hispanic Black, and 29% Hispanic; 85% non-elderly; and 52% female. Report of diagnosis with a chronic condition presented as a strong main effect, with odds of PGx drug exposure at least four times higher across all conditions (p < .0001). The chronic conditions with the highest odds of PGx exposure were diabetes (OR=5.98; 95% CI: 4.94–7.24; p < .0001) and cardiovascular disease (OR=4.95; 95% CI: 4.23–4.86; p < .0001). Increasing age was significantly associated with PGx drug exposure (p < .001). Black patients also had higher odds of PGx medication exposure than Whites (OR= 1.23; 95% CI: 1.15–1.32; p < .0001). In our interactions analyses, having any type of cancer increased the odds of PGx exposure specifically for Blacks (OR=10.6; 95% CI: 7.67–13.5; p < .0001 for Black patients vs. OR=9.0; 95% CI: 7.92–10.0; p < .0001 for White patients).

Conclusion We found an overall increase in the odds of PGx drug exposure due to having any chronic condition, and in particular, greater odds of PGx drug exposure for Black vs. White patients with cancer. These findings suggest a potentially meaningful impact of genetically-guided prescribing for minority patient populations managing chronic conditions.

ROLE OF PHOSPHOLIPASE D IN MODULATING MAMMALIAN TARGET OF RAPAMYCIN (mTOR) SIGNALING IN PRIMARY EFFUSION LYMPHOMA (PEL) CELLS

Khalil-Ur-Zaman Qadri, Robert Deblander, Adina Dobre, Asha Kumari, Olivia Powrozek, Neelam Sharma-Walia. Rosalind Franklin University of Medicine and Science

Introducation/Background Kaposi’s sarcoma-associated herpesvirus (KSHV), also termed as human herpesvirus 8 (HHV-8), is etiologically associated with Kaposi’s Sarcoma (KS), B cell lymphoproliferative primary effusion lymphoma (PEL), and Multicentric Castleman’s disease (MCD). Current treatments for KS and PEL rely on systemic chemotherapeutics developed for non-virus-associated cancers that target DNA replication of all dividing cells. There is an emerging need to find specific therapeutic targets for alternative treatment options for KS and PEL. Phospholipase D (PLD) is an enzyme that belongs to the phospholipase superfamily. It hydrolyzes phosphatidylcholine to make phosphatidate (PA) and choline. PA can affect many cellular signaling pathways, with one of them being mammalian targets of rapamycin (mTOR), which plays a huge role in cancer cell survival and growth. There are two isozymes of PLD, PLD1, and PLD2. PLD1 (120 kDa) is an enzyme present in the inner membranes of secretory granules, endosomes, lysosomes, and Golgi complex in the mammalian cells. Here, we hypothesized that PLD1 inhibitor treatment inhibits mTOR signaling in KSHV infected cells.

Objective(s) To obtain novel information highlighting the functionality of PLD1 inhibitors in modulating mTOR signaling in KSHV infected PEL cell lines.

Methods Materials: Human cell lines BCBL-1 (PEL (+)/EBV (-)/KSHV (+)) and BC-3 (PEL (+)/EBV (+)/KSHV; Control cell line BJAB (EBV(-)/KSHV(-)/Burkitt Lymphoma (+)). Methods PEL (BCBL-1, BC-3) and control (BJAB) cells were untreated or treated with a non-cytotoxic dose of PLD1 inhibitor for 48h. Cell extracts were harvested and Western blotted using total and phospho antibodies of AKT, ERK, STAT-3, and mTOR.

Results KS tissue sections and KSHV infected PEL cells abundantly expressed appreciable level of PLD1. BCBL-1 cells also showed staining for PLD1. Treatment with PLD1 inhibitor VU0155069 down regulated AKT, ERK, STAT-3, and mTOR phosphorylation in KSHV infected BCBL-1 and BC-3 cells as compared to control BJAB cells. PLD1 inhibition in PEL cells could potentially regulate KSHV infected cell proliferation and gene expression.

Conclusion Our results suggest that PLD1 could be a therapeutic target for KSHV infected PEL cells, but further studies are needed to conclude if inhibition could be a primary treatment. A potential avenue to study could be combining inhibitors of PLD1 and other enzymes, such as mTOR, in infected cell lines and seeing if growth and proliferation is further affected.

Hematology and oncology

HUMORAL IMMUNE RESPONSE FOLLOWING COVID-19 VACCINATION IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA AND OTHER INDOLENT LYMPHOMAS: A LARGE, SINGLE CENTER OBSERVATIONAL STUDY

Peter Doukas, Frederique St Pierre, Jennifer Boyer, Mariana Nieves, Shuo Ma. McGaw Medical Center of Northwestern University; Division of Hematology-Oncology, Northwestern Feinberg School of Medicine

Introduction/Background Chronic lymphocytic leukemia (CLL) and other Non-Hodgkin’s lymphomas (NHLs) are associated with broad immunosuppression, conferring a greater risk for infection-related morbidity and mortality. During the SARS-CoV-2 pandemic, patients with these conditions have been shown to be more susceptible to severe cases of infection. Vaccination against SARS-CoV-2 generally protects against severe disease, but there is scarce data on immune response in those with lymphoid malignancies.

Objective(s) Our study aims to analyze antibody (Ab) response to vaccination against SARS-CoV-2 in patients with CLL, Waldenstrom macroglobulinemia (WM) and other NHLs.

Methods There were 398 patients with lymphoid malignancies seen between January and October 2021 screened for eligibility. Ab titers using the Access SAR-COV-2 assay developed by Beckman Coulter Inc were obtained after the completion of a vaccination series with Pfizer (n=146), Moderna (n=90), Johnson & Johnson (n=1) or multiple brands (n=3). A response was defined as a positive total Ab or spike protein Ab. Groups were compared using chi-square tests, and a p-value of < 0.05 was statistically significant.

Results There were 240 patients with post-vaccination SARS-CoV-2 Ab results included. Ab response was 50% in CLL, 67% in WM, and 71% in the remaining NHLs. In the CLL cohort (n=181), current or prior cancer therapy at any time
led to a lower rate of positive Ab’s compared to treatment-naive patients (36% vs. 68%; p=0.000019), and response was particularly low in patients who had received anti-CD20 immunotherapy at any time (28% vs. 61%; p=0.000032). There was a trend towards lower Ab response in patients who received anti-CD20 agents within a year from vaccination compared to those who had these therapies more than one year prior (20% vs. 37%; p=0.14). For CLll patients, there was a significant difference in Ab response when receiving the Moderna series (61%) compared to Pfizer (44%) (p=0.028). More information is summarized in table 1.

Conclusion This study provides data from a large cohort of patients with CLL and other NHLs on Ab response to SARS-CoV-2 vaccination. Active or prior therapy for CLL was associated with lower rates of Ab response to vaccination, especially when treated with anti-CD20 therapy, which is consistent with prior publications. However, we also found a significant increase in Ab response rates after Moderna SARS-CoV-2 vaccination in treated CLL patients compared to other vaccination series.

Abstract 54 Table 1 Antibody response rate in CLL, WM and other NHL after SARS-CoV-2 vaccination

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>All Patients</th>
<th>Moderna</th>
<th>Pfizer</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL (n = 181)</td>
<td>50% (91/181)</td>
<td>61% (44/72)</td>
<td>44% (47/106)</td>
<td>0.028</td>
</tr>
<tr>
<td>• No Treatment (n = 79)</td>
<td>68% (54/79)</td>
<td>71% (25/35)</td>
<td>66% (29/44)</td>
<td>0.60</td>
</tr>
<tr>
<td>• Any Treatment (n = 102)</td>
<td>36% (37/102)**</td>
<td>51% (19/37)</td>
<td>29% (18/62)</td>
<td>0.026</td>
</tr>
<tr>
<td>• BTK Inhibitor (n = 76)</td>
<td>33% (25/78)**</td>
<td>54% (14/26)</td>
<td>23% (11/48)</td>
<td>0.0072</td>
</tr>
<tr>
<td>• Anti-CD20 Ab (n = 68)</td>
<td>32% (21/66)**</td>
<td>42% (10/24)</td>
<td>26% (11/42)</td>
<td>0.19</td>
</tr>
<tr>
<td>• BCI-2 Inhibitor (n = 30)</td>
<td>37% (11/30)</td>
<td>46% (6/13)</td>
<td>29% (5/17)</td>
<td>0.35</td>
</tr>
<tr>
<td>WM (n = 21)</td>
<td>67% (14/21)</td>
<td>88% (7/8)</td>
<td>54% (7/13)</td>
<td>0.11</td>
</tr>
<tr>
<td>Other NHLs (n = 38)</td>
<td>71% (27/38)</td>
<td>80% (8/10)</td>
<td>70% (19/27)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

*Comparing antibody positivity in respective subgroups among patient who received either the Moderna or Pfizer vaccination. P-value calculated using chi-square testing and a value of < 0.05 is considered statistically significant. ** Some patients excluded from subsequent p-value calculation due to receiving doses from different vaccine brands. †Denotes current or prior therapy with specified CLL therapy and antibody response to vaccination. Some patients are included in multiple rows due to receiving multiple classes of treatment.

Abstracts Table 5

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>All Patients</th>
<th>Moderna</th>
<th>Pfizer</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL (n = 181)</td>
<td>50% (91/181)</td>
<td>61% (44/72)</td>
<td>44% (47/106)</td>
<td>0.028</td>
</tr>
<tr>
<td>• No Treatment (n = 79)</td>
<td>68% (54/79)</td>
<td>71% (25/35)</td>
<td>66% (29/44)</td>
<td>0.60</td>
</tr>
<tr>
<td>• Any Treatment (n = 102)</td>
<td>36% (37/102)**</td>
<td>51% (19/37)</td>
<td>29% (18/62)</td>
<td>0.026</td>
</tr>
<tr>
<td>• BTK Inhibitor (n = 76)</td>
<td>33% (25/78)**</td>
<td>54% (14/26)</td>
<td>23% (11/48)</td>
<td>0.0072</td>
</tr>
<tr>
<td>• Anti-CD20 Ab (n = 68)</td>
<td>32% (21/66)**</td>
<td>42% (10/24)</td>
<td>26% (11/42)</td>
<td>0.19</td>
</tr>
<tr>
<td>• BCI-2 Inhibitor (n = 30)</td>
<td>37% (11/30)</td>
<td>46% (6/13)</td>
<td>29% (5/17)</td>
<td>0.35</td>
</tr>
<tr>
<td>WM (n = 21)</td>
<td>67% (14/21)</td>
<td>88% (7/8)</td>
<td>54% (7/13)</td>
<td>0.11</td>
</tr>
<tr>
<td>Other NHLs (n = 38)</td>
<td>71% (27/38)</td>
<td>80% (8/10)</td>
<td>70% (19/27)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

1Syeda Afzoe, 2Ahmed Pantho, 3Zuberi Ashraf, 4Liaquat Hossain, 5Thomas Kuehl, 6Kimberly Pilkinton, 7David Zawieja, 1Mohammad Uddin. 1Orion Institute for Translational Medicine; 2Emergent Biotechnologies LLC; 3UT Austin; 4Advance Pharmaceutical Inc; 5Baylor Scott and White/Texas AandM Health Science Center College of Medicine; 6University of Houston Medical School; 7Texas AandM Health Science Center College of Medicine

Introduction/Background Liver cancer (LC) is the sixth leading cause of death from cancer malignancies. Although there have been tremendous improvements in therapies, patients with advanced HCC have longer survival times than they used to, but these therapies are not curative. Currently a major obstacle in cancer therapy is the inability to target tumor cells specifically thereby leaving the normal cells unaffected. Targeting a protein essential and present only in cancer cells could be an ideal therapeutic approach that selectively targets LC and spares normal hepatocytes. Recently, an unmet need of hexokinase, hexokinase domain containing one (HKDC1), was shown to have significant overexpression in LC compared to healthy liver tissue.

Objective(s) This study was aimed at revealing the previously unidentified player (HKDC1) in HCC and provide greater insight into its role in HCC progression, knowledge that is currently lacking and that promises to yield novel insights into cancer biology.

Methods Using a combination of in vitro tools and in vivo mouse models, we examined the role of HKDC1 in LC development and progression.

Results Our results show that HKDC1 ablation stops LC development and progression via its action at the mitochondria by promoting metabolic reprogramming and a shift of glucose flux away from the TCA cycle. HKDC1 ablation leads to mitochondrial dysfunction resulting in less cellular energy which cannot be compensated by enhanced glucose uptake. Moreover, we show that the interaction of HKDC1 with the mitochondria is essential for its role in LC progression, and without this interaction, mitochondrial dysfunction occurs.

Conclusion HKDC1 is highly expressed in LC cells, but only to a minimal degree in hepatocytes under normal conditions therefore targeting HKDC1, specifically its interaction with the mitochondria, reveals a highly selective approach to target cancer cells in LC.

55 THE HEXOKINASE HKDC1 INTERACTION WITH THE MITOCHONDRIA IS ESSENTIAL FOR LIVER CANCER PROGRESSION

Mid Wasim Khan, Alexander Terry, Medha Priyadarshini, Brian Layden. University of Illinois at Chicago

10.1136/jim-2022-MW.M54

Introduction/Background Liver cancer (LC) is the sixth leading cause of death from cancer malignancies. Although there have been tremendous improvements in therapies, patients with advanced HCC have longer survival times than they used to, but these therapies are not curative. Currently a major obstacle in cancer therapy is the inability to target tumor cells specifically thereby leaving the normal cells unaffected. Targeting a protein essential and present only in cancer cells could be an ideal therapeutic approach that selectively targets LC and spares normal hepatocytes. Recently, a putative fifth hexokinase, hexokinase domain containing one (HKDC1), was shown to have significant overexpression in LC compared to healthy liver tissue.

Objective(s) This study was aimed at revealing the previously unidentified player (HKDC1) in HCC and provide greater insight into its role in HCC progression, knowledge that is currently lacking and that promises to yield novel insights into cancer biology.

Methods Using a combination of in vitro tools and in vivo mouse models, we examined the role of HKDC1 in LC development and progression.

Results Our results show that HKDC1 ablation stops LC development and progression via its action at the mitochondria by promoting metabolic reprogramming and a shift of glucose flux away from the TCA cycle. HKDC1 ablation leads to mitochondrial dysfunction resulting in less cellular energy which cannot be compensated by enhanced glucose uptake. Moreover, we show that the interaction of HKDC1 with the mitochondria is essential for its role in LC progression, and without this interaction, mitochondrial dysfunction occurs.

Conclusion HKDC1 is highly expressed in LC cells, but only to a minimal degree in hepatocytes under normal conditions therefore targeting HKDC1, specifically its interaction with the mitochondria, reveals a highly selective approach to target cancer cells in LC.

56 PRE-CLINICAL EVALUATION OF CINOFUBOTALIN AS A POTENTIAL ANTI-OVARIAN CANCER AGENT

1Syeda Afzoe, 2Ahmed Pantho, 3Zuberi Ashraf, 4Liaquat Hossain, 5Thomas Kuehl, 6Kimberly Pilkinton, 7David Zawieja, 1Mohammad Uddin. 1Orion Institute for Translational Medicine; 2Emergent Biotechnologies LLC; 3UT Austin; 4Advance Pharmaceutical Inc; 5Baylor Scott and White/Texas AandM Health Science Center College of Medicine; 6University of Houston Medical School; 7Texas AandM Health Science Center College of Medicine

10.1136/jim-2022-MW.M55

Introduction/Background Epithelial ovarian cancer (EOC) is a deadly disease affecting nearly 20,000 people in the United States every year. There is considerable research looking into secondary treatments for recurrent EOC or after primary treatment failure. Despite our attempts at developing directed therapies against specific mutations, little improvement has been made.

Objective(s) We are continuing our investigation to test CINOs effects on EOC in an in vivo nude mouse model. CRL-1978, previously studied in an in vitro model, is used here to study the effects on tumor growth with CINO treatment. In this pilot study, we aim to show that CINO has antineoplastic effects on EOC in an in vivo nude mouse model. CRL-1978, previously studied in an in vitro model, is used here to study the effects on tumor growth with CINO treatment. In this pilot study, we aim to show that CINO has antineoplastic
Methods Male nu/nu mice, four to six weeks old, are injected with CRL-1978 ovarian cancer cells subcutaneously in the right flanks. When tumor volumes are measured at approximately 200–300 mm$^3$, treatment is initiated. The mice receive a 0.1 ml intraperitoneal injection twice a day for seven days according to their treatment group: vehicle (no CINO; DMSO), 1.0 mg/kg CINO, and 5.0 mg/kg CINO. Upon completion of treatment mice are monitored for up to a week before euthanasia. Xenografts are excised from mice then measured, weighed, and preserved by freezing at -80°C, lateral and transverse sections placed in optimum cutting temperature, and 10% buffered formalin. The sections that are placed in 10% buffered formalin are then sent to Histology, and H&E slides are made for each sample. The sections are then sent to Histology for microscopic examination. The results are presented as mean ± standard deviation (SD). Comparisons between more than two groups are performed by analysis of variance (one-way ANOVA). $p < 0.05$ is considered statistically significant.

Results There is a subjective but not statistically significant appearance that tumors were somewhat smaller in the vehicle group at the start of treatment. A statistically significant decrease ($p< 0.05$) in tumor size was observed after treatment with both 1 and 5 mg/kg concentrations of CINO when compared to vehicle.

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

Introduction/Background Lung cancer screening (LCS) with low-dose CT of the chest (LDCT) has been shown to save lives. However, implementation of this program in rural America is challenging because these areas are sparsely populated and medically underserved. It is estimated that one in five Americans currently live in rural areas and because rates of smoking and cancer are higher in these regions relative to urban areas. Hence, high-risk current and former smokers who reside in rural America may not undergo regular LCS as recommended by the U.S. Preventive Services Task Force. An emerging approach to address this unmet health care delivery need is deploying telehealth technologies in rural areas. We conducted a proof-of-principle quality improvement project to determine whether telehealth promotes participation of eligible veterans who reside in rural Wisconsin and the nearby upper peninsula of Michigan in LCS.

Objective(s) The objective of this project is to increase LCS participation among high-risk veterans by using telemedicine modalities to facilitate the early diagnosis of lung cancer and to reduce lung cancer-specific mortality with early interventions.

Exclusions (n=6) 1 veteran left the panel 2 veteran died 3 veterans already had LDCT in chart (3%)

Telemedicine RN contacted the veterans via phone call to discuss benefits of LDCT for early diagnosis of lung cancer (n=83)

Discussed in first attempt (n=46) Could not reach in first attempt (n=38)

Discussed in second attempt (n=11) Could not reach in second attempt (n=27)

Total contacted and discussed in 2 attempts (n=57)

Ineligible (n=16) Eligible (n=41)

Agreed (n=29) Refused (n=12)
Methods Electronic health records of 117 veterans 50–80 years of age cared for by one of us (SH) who were prescribed smoking cessation medications at a Veterans Affairs (VA) Community Based Outpatient Clinic (CBOC) in Green Bay, WI within 365 days were retrieved. This CBOC provides primary care for approximately 3,000 veterans who reside in rural northern Wisconsin and the nearby upper peninsula of Michigan. Veterans eligible for LCS without prior LDCT on record were identified and contacted over a period of two months for enrollment in LCS. Veterans who agreed to participate through a shared-decision making process were referred for LDCT and followed for four months thereafter. At the conclusion of the observation period, the number of veterans referred for LDCT and the number of LDCT performed were recorded. In addition, medical imaging reports were reviewed and scored according to Lung-RADS® Version 1.1.

Results Initially, 90 veterans (77%; 90/117) were eligible for LCS. Of those, only three (3.3%) already participated in the LCS program and underwent LDCT. In addition, three veterans were excluded from analysis, one left the program and two died during the observation period. We then contacted 83 LCS-eligible veterans of which 38 failed to respond. These veterans were contacted again four to six weeks later of which 27 failed to respond. In total, 29 veterans agreed to participate in LCS (35%, 29/83), 16 were ineligible because they quit smoking >15 years ago, and 12 declined (figures 1 & 2). Seventeen LDCT (59%; 17/29) were performed during the observation period (p< 0.05 compared to pre-enrollment). Of those, eight veterans were diagnosed with Lung-RADS 1, seven with Lung-RADS 2, one with Lung-RADS 3, and one with Lung-RADS 4B (figure 3).

Conclusion The new finding of this proof-of-principle, prospective quality improvement project is that telehealth encounters with LCS-eligible veterans residing in rural Wisconsin and the nearby upper peninsula of Michigan are associated with higher referral to and completion of LDCT. Abnormal findings detected in LDCT were addressed by follow-up LDCT and/or referral to specialty care as indicated. Accordingly, we suggest that LCS-eligible veterans who reside in rural areas are responsive to telehealth encounters that promote participation in LCS. Whether this initiative-taking, community-based telehealth approach to LCS in rural America also promotes veteran adherence to follow-up LDCT and/or clinic appointments with healthcare providers during the screening period remains to be determined.

Abstract 57 Figure 2 Increase in LCS participation after intervention

Abstract 57 Figure 3 Referral to LCS program and outcome

Abstract 58

IMPACT OF CLONAL HEMATOPOIESIS ON PATHOGENESIS AND CLINICAL OUTCOMES OF ACUTE LYMPHOBlastic LEUKEMIA

1Caner Saygin, 2Todd Knepper, 1Alexandra Rojek, 1Jeremy Segal, 1Peng Wang, 2Bijal Shah, 1Wendy Stock. 1University of Chicago; 2Moffitt Cancer Center

Introduction/Background Acute lymphoblastic leukemia (ALL) represents 20% of adult leukemias. Recent technologic advances have enabled detailed characterization of the genetic basis of leukemogenesis in ALL, including somatic structural DNA rearrangements and sequence mutations that disrupt lymphoid development, signaling, tumor suppression, and epigenetic modification. These studies also showed differences in the molecular profiles of pediatric vs adult ALL. However, adults with ALL, especially older adults (≥40 years), were underrepresented in these large series. Clinical outcomes of older adults with ALL are inferior to younger patients (Hematopoietic stem cells accumulate DNA mutations with aging, and age-related clonal hematopoesis (ARCH) has been linked to increased incidence of myeloid malignancies. The prevalence of ARCH increases logarithmically as the population ages, but its role in lymphoid leukemogenesis has not been fully established. We hypothesize that ARCH is a common precursor lesion for the development of ALL in older adults, and
ARCH-associated ALL is a unique entity with distinct molecular characteristics and clinical outcomes.

**Objective(s)** To determine the molecular and clinical characteristics of ARCH-associated ALL.

**Methods** We retrospectively studied adults with ALL treated at the University of Chicago and Moffitt Cancer Center between July 2014 and April 2021. Genetic profiling of tumor samples was performed by using Miseq Illumina next-generation sequencing (NGS) platform with a comprehensive sequencing panel covering commonly mutated myeloid and lymphoid genes. We classified pathogenicity using American College of Medical Genetics and Genomics guidelines. Single-cell DNA and protein sequencing was performed by using the Mission Bio, Inc. amplicon-based sequencing platform.

**Results** In total, 353 patients were studied: 290 (82%) had B-ALL, 50 (14%) had T-ALL and 13 (4%) had ETP-ALL (figure 1A). Overall, median age at diagnosis was 47 years (range, 18–88 years), and 213 patients (60%) were ≥40 years at diagnosis. T-lineage ALL (both typical T-ALL and ETP-ALL) was more common in younger adults (p = 0.03) and men (p = 0.014). Cytogenetic groups were as follows: 24% had Ph+ ALL, 13% had Ph-like ALL, and 3% had ALL with KMT2A rearrangement. The most frequent mutation in our adult ALL cohort was the loss of CDKN2A gene (32%), followed by mutations in TP53 (17%), IKZF1 (16%), NOTCH1 (9%), NRAS (9%), and JAK2 (6%) genes. Mutations involving the recurrently mutated genes in ARCH were seen in 105 of 353 patients (30%) in this study with the following order of frequency: TP53 (17%), DNMT3A (5%), TET2 (4%), RUNX1 (3.5%), ASXL1 (3%), IDH1/2 (2%), CUX1 (1%), and U2AF1 (1%). Variant allelic frequencies (VAFs) for the ARCH-associated mutations were higher than the mutations involving signaling pathways, which suggests the ancestral nature of the former and secondary nature of the latter (figure 1B). We investigated the association between different classes of mutations and clinical variables at diagnosis (figure 1C). The odds-ratios of the associations between continuous variables (age, white blood cell count, blast percentages) and the presence or absence of mutations (categorical) were calculated with the logistic regression analysis, with adjustment for multiple testing using the Benjamini–Hochberg method. Only associations with a q value (p value corrected for multiple hypothesis testing) was significant.

**Conclusion** Our results indicate that ARCH is commonly identified as an ancestral event in older adults with ALL, with TP53 mutations being the most prevalent. Both lymphoblasts...
and non-malignant myeloid cells share ARCH-associated mutations (e.g., TP53, ASXL1) in ALL patients, suggesting a common HSC origin for both compartments. Collectively, these data suggest that ARCH may constitute a fertile soil for acute lymphoblastic leukemogenesis and further studies are warranted to interrogate the dynamic interplay between myeloid and lymphoid compartments of these patients.

AQUAPORIN-3: GUARDIAN OF REACTIVE OXYGEN SPECIES DURING KAPOSI’S SARCOMA-ASSOCIATED HERPES VIRUS (KSHV) INFECTION BY REGULATING HOST CELL ANTIOXIDANT DEFENSE

Melanie Klemond, Morgan Mroz, Olivia Powrozek, Neelam Sharma-Walia. Rosalind Franklin University

Introduction/Background Kaposi’s sarcoma-associated herpesvirus (KSHV) is the etiological cause for primary effusion lymphoma (PEL), a highly aggressive non-Hodgkin B-cell lymphoma. PEL is characterized by the expression of KSHV latency genes within B cell plasma cells. Currently, there is no specific chemotherapeutic cure for PEL. Our previous report showed increased expression of Aquaporin 3 (AQP3), a water-, glycerol-, and H2O2- (a stable reactive oxygen species; ROS) transporting protein in KSHV-infected PEL cells. ROS participates in both the lytic and latent cycles of KSHV infection. Inhibition of ROS by antioxidant N-acetylcysteine (NAC) has not only been shown to prevent KSHV tumorigenesis but also to reduce tumor size by inhibiting proliferation and angiogenesis in endothelial Kaposi sarcoma mouse models. AQPs facilitate the uptake of ROS into cells, thus mediating the downstream intracellular signaling involved in cancer biology. We hypothesized that AQP3 mediates the transportation of ROS within PEL cells and regulates antioxidant enzymes in the infected cells.

Objective(s) The primary objective of this study is to evaluate the role of water transporting aquaporins in regulating the enzymes of the antioxidant defense system of KSHV infected cells. Our long-term goal is to understand if aquaporin inhibitors could be used as a therapeutic in KSHV associated malignancies.

Methods Materials: Human B-cells (healthy control), Control (BJAB) – Burkitt Lymphoma Cell, which is KSHV negative and EBV negative. PEL (BCBL-1, BC-3) – KSHV positive and EBV negative cells. Methods: PEL cells with silencing of AQP3 via siRNA transfection (four) were used for the preparation of RNA. RNA was converted to cDNA, which was used for assessing the gene expression analyses using an Oxidative stress array. We have standardized the non-cytotoxic concentration of a novel AQP3 inhibitor; DFP00173 and will use it in future experiments.

Results KSHV positive PEL cells transfected with AQP3 siRNA showed a significant reduction in the gene expression of antioxidant enzymes such as NADPH oxidase (NOX), and Superoxide dismutase (SOD), which are key cellular antioxidant enzymes responsible for the regulation of oxidative stress.

Conclusion Aquaporins have the potential to regulate KSHV infected cell antioxidant enzymes gene expression and maintain host cellular ROS. Therefore, targeting Aquaporins could potentially be used in treatment to control KSHV infection and ameliorate PEL.
ROLE OF AQUAPORIN-3 IN REGULATING REACTIVE OXYGEN SPECIES IN KAPOSI’S SARCOMA-ASSOCIATED HERPES VIRUS (KSHV) INFECTED PRIMARY EFFUSION LYMPHOMA (PEL) CELLS

Morgan Mroz, Melanie Klemond, Olivia Powrozek, Neelam Sharma-Walia. Rosalind Franklin University

10.1136/jim-2022-MW.59

Introduction/Background Kaposi’s sarcoma-associated herpesvirus (KSHV) is known to be the etiological cause for the proliferation disorder called primary effusion lymphoma (PEL), a non-Hodgkin B-cell lymphoma. PEL is characterized by the expression of KSHV latency genes within B cell plasma cells. Currently there is no specific chemotherapy cure for PEL. Reactive oxygen species (ROS) have previously been demonstrated to participate in both the lytic and latent cycles of KSHV infection. Inhibition of ROS by antioxidant N-acetylcysteine (NAC) has not only been shown to prevent KSHV tumorigenesis, but also to reduce tumor size by inhibiting proliferation and angiogenesis in endothelial Kaposi sarcoma mouse models. Aquaporins (AQPs) are integral membrane proteins known to facilitate the uptake of ROS into cells, thus mediating the downstream intracellular signaling involved in cancer biology. The previously reported Increased expression of AQP3 in KSHV-infected was supported in this lab via Western blot, and it was hypothesized that AQP3 mediates the transportation of ROS within PEL cells. Owing to AQP3 involvement in ROS transportation, this study suggests AQP3 might be a promising therapeutic target for PEL cells infected with KSHV.

Objective(s) To evaluate the role of aquaporin-3 in regulating the transport of reactive oxygen species in KSHV infected cells to determine if aquaporin inhibitors may be a viable therapeutic agent for KSHV associated malignancies.

Methods

Materials experimental cell lines BCBL-1 (PEL(+)/EBV (-)/KSHV (+)) and BC-3 (PEL(+)/EBV (+)/KSHV); Control cell line BJAB (EBV(+)/KSHV(+)/Burkitt Lymphoma (+)).

Methods

Cell lines underwent either AQP3 si-RNA or AQP scramble-RNA transfection. Cells were then incubated with CM-H2DCFDA, a fluorescent dye that is a useful indicator for ROS in cells. Fluorescence was measured via flow cytometry and indicated ROS levels. In addition, the PEL cell lines were treated with novel AQP3 inhibitor DFP00173 at the standardized non-cytotoxic concentration. Bioluminescent cytotoxicity assay was performed to determine the cytotoxic dose of the inhibitor. These inhibited PEL cell lines were then incubated with the fluorescent dye CM-H2DCFDA and ran through flow cytometry.

Results Flow cytometry indicated a significant decrease in ROS levels for PEL cells with silencing of AQP3 via siRNA transfection, or treatment with a novel AQP3 inhibitor; DFP00173. DFP00173 treatment further demonstrated selective cytotoxic effects on BCBL-1 and BC-3 cells, but not BJAB cells, at concentrations of 0.05μM using a bioluminescent cytotoxicity assay.

Conclusion AQP3’s involvement in ROS transportation makes the receptor a potential target for therapeutic intervention to control KSHV associated PEL.

MYELOPROLIFERATIVE HYPEREOSINOPHILIC SYNDROME WITH CONCOMITANT ISCHEMIC EVENTS

Roxanne Aleman, Spencer Deleveaux, Mauna Pandya. Advocate Christ Medical Center

10.1136/jim-2022-MW.60

Introduction/Background Eosinophils are versatile reactionary cells that play a key role in the inflammatory response. Excessive proliferation and aggregation of eosinophils have been implicated in the pathogenesis of ischemic neurologic and cardiac events. We present a rare case of hyper eosinophilic syndrome (HES) in a patient hospitalized for simultaneous acute cerebrovascular accident (CVA) and acute coronary syndrome.

Objective(s) A 53-year-old male with a past medical history of hypertension and diabetes mellitus presented with new onset bifrontal headache, right arm numbness and apraxia, and concurrent typical angina. On physical examination, he was found to have small non-tender raised nodules on the bilateral upper and lower limbs. MRI of the brain demonstrated multifocal infarcts and biochemical investigation revealed elevating troponins. CT imaging demonstrated splenomegaly of 16.4 cm. He was admitted for management of CVA and non-ST segment elevation myocardial infarction (NSTEMI). Complete blood count (CBC) revealed leukocytosis (34.4 K/mL) with an eosinophilia of 83% and an absolute eosinophil count (AEC) of 29.2 x10^3 eosinophils/μL. Serum tryptase at this time was 29.2μg/L. The patient was started on a high dose steroid, and resolution of his apraxia. Due to high suspicion for hyper eosinophilic syndrome, FISH panel and bone marrow biopsy was performed. A small focus of marrow on his biopsy showed abundant eosinophils and bland spindle cells (>15 mast cells in aggregate). FISH panel was positive for 4q12 rearrangement, consistent with a FIP1L1/PDGFRA fusion mutation. Skin biopsy of his lesions demonstrated superficial and deep inflammation with eosinophils. Diagnosis of myeloproliferative HES variant with features of mastocytosis was made and he was started on imatinib.

Methods The defining features of HES consist of eosinophilia greater than 1500/μL for greater than 6 months, with evidence of eosinophil induced tissue infiltration and injury. The ability of eosinophils to induce pathologic outcomes is influenced by a variety of parameters, including the number of eosinophils present, their location, and the degree of activation. Published data suggests that neurologic and cardiac ischemic events typically occur in HES patients with a higher leukocyte count and AEC than what is seen with our patient. Although the main lab criteria of HES was met, our case highlights that simultaneous clinical manifestations can occur in the absence of markedly high peripheral eosinophilia. As with most cases involving unexplained hypereosinophilia, a wide range of diagnostic testing was necessitated. The presence of a PDGFRA fusion mutation established a clonal disorder in our patient, supporting the diagnosis of myeloproliferative HES variant. Lack of mast cells on skin biopsy, but the presence of eosinophils further supported MPN HES variant rather than a true systemic mastocytosis. Despite recent advances in molecular and immunologic therapies, treatment for HES remains challenging due to the wide variety of etiological classifications necessitating targeted treatments. At the time of submission, KIT mutation analysis is
pending. If a KIT D816V mutation is identified, this would support use of midostaurin or the recently approved avapritinib for treatment of overlap syndrome.

**Abstract 62 Figure 1  Chest X-ray**

**Abstract 62 Figure 2  CT chest**

**MANTLE CELL LYMPHOMA, AN UNCOMMON PRESENTATION OF NON-HODGKIN LYMPHOMA**

Olaniyi Fadeyi, Lakshita Gupta, Gautam Anugu, Asaad Hakim. Womack Army Medical Center

10.1136/jim-2022-MW.61

**Introduction/Background** Mantle cell lymphoma (MCL) is a rare subtype of NHL with very poor prognosis. It could be indolent or aggressive depending on the stage at presentation. Patients tend to complain of fatigue, fever, night sweat, weight loss and loss of appetite. Patients may also present with splenomegaly, lymphadenopathy, lymphocytosis, malignant effusion and respiratory failure. Diagnosis of MCL is based on lymph node biopsy and evidence of Cyclin D1 expression. Further histological assessment may reveal pleomorphic and blastoid histological patterns which are more aggressive when compared with nodular and diffuse patterns. Based on recent advances in management, MCL international prognostic index (MIPI) which incorporates parameters like age, performance status, LDH and white blood count is now used to stratify patients as low risk, intermediate risk and high risk when trying to determine appropriate treatment course. We therefore report an advanced case of MCL, a rare subtype of NHL characterized by malignant and recurrent pleural effusion.

**Objective(s)** A 61-year-old male with past medical history of CVA, spastic left hemiplegia and seizure disorder presented to the ED from nursing home with c/o fever, shortness of breath and low oxygen saturation. Physical exam revealed tachycardia, tachypnea, weakness, rhonchi and decreased breath sounds over the left hemithorax. ABG was significant for respiratory acidosis. Preliminary laboratory results as shown on the table revealed anemia and severe leukocytosis with lymphocytic predominance. Chest x ray as shown on figure 1 was significant for large left-sided pleural effusion along with compressive atelectasis. This same finding was confirmed on CT chest as revealed on figure 2. Diffuse cervical lymphadenopathy was noticeable on CT of neck. During hospital admission, thoracentesis was completed twice with 2.4L of fluid removed on each occasion. Pleural fluid analysis showed exudative effusion with lymphocytic predominance. Cytogenetic analysis was significant for translocation between chromosome 11 and 14. Fluorescence in situ hybridization (FISH) panel analysis was positive for CCND1-IGH fusion with loss of one ATM signal on chromosome 11 which is typical of MCL. Bone marrow biopsy result was consistent with MCL. Our patient was diagnosed with MCL, a rare subtype of NHL. He was eventually scheduled to start R-CHOP therapy.

**Methods** MCL, typically defined by the translocation t (11,14) along with overexpression of Cyclin D1, remains an incurable disease with an overly aggressive clinical course. Presence of certain factors such as advanced age, elevated LDH, leukocytosis, complex karyotype, blastoid variant morphology, male sex and P53 abnormalities are closely associated with poor outcomes. This patient presented with an elevated LDH, severe leukocytosis with lymphocytic predominance and complex karyotype. Also, he had recurrent pleural effusion which is typical of advanced stage cancer. It has been reported that pleural effusions mostly characterized by lymphocytic exudates occur in approximately 20% of patients diagnosed with NHL. Meanwhile, recent advances based on better understanding of MCL has led to better outcomes due to use of novel approaches in management. For instance, patients with indolent disease (non-nodal presentation: lymphocytosis, splenomegaly) without any noticeable symptoms can be observed until symptoms develop. Based on recent guidelines, a watch-and-wait approach is recommended for indolent MCL and SOX11-negative disease. In a population-based study carried out in Canada for patients with indolent course of MCL, there was no significant difference between the observed and the treatment groups when factors such as age, sex, leukocyte count, platelet count and TP53 were considered. However, for patients with indolent disease who develop symptoms, NCCN guidelines recommend re-biopsy and T53 mutation testing to establish the appropriate treatment course. Furthermore, in patients presenting at stage I/II, NCCN suggests either chemotherapy with less aggressive regimens, radiotherapy or a combination of both. However, in advanced stages, patients are classified into young/fit vs old/unfit. Young/fit patients are considered for aggressive induction of chemotherapy followed by hematopoietic stem cell transplant (HSCT) while old/unfit patients are started on R-CHOP. Our patient is
old and unfit due to obvious comorbidities thereby making him unsuitable for HSCT. He was scheduled to start R-CHOP.

In conclusion, this case report highlights a rare presentation of NHL alongside different pathways for managing the disease based on the stage at presentation and presence of symptoms.

REFERENCES


63

UNUSUAL PRESENTATION OF AMYLOIDOSIS AS A PELVIC PSEUDO-TUMOR

Olaniyi Fadeyi, Ali Esmaeili, Phoung Nguyen, Asaad Hakim. Womack Army Medical Center

Introduction/Background Multiple myeloma is caused by abnormal proliferation of plasma cells in the bone marrow. Approximately 15% of patients with AL amyloidosis have multiple myeloma. Amyloidosis is formed by abnormal folding of soluble proteins which become insoluble fibrils that are found in various tissues and organs. It could be systemic or localized depending on how extensive pathologic fibrils are deposited. AL amyloidosis is the most common type of systemic amyloidosis which is often linked with plasma cell disorder and monoclonal light chains. It is a rare and poorly prognostic disease closely associated with monoclonal gammopathy of undetermined significance, multiple myeloma and Waldenström macroglobulinemia. Body organs mostly affected are kidneys and heart. However, vague symptoms at presentation often contribute to delays in diagnosis and prompt initiation of treatment. It is therefore imperative to consider early work-up for AL amyloidosis in patients with unexplained proteinuria, neuropathy, hepatomegaly, cardiomyopathy and myeloma-like symptoms. We therefore present a case of multiple myeloma diagnosed in a patient with AL amyloidosis.

Objective(s) A 59-year-old without any significant PMH presented to the ED with c/o several weeks of back pain, lower extremity weakness, abdominal pain, nausea, vomiting and poor oral intake. Physical examination was significant for generalized weakness, abdominal tenderness and distention. Results of peripheral blood examination, serum biochemistry test and urinalysis are shown on the Table. Also, serology markers of myocardial injury including BNP and troponin were all elevated as depicted on the Table. Chest X-ray revealed cardiomegaly. EKG showed LVH with secondary repolarization abnormality. Echo revealed concentric LVH and moderate diastolic dysfunction with EF at 60%. CT chest, abdomen and pelvis without contrast showed soft tissue mass involving the sacrum along with multiple lytic and blastic lesion involving the thoracic and lumbar spine. MRI thoracic and lumbar spine without contrast revealed several vertebral compression fractures in the thoracic spine. Skeletal bone survey showed ‘salt and pepper’ appearance in the skull (figure 1) alongside lytic bone lesion (figure 2). Result of CT guided biopsy of the right anterior pelvic wall soft tissue mass was remarkable for amyloidosis without any evidence of malignant
cells. Also, CT-guided biopsy of the soft tissue mass in the right posterior sacral region revealed atypical plasma cell infiltrate consistent with myeloma or plasmacytoma. Bone marrow biopsy with flow cytometry revealed 90% plasma cell count with lambda light chain and hypercellular bone marrow. Peripheral blood smears showed severe normocytic anemia with rouleaux formation. SPEB was remarkable for M spike. This patient was diagnosed with multiple myeloma secondary to AL amyloidosis and started on high dose pulse dexamethasone. She was immediately transferred to HLOC for inpatient chemotherapy.

Methods Multiple myeloma and AL amyloidosis are similar diseases associated with clonal proliferation of plasma cells. In multiple myeloma, simultaneous presence of amyloidosis is an indicator for unfavorable outcome. Also, AL amyloidosis in patients with multiple myeloma is an independent adverse prognostic factor even in the absence of amyloid organ involvement at the time of diagnosis. To diagnose multiple myeloma secondary to AL amyloidosis, diagnostic conditions for both diseases must be established. In this case, clinical signs of end organ damage for multiple myeloma were all noticeable. Imaging and bone marrow biopsy results were very consistent with this disease. Similarly, biopsy of soft tissue mass in the right anterior pelvic wall was remarkable for amyloidosis as revealed by Congo red stain. Both diseases can affect the kidney. Amyloid nephropathy may present with nephrotic syndrome, asymptomatic proteinuria, acute or chronic kidney disease. On presentation, this patient had significantly elevated BUN and Creatinine. Urinalysis was significant for proteinuria. Renal US revealed echogenic kidneys compatible with medical renal disease. Hemodialysis was initiated by Nephrology due to worsening renal function. As shown in previous studies, development of chronic renal failure in patients with AL amyloidosis is an independent prognostic factor for worse outcomes. AL amyloidosis can also affect the heart. Elevated serology markers of myocardial injury and Echo findings were all suggestive of heart failure associated with amyloid cardiomyopathy. While the ejection fraction may be normal, impaired ventricular filling could grossly limit cardiac output. High levels of N-terminal pro-brain natriuretic peptide and troponins are sensitive marker for cardiac dysfunction associated with AL amyloidosis. Meanwhile, prompt initiation of treatment could improve clinical outcome. Anti-plasma therapy is the cornerstone of treatment to facilitate hematologic remission and organ recovery. Use of high dose chemotherapy and hematopoietic stem cell transplantation to suppress plasma cell clones and concentration of toxic light chains tend to improve organ function and prolong survival. However, amyloid-related dysfunction of one or more organs could limit the use of aggressive treatment. Therefore, dose reductions and schedule modifications of chemotherapy regimens along with close assessment of hematologic and organ responses remain the best approach. Despite the toxicity, use of high-dose melphalan followed by autologous peripheral blood stem cell transplantation is very effective in treating AL amyloidosis. Also, combination of bortezomib, cyclophosphamide and dexamethasone are well tolerated and also associated with significant improvement of symptoms. This patient was initially started on high dose pulse dexamethasone and later placed on cyclophosphamide along with bortezomib. Although multiple myeloma is relatively common, it is rarely found with AL amyloidosis. This case report highlights rare presentation of both diseases along with the challenges associated with treatment.

REFERENCES
aspartate transaminase 89 U/L (normal: 0–41 U/L) and alanine transaminase 35 U/L (normal: 0–40 U/L), lactate 11.3 mmol/L (normal: 0.5–2.2), total protein 5 g/dL (normal: 6–8.3 g/dL), albumin 2.4 g/dL (normal: 3.5–5.7 g/dL), troponin 0.07 ng/mL (normal: < 0.04 ng/mL) and brain natriuretic peptide 65 pg/ml (normal: 0–100 pg/ml). Coagulation studies showed prothrombin time 19.7 sec (normal: 9.5–12.6 sec), international normalized ratio 1.65 (normal: 0.9–1.2), partial prothrombin time 63.8 sec (normal: 26–37 sec). Electrocardiogram showed sinus tachycardia without ST or T waves changes. Echocardiography showed preserved left ventricular systolic function with no regional wall motion abnormalities. Chest computed tomography (CT) angiography was negative for pulmonary embolism; however, it showed multiple ribs and sternal fractures in addition to right lower lobe consolidation. Imaging CT of the abdomen, pelvis and brain were unremarkable. Peripheral blood smear showed atypical monocytic cells consistent with acute monocytic leukemia (figure 1).

He continued to receive post-cardiac arrest care in the intensive care unit, which was attributed to hypoxia due to aspiration pneumonia. He received intravenous fluids, vaso pressors, packed red blood cells transfusion, and broad-spectrum antibiotics. Repeated blood work up on the following day showed a significant decrease in WBC count to 11.5×10E9/L with 45.6% of cells were monocytes. He remained unresponsive and did not follow commands. The family decided to withdraw care given the patient’s poor prognosis and underlying anoxic brain injury. He expired after two days after the initial presentation.

Methods Leukocytosis is a commonly encountered issue during clinical practice. It is important to distinguish between malignant and non-malignant causes of leukocytosis. Here, in our case, on initial presentation, severe leukocytosis with monocytic predominance was noted with a peripheral blood smear that was consistent with an underlying acute monocytic leukemia. In certain situations, hyperleukocytosis due to an underlying malignancy can be a precipitating factor for cardiac arrest. However, in our case, blood work-up showed a dramatic decrease of WBC count on the following day. This made an underlying acute leukemia a less likely diagnosis. Hyperleukocytosis is mostly a bone marrow reaction due to the current underlying condition rather than acute leukemia. However, an undiagnosed chronic myelomonocytic leukemia is possible given persistent monocytosis on the repeated blood workup. Bone marrow biopsy and aspirate are needed to confirm the diagnosis; however, unfortunately, our patient expired two days after presentation. In conclusion, leukocytosis after cardiac arrest can be reactive and can mimic acute monocytic leukemia. A repeat complete blood count is recommended before pursuing further management.

Abstract 64 Figure 1 Peripheral blood smear on the initial presentation showing atypical monocytic cells consistent with acute monocytic leukemia

Bone marrow biopsy and aspirate are needed to confirm the diagnosis; however, unfortunately, our patient expired two days after presentation. In conclusion, leukocytosis after cardiac arrest can be reactive and can mimic acute monocytic leukemia. A repeat complete blood count is recommended before pursuing further management.

A RARE CASE OF WARFARIN-INDUCED NON-UREMIC CALCIPHYLAXIS

Amanda Cecchini, Fares Ghanem, Suhib Fahmawi, Huthaifah Aburumman, Diana Nunley, East Tennessee State University

Introduction/Background Calciphylaxis is a rare phenomenon characterized by the calcification of arterioles and capillaries that supply cutaneous and subcutaneous tissue. This calcification causes narrowing of the blood vessels and results in decreased perfusion of the dermal tissues. Poor perfusion leads to cutaneous ischemia and necrosis. This is most commonly seen in end-stage renal disease (ESRD) patients on dialysis, however in extremely rare cases, may be due to other causes such as hyperparathyroidism, malignancy, severe hepatic disease, and medications such as corticosteroids and warfarin. We present a case of calciphylaxis in a patient with normal renal function which was attributed to warfarin anticoagulation therapy.

Objective(s) A 44-year-old female presented to the emergency department with a chief complaint of a bleeding, infected wound on her left leg. Past medical history was significant for type II diabetes mellitus, Factor V Leiden mutation with history of deep vein thrombosis and pulmonary embolism on chronic warfarin anticoagulation, and morbid obesity with severe debilitation. The patient attributed the inciting factor for the wound formation to irritation from the tubing of her chronic Foley catheter. She was evaluated by the surgical team and subsequently underwent wound debridement of the necrotic tissue and incision and drainage of an underlying abscess.

On histopathology, a medial thigh tissue sample showed necrosis with vascular thrombosis and calcified vascular walls consistent with calciphylaxis. A repeat wound debridement was performed three days later, and histopathology again confirmed the diagnosis of calciphylaxis.
On presentation and throughout the patient’s hospitalization, her creatinine ranged from 0.65–0.83 mg/dL, and her GFR ranged between 85–117 mL/min, ruling out uremia as a cause. Hematology was consulted for concern for warfarin-induced calciphylaxis and recommendations for future anticoagulation. Hematology recommended discontinuation of warfarin and initiation of full-dose enoxaparin until the wound healed, followed by initiation of lifelong rivaroxaban therapy.

Methods Calciphylaxis is an uncommon phenomenon, however non-uremic calciphylaxis is exceedingly rare, with only 116 cases identified in medical literature as of 2016. According to a 2017 study in JAMA Dermatology, only 18 cases of warfarin-associated non-uremic calciphylaxis have been reported. It is stipulated that warfarin, a vitamin K antagonist, may induce calciphylaxis via preventing the depletion of the molecular form of vitamin K that aids in carboxylation of certain coagulation factors such as matrix gla-protein, which prevents the deposition of calcium within arteries. Without this protein, calcium is deposited in arteries, causing arterial narrowing and thrombosis resulting in ischemia and skin necrosis. There are few treatment options available, mainly sodium thiosulfate, which chelates and helps dissolve calcium deposits. Additionally, aggressive wound care is essential for healing.

Not only is this process painful and distressing to patients, but it also carries a poor prognosis, with a mortality rate of greater than 50% within one year of diagnosis, however this data is largely based on studies of ESRD patients. Patients who have calciphylaxis from alternate causes may have more favorable prognosis. Additionally, better understanding of the pathophysiology of calciphylaxis may help researchers develop more targeted, effective treatments.

66 CENTRAL NERVOUS SYSTEM INTRAVASCULAR LARGE B CELL LYMPHOMA: IS THERE A BEST APPROACH?
Sayan Mullick Chowdhury, Narendranath Epperla. The Ohio State University
10.1136/jim-2022-MW.65

Introduction/Background Intravascular large B cell lymphoma (IVLCL) is a rare form of extra-nodal non-Hodgkin lymphoma which involves growth of lymphoma cells in the lumina of small veins, arteries and capillaries. IVLCL is a rare entity and almost all the information available currently is from individual case studies/series and small retrospective studies. Currently, the standard of care treatment for IVLCL is chemioimmunotherapy with R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone). However, IVLCL patients typically have a dismal prognosis despite treatment. Here we report a case of IVLCL involving the central nervous system (CNS) with good response and durable remission to RM-CHOP (R-CHOP with high dose methotrexate) followed by auto-HCT (autologous hematopoietic cell transplantation) consolidation.

Objective(s) The patient initially presented in early April 2019 with neurologic symptoms including ataxia, cognitive changes, and dizziness. He underwent extensive work-up including cerebral angiogram that was consistent with CNS vasculitis. He was treated with high dose steroids followed by MMF (mycophenolate mofetil). Patient was then readmitted in late April 2019 with progressively worsening neurologic symptoms including cognitive changes and ataxia. In order to discern the etiology, he underwent brain biopsy in May 2019 that came back positive IVLCL. Patient was started on C1 RM-CHOP in May 2019 and completed the 6 cycles in Aug 2019 achieving CR (complete response) on EOT (end of treatment) imaging (Both PET and MRI brain). He underwent auto-HCT consolidation with carmustine and thiopeta conditioning in October 2019 with sustained CR on day+ 90 scans (PET scan and MRI brain, Jan 2020). He continues to have surveillance MRI brain every 3–4 months and has remained in CR (last imaging, Jan 2022) for over 24 months since the consolidation auto-HCT.

Methods IVLCL is a rare disease that typically has dismal outcomes in most patients despite treatment. Several reports have shown that the risks of recurrence in IVLCL patients, with CNS involvement is significantly high and prognosis is often very poor\textsuperscript{1,2}. Studies have shown that half of the patients with IVLCL who were treated with anthracycline-based
chemotherapy relapsed and died within 18 months of diagnosis. Addition of rituximab has improved those outcomes and as such the current standard of care for new IVLCL diagnosis is R-CHOP. In this case report we show that the combination of RM-CHOP followed by consolidation auto-HCT can result in sustained long term remission in patients with IVLCL involving the CNS. This approach needs to be explored in a systematic fashion in larger cohort to validate our findings.

REFERENCES

LUNG RHABDOMYOSARCOMA
Huthafaah Aburumman, Fares Ghanem, Mohammad Darweesh, Bahaaeldin Youssef, Rami Dalbah, Diana Nunley, East Tennessee State University
10.1136/jim-2022-MW.66

Introduction/Background Rhabdomyosarcoma (RMS) is rare in adults, accounting for only 3% of soft tissue tumors in adults. Adults with rhabdomyosarcoma exhibit a worse prognosis compared to children with RMS. We describe a rare entity of rhabdomyosarcoma with an undetermined subtype in the lung.

Objective(s) We present a case of a 67-year-old lady who presented with deconditioning and significant weight loss for the past month. She had a medical history of COPD and smoking. CT angiogram revealed a 14x12 cm mediastinal mass extending to the left hilum with associated narrowing of the left-sided pulmonary arteries and bronchi consistent with neoplasia, in addition to several cavitary nodules in the left lung suggestive of metastatic lesions. CT-guided biopsy revealed increased nuclear: cytoplasm ratio (N:C), mitotic figure with apoptotic bodies, and tumor necrosis. The Immuno-stains were positive for CD56 and synaptophysin. The immunohistochemical properties of the mass were suggestive of high-grade neuroendocrine lung tumor, but additional staining was required to categorize the tumor lineage. Samples were sent to a quaternary center for a final pathology report. CT scan of the head was performed instead of a Brain MRI due to the patient’s claustrophobia. Brain imaging revealed no intracranial pathology, and the PET scan did not show any extra-thoracic lesions. The final pathology report revealed tumor cells staining positive for desmin, myogenin, and myoD1 which supported a diagnosis of rhabdomyosarcoma of unspecified subtype. The tumor was deemed unresectable, so a decision was made to treat it with radiotherapy and chemotherapy. An echocardiogram and a MUGA (multiple-gated acquisition) scan were done before initiating chemotherapy and they showed impaired cardiac function and contractility with ejection fraction (EF) of 40% and 49.5%, respectively. Therefore, chemotherapy consisting of Doxorubicin was initiated.

Methods Although small cell lung carcinoma (SCLC) is more common in an adult with a smoking history, rhabdomyosarcoma should be kept in mind. Especially when taking into consideration the overlap of some immune-stains between the two entities. That being the case, we want to emphasize the importance of staining for myogenic markers (e.g., desmin, myogenin, and myoD1) to differentiate between SCLC and RMS. In our case, the initial immunohistochemical stain results narrowed the differential diagnosis down to small cell lung carcinoma, malignant lymphoma, and rhabdomyosarcoma. Thus, we needed additional staining to determine the tumor type. The treatment of RMS in adults uses the same principles as in children and consists of chemotherapy, radiotherapy, and surgery. Our patient was a poor surgical candidate due to her multiple comorbidities and the rapid deterioration in her functional status. Therefore, the plan was to treat with radiotherapy and chemotherapy. The choice of chemotherapy was influenced by the borderline EF on MUGA scan. Hence, a single agent chemotherapy Doxorubicin was initiated with plans for outpatient radiotherapy and an outpatient echocardiogram.
follow-up. Treatment strategies for RMS in adults are still in the process of being elucidated, due to the rare nature of this cancer. Hopefully, the new advances in molecular biology will provide new opportunities for treatments in the upcoming years.

Touch preparation shows three-dimensional cohesive clusters of tumor cells with pleomorphic nuclei in a necrotic background (figure 1A and B). Histologic sections from the lung mass show infiltrative tumor cells arranged in flat sheets with abundant necrosis and mitotic figures (figure 1C and D). Cytomorphology of neoplastic cells shows a high nuclear to cytoplasmic ratio, stippled chromatin, and abundant eosinophilic cytoplasm.

SARCOMATOID VARIANT OF SALIVARY DUCT CARCINOMA MANIFESTING AS FACIAL NERVE PALSY

Saman Karimi, Ammar Karo, Maria Gonzalez. University of Illinois at Chicago

Introduction/Background Salivary Duct Carcinoma (SDC) is a highly aggressive tumor that accounts for 10% of all salivary gland malignancies. It occurs in elderly with a gender predilection for males, and predominantly arises from the major salivary glands, namely the parotid glands. Several variants of SDC have been described in the literature including micropapillary, osteoclast-type giant cells, basal-like, sarcomatoid and mucin rich variants. The sarcomatoid variant of SDC is exceptionally rare and associated with aggressive clinical course, regional and distal metastasis and a poor five-year survival rate of 32%-44%. Facial nerve palsy has been reported in 12% of SDC. Herein, we present a rare case of sarcomatoid variant of SDC in an elderly female with right facial nerve palsy on initial presentation to our institution.

Objective(s) An 84-year-old female with a five-year history of right parotid mass presents with chief complaint of several weeks of gradual right facial nerve palsy. A right radical parotidectomy was performed and gross examination revealed an unencapsulated, solid, firm, white-tan lesion measuring 9.6 x 9.5 x 6.5 cm. Microscopically, a biphasic neoplasm was identified with one component consisting of a well-circumscribe, nodule of solid architecture, with pleomorphic tumor cells with ample, granular cytoplasm arrange in a band-like single cell pattern with numerous abnormal mitoses and extensive necrosis, perineural and lymphovascular invasion. The second component was comprised of sarcomatoid, polygonal-shaped lesional cells, with irregular nuclear contour, prominent nucleoli with spindle cell and rhabdoid morphology. No heterologous elements were identified. The lesional cells expressed Cytokeratin AE1/AE3, CK-HMW, GATA3, HER2/neu, had a high proliferation index by Ki-67 immunostaining and lacked expression of vimentin, desmin and myogenin. Given the histomorphology and immunoprofile of the lesion, we favored a diagnosis of sarcomatoid variant of SCD.

Methods Sarcomatoid variant of SDC is a highly aggressive and extremely rare entity with poor prognostication. Differential diagnosis for sarcomatoid SDC include carcinosarcoma, salivary duct carcinoma ex-pleomorphic adenoma, metastatic ductal breast carcinoma, high grade mucoepidermoid carcinoma, and salivary duct carcinoma with rhabdoid features. We report this case for its infrequent histomorphological features, associated facial nerve and the important of accurate diagnosis and therapeutic management.

Infectious disease

AGE-DEPENDENT INNATE HOST RESPONSES TO INFLUENZA VIRUS IN THE BRAIN

Jordan Metcalf, Samuel Feher, Benjamin Cassidy, Lili Tian, Wei Zhang, Douglas Drevets, Wenxin Wu. University of Oklahoma Health Sciences Center

Abstract 67 Figure 2
Introduction/Background

Influenza A virus (IAV) infection is a major cause of morbidity and mortality. In 2009, a pandemic caused by the novel H1N1 IAV infected over 300,000 individuals with at least 16,000 confirmed deaths worldwide. Of note, the elderly (>65 years) have increased morbidity and mortality due to influenza. Interestingly, confusion is a typical symptom in this age group.

Objective(s)

We sought to compare the lung and brain innate response to IAV infection in young versus old mice.

Methods

We compared the weight loss and host immune responses of young (12 week) and old (70 week) mice following challenge with IAV PR8 (H1N1). After five days of infection, lung and brain tissue was collected for qRT-PCR and RNA-seq to determine the host innate response to the virus. Lung injury and inflammation were assessed by wet lung/body weight ratio and bronchoalveolar lavage (BAL) total cell number. Virus diluents (mock) were used as negative controls.

Results

Old mice showed less weight loss and viral RNA (NP) replication in the lung compared to corresponding young mice over the first five days after infection. The total immune cells in BALF and lung-to-body ratio were similar for old and young mice. We did not find significant mRNA expression differences in the lung between old and young at day five after infection in terms of pattern recognition receptors (PRRs), proinflammatory cytokines and IFNs. For example, RIG-I, TLR3 and IL-6 mRNA expression levels were similar after infection. Males of both young and old mice had much less lung IL-28 than females. RNA-seq data from brain tissue showed that PRRs including RIG-I, TLR2 and TLR4 mRNA expression levels were significantly higher in old mice than those in young mice although there was no viral replication detected in the brain in either age group. The important transcription factors for interferon induction, IRF7, IRF3 and STAT1, were all higher in old mice. We also found that that innate immune and inflammatory proteins, such as Ifnar2, Il1h1, Il30, psmb8, mpeg1, Rsad2, were significantly higher in brains of old mice. IRF7 mRNA expression differences were confirmed by RT-PCR.

Conclusion

Our results in our aging mouse model of IAV infection suggest that virus-caused lung injury and inflammation in the lung is not the direct cause of central nervous system (CNS) morbidity. Elevated innate immune and inflammatory proteins in the brain induced by IAV lung infection without CNS dissemination might be a cause of confusion in older patients. This discovery will be important in designing strategies for the development of novel treatments to decrease the morbidity of influenza infections in the elderly.

70 DIFFERENTIAL CYTOKINE EXPRESSION RESPONSES TO CORONAVIRUS INFECTION IN ASTHMATIC CELLS

Sara Kazmi, Benjamin French, Joshua Breidenbach, Andrew Kleinhans, James Willey, Jeffrey Hamersley, Mark Wooten, Erin Crawford, Nikolai Modyanov, Deepak Malhotra, Steven Haller. University of Toledo

Introduction/Background

The coronavirus disease 2019 (COVID-19) pandemic is among the new surge of cases with the Omicron variant, surpassing over 880,000 new U.S. cases in a single day as of January 4, 2022. COVID-19 has resulted in substantial morbidity and mortality worldwide and is caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a member of the Coronaviridae family. Human Corona Virus OC43 (HCoV-OC43, or OC43) is another member of the Coronaviridae family, and is also known to cause respiratory infections such as the common cold. Both viruses are members of the Betacoronavirus genus and are enveloped, positive-sense, single-stranded RNA viruses. While SARS-CoV-2 and OC43 share some regions of high homology, including the S2 subunit of the spike protein and its S2’ cleavage site, OC43 is a biosafety level 2 (BSL-2) pathogen making it a more readily available model than SARS-CoV-2, which has been designated as a BSL-3 pathogen. Asthma is a very common chronic inflammatory airway condition, with an estimated 8% of Americans being afflicted. Asthma is one of many pre-existing conditions that has been identified by the CDC as a risk factor for worsened coronavirus infection outcomes. However, not all the data from COVID-19 hospitalizations supports this. Further research is needed to understand if and how coronaviruses disproportionately impact patients with asthma.

Objective(s)

To characterize the transcriptomic profiles of human airway epithelium from both healthy and asthmatic donors in response to OC43 coronavirus infection. We tested the hypothesis that OC43 coronavirus infection would elicit an augmented response of key pro-inflammatory, cell signaling, and viral response pathways in asthmatic vs healthy airway epithelium.

Methods

To address these knowledge gaps, an in vitro 3D primary human airway model was utilized, in which airway epithelial cells collected from either asthmatic or healthy donors were infected with OC43 (6.9x10⁵ viral genome copy number/mL for 24 hours). The transcriptome was assessed by RNA sequencing from both healthy and asthmatic cells infected with OC43 or exposed to vehicle (4 groups, n=3/group). Genes whose expression had a coefficient of variance of ≥1 were removed for unreliability. Viral genome copy number as a measure of viral replication efficiency was assessed by both RT-PCR and RNA sequencing.

Results

Interestingly, OC43 viral replication efficiency was significantly decreased in asthmatic vs healthy airway epithelium 24 hours post infection as measured by both RT-PCR and RNA sequencing. Transcriptomic profiling of RNA sequencing data revealed a differential response pattern to OC43 infection between the asthmatic and healthy airway epithelium. For this analysis, a gene was considered upregulated if the log2 fold change (log2FC) was greater than or equal to 0.25 or downregulated if the log2FC was less than or equal to -0.25. Pathway analysis done with G-Profiler demonstrated an increased number of PI3K-FGFR2 related genes (FDR= 0.0210) such as FGFR2 (log2FC= 0.66), and lung fibrosis related genes (FDR= 0.0074) such as EDN1 (log2FC= 0.37), in the healthy epithelium infected with OC43 compared to asthmatic epithelium. An increase in genes pertaining to ‘transcription by RNA polymerase II’ (FDR= 0.0023) was detected in the infected asthmatic epithelium, compared to infected healthy epithelium, including an increase in IFNB1 (log2FC= 0.46) and TLR2 (log2FC= 0.44). In total, infected healthy cells had an increase in 1,672 genes, while infected asthmatic cells showed an increase in 1,523 genes. Of these upregulated genes, only 396 were upregulated in both the infected healthy and infected asthmatic epithelium, with clear differences in the pattern of a uniquely upregulated genes (table 1). The patterns of downregulation between infected healthy and infected asthma epithelium were similar in that they generally pertained to cytokine signaling pathways. However, there were
differences between the groups in the specific cytokines being downregulated. Pathway analysis conducted in G-Profiler showed that in the infected healthy epithelium, downregulated genes grouped into the categories ‘cytokine activity’ (FDR=0.0025) and ‘cytokine-cytokine receptor interactions’ (FDR=0.0046), while the infected asthmatic epithelium did not group into such categories. Infected healthy epithelium showed decreases in certain cytokines/chemokines and their receptors such as IL-17D (log2FC= -0.37), IL-4R (log2FC= -0.33), and CCL5 (log2FC= -0.31) and CCL14 (log2FC= -0.45), while OC43 infected asthmatic epithelium demonstrated significant downregulation of key cytokines/chemokines and their receptors such as CCL4 (log2FC= -1.07), CCL17 (log2FC= -0.46), IL2RG (log2FC= -0.36), and IL4I1 (log2FC= -0.48). In total, the infected healthy epithelium showed decreased expression of 1,715 genes, where the infected asthmatic epithelium showed a decrease in 1,604 genes, of which only 407 genes were shared, with clear differences in the pattern of a uniquely downregulated genes (table 1).

Conclusion The results of this study suggest that key differences in response to beta coronavirus OC43 infection exist in asthmatic vs healthy airway epithelium. These differences included significantly reduced OC43 viral replication efficiency as well as significant increases in genes related to transcription by RNA polymerase II and decreases in key cytokines/chemokines and their receptors in asthmatic vs healthy airway epithelium.

---

**BLASTOMYCES DERMATITIDIS SEPTIC ARTHRITIS IN A RENAL TRANSPLANT PATIENT**

Stacy Ploom, Marcus Coooley, Dubert Guerrero, Avish Nagpal. University of North Dakota

Introduction/Background Blastomycosis refers to disease caused by the dimorphic fungus Blastomyces dermatitidis. This infection occurs most often in persons living in areas of the United States and Canada surrounding the Ohio and Mississippi River valleys and the Great Lakes. Most infections are localized to the lungs, however, 25%-40% of those infected will develop extrapulmonary infection manifested by cutaneous, osteoarticular, genitourinary, or CNS disease. Here, we present a case of a 78-year-old immunosuppressed renal transplant patient diagnosed with septic arthritis of the ankle.

Objective(s) A 78-year-old male with history of living related donor renal transplant in 1996 complained of left ankle pain and swelling over six months. He failed conservative management with pain medications, a course of oral steroids for possibility of crystal-induced arthropathy and empiric antibiotics for possible infection. He underwent an MRI which revealed some enhancement but no fluid collection. He underwent incision and debridement. Only one of four tissue sample cultures grew Staphylococcus epidermidis that only grew in broth media. Histopathology eventually revealed the presence of broad-based budding yeast consistent with blastomycosis. Antimicrobials were switched to itraconazole. Swelling improved but he continued to have joint pains affecting his quality of life. He eventually underwent below the knee amputation.

Methods This case highlights the extrapulmonary manifestation of blastomycoses infection in immunosuppressed patients. Patients with septic arthritis caused by blastomycosis can present with a classical triad of fever, joint pain (monoarticular) and restricted range of motion. Blastomycosis septic arthritis is most often seen in the knee, though any joint can

---

<table>
<thead>
<tr>
<th>Abstract 70 Table 1</th>
<th>Differentially expressed gene patterns in healthy versus asthmatic epithelial responses to OC43 infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Upregulated</strong></td>
<td>Infected Healthy</td>
</tr>
<tr>
<td><strong>Downregulated</strong></td>
<td></td>
</tr>
</tbody>
</table>
be affected. The most common mechanisms of infection for blastomyceses septic arthritis are hematogenous spread (e.g., abscesses, wound infection) or direct contamination (e.g., open wounds around joint). Treatment options for blastomycosis include antifungals such as amphotericin B for systemic infections and Fluconazole or Itraconazole for local infections. Surgical irrigation and debridement are required if there are loculations and amputation may be required in severe cases which eventually occurred in our patient. Clinicians should be aware of the possibility of endemic fungal septic arthritis such as blastomyocysis in immunosuppressed patients presenting with chronic joint symptoms.

**Enterococcus Faecalis Empyema as a Complication of Cholecystitis**

Mohammad Al Bataineh, Aseel Alkhader, Omar Hussein, Mahmoud Mansour, Baraa Saad. University of Missouri-Columbia, Jordan University of Science and Technology

**Objective(s)**

We present a case of a 72-year-old male who initially presented to the hospital complaining of nausea, vomiting, and right upper quadrant abdominal pain. Physical exam was significant for right upper quadrant abdominal tenderness and positive Murphy’s sign. A computed tomography scan of the abdomen was performed, which showed an enlarged gallbladder with fatty induration and sludge consistent with acute cholecystitis. The patient was started on Piperacillin-Tazobactam therapy. The surgical team was consulted for cholecystectomy; however, the patient was deemed high-risk for surgery due to severe malnutrition and other medical comorbidities. Subsequently, a percutaneous cholecystostomy tube was placed by Interventional Radiology. The patient improved over the next few days and was eventually discharged to a skilled nursing facility.

Three weeks following the presentation, the patient returned to the emergency department complaining of shortness of breath and pleuritic chest pain of one-week duration. Chest X-ray showed moderate-sized right pleural effusion. Thoracentesis showed exudative effusion and negative cultures. Three days later, the pleural fluid reaccumulated and thoracentesis was done again showing similar results. The pleural effusion was suspected to be secondary to inflammation of the gallbladder and the surgical team was consulted for cholecystectomy, but the patient was still a poor surgical candidate. Patient was eventually discharged after improvement of symptoms and was scheduled to follow-up with the surgery clinic for further evaluation. A cholangiogram was done three weeks later which showed non-dilated cystic and common bile ducts and no filling defects. Upon further discussion with the patient the cholecystostomy tube was removed, and the patient was notified of risk of recurrence.

Three days after removal of the cholecystostomy tube, the patient presented to the ED complaining of worsening shortness of breath and pleuritic chest pain. Chest X-ray showed a loculated large right-sided pleural effusion. Chest tube was placed, and cultures were sent that grew pan-sensitive E. coli and pan-sensitive Enterococcus faecalis. Patient was treated with Unasyn along with six doses of tPA and DNase, and the cardiothoracic surgery team was consulted for right lung decortication. However, the patient was not considered a surgical candidate at that time due to malnutrition. After two weeks of hospitalization and treatment with antibiotics, the patient had great improvement in symptoms and was planned for discharge with the chest tube in place, Augmentin, nutritional rehabilitation, and to follow up with cardiothoracic surgery after optimizing his nutritional status.

**Methods**

Plural empyema is defined as pus in the pleural cavity or effusion with bacteria seen on gram stain. Anaerobic and gram-positive bacteria account for 41% of complicated pleural effusions, mostly staphylococcus aureus, and streptococcus pneumonia. Enterococci account only for 0.7% of the cases, most of which were patients who had undergone abdominal surgeries or had liver cirrhosis. We present a unique case of Enterococcus faecalis empyema in an immunocompetent patient with no history of abdominal surgeries or cirrhosis.

Empyema is a life-threatening condition with a reported mortality of 41%. Early diagnosis with thoracentesis and targeted antibiotic therapy are of great importance. Regardless of the rarity of Faecalis as a cause of empyema it should always be kept in mind even in the absence of the common factors including a recent abdominal surgery or cirrhosis.

**REFERENCES**


**Nephrology**

**Computational and Experimental Analysis Reveals the Arachidonic Acid Metabolite 20-Hydroxyeicosatetraenoic Acid is a Novel Ligand of the Na/K-ATPase**

Dhilhani Faleel, Shuang Zhang, Abayomi Adegbeye, Jacob Connolly, Travis Stevens, Deepak Malthota, Steven Haller, John Fulk, David Kennedy. University of Toledo; University of Jos and Jars Computation Biologic Centr; University of Texas Southwesten

**Introduction/Background**

Chronic inflammation is a major risk factor that contributes to chronic kidney disease (CKD) progression. Arachidonic acid metabolites such as 20-Hydroxyeicosatetraenoic acid (20-HETE) are well known pro-inflammatory mediators that are elevated in the setting of CKD. While 20-HETE can promote chronic inflammation in the kidney, the mechanism is not fully understood. 20-HETE is known to inhibit Na/K-ATPase (NKA) pumping activity in renal proximal tubules. We and others have demonstrated...
both clinical and experimental evidence that stimulation of a NKA-Src signaling complex by endogenous NKA ligands, such as cardiotonic steroids, leads to persistent renal inflammation and fibrosis in settings such as CKD. Whether 20-HETE directly interacts with the NKA and promotes pro-inflammatory NKA signaling is unknown.

Objective(s) We sought to determine the ability of 20-HETE to bind with the NKA relative to other known NKA ligands using a computational molecular modeling approach. We further sought to test the ability of 20-HETE to stimulate NKA mediated signaling in renal proximal tubule cells.

Methods Computational molecular modeling to investigate the interaction of 20-HETE and NKA was performed using Maestro software analysis (Schrodinger 2021–2). In vitro experiments of NKA signaling were performed with both 20-HETE and its stable analog, 5,14-20-HEDE, in renal LLC-PK1 proximal tubule cells.

Results First, we performed induced fit docking to predict the binding free energy of both 20-HETE and its stable analog, 5,14-20-HEDE, in comparison with the well-established cardiotonic steroid NKA ligand telocinobufagin. This docking analysis predicted that 20-HETE and 5,14-20-HEDE interact with the NKA with similar binding free energy as cardiotonic steroids (Predicted binding free energies: telocinobufagin = -9.2; 20-HETE = -8.18). Further this computational modeling demonstrated that all of these molecules interact in the same binding pockets of the NKA. Next, our in-vitro experiments showed that 20-HETE and its analog 5,14-20-HEDE increased MAPK activation in a dose dependent manner from 10 nM to 10 uM in LLC-PK1 cell lines. This MAPK activation was significantly altered after pretreatment with pNaKtide, a specific inhibitor of the NKA-Src signaling complex (1uM pNaKtide, 30 minutes).

Conclusion The result of this study suggests that 20-HETE interacts with NKA in similar manner as cardiotonic steroids and is capable of inducing NKA signaling in renal proximal tubules.

Abstract 74 Figure 1 CODEX image of glomerulitis. CD8 T cells and CD11c mononuclear phagocytes in glomerulitis in a kidney transplant biopsy

optimized for use in human kidney tissue. We performed a CODEX experiment using this antibody panel on a fresh frozen human kidney transplant biopsy. This biopsy was a force biopsy. Analysis of the findings was performed using the CODEX multiplex analysis viewer (MAV). This study was performed with a Washington University IRB consent.

Results The biopsy studied had a diagnosis of chronic antibody mediated rejection. Banff scores included g1 and ptc 2. Class I and II DSAs were also present. CD8 T cells and CD11c mononuclear phagocytes were identified in the glomeruli of this ABMR biopsy. The glomerular endothelium expressed HLA-DR molecules. CD4 T cells and CD206 and CD163 cells were not found in glomeruli. Across the whole biopsy, spatial interactions between immune cells were greatest between macrophages and CD8 T cells.

Conclusion Using CODEX we identified CD8 T cells and CD11c cells in the glomeruli of a human kidney transplant with ABMR and glomerulitis. Interestingly, CD4 T cells and CD163 and CD106 macrophages were not found in the glomeruli of this rejecting biopsy. An important limitation of this study is that NK cell markers were not used in this biopsy. Furthermore, more biopsies need to be studied in parallel with normal controls for definitive conclusions to be made.
and high-dose insulin. Rescue therapies include lipid emulsion therapy, glucagon, pacemaker, and extracorporeal membrane oxygenation support. Routine methods of dialysis for removal of CCB have not been successful due to the protein-bound nature of CCBs. Extracorporeal albumin dialysis, including molecular adsorbent recirculating system (MARS) or single-pass albumin dialysis (SPAD), may provide a therapeutic option. In the pediatric population, even small doses can have fatal consequences but management is still typically based upon adult strategies. Bartlett and Walker developed the first proposed algorithm for management of CCB poisoning in the pediatric population. We present a case of amloidipine toxicity with refractory cardiovascular collapse and successful treatment of single-pass albumin dialysis (SPAD) in a pediatric patient. We aim to describe the clinical implications of amloidipine toxicity, clinical and pharmacologic challenges with large pediatric patients and high dose medications, and successful treatment strategies.

Objective(s) A 17-year-old 103 kg female who presented to an outside hospital roughly three hours after intentional overdose of unknown amounts of acetaminophen, ibuprofen, amoxicillin, and amloidipine, with an estimated ingestion of 500 to 550 mg of amloidipine. Initially oriented, she became unresponsive during a seizure episode and was subsequently intubated. Fluid resuscitation, calcium infusion, and an insulin infusion at 0.1 U/kg/hr were initiated for hypotension, with improvement in her hemodynamics. She was transferred to Children’s Hospital & Medical Center (CHMC) for ongoing care. Doses of ephinephrine and norepinephrine were initiated and escalated during transport for ongoing hypotension. Glucagon and sodium bicarbonate infusions were initiated on arrival to CHMC, along with escalation of insulin and calcium infusions. Her hemodynamics continued to worsen and venoarterial ECMO was initiated nine hours after arrival.

Hypotension persisted after ECMO initiation and despite high dose ephinephrine, norepinephrine, and vasopressin. A lipid emulsion provided only 12 hours of hemodynamic stability. Methylenedie blue was trialed with no improvement in hemodynamics. The patient developed fluid overload of 15% following ongoing resuscitation and high volume rates due to the high doses of inotropes and insulin (roughly 10 L/day), hemodynamic intolerability of diuretics, and acute kidney injury. Renal replacement therapy was initiated on hospital day 3 as single-pass albumin dialysis (SPAD) to facilitate clearance of amloidipine. SPAD was performed in series with ECMO using a continuous renal replacement therapy machine (NxStage System One machine, NxStage Medical, Lawrence, MA). Continuous veno-venous hemodialysis (CVVHD) was performed using a CAR-505 filter (polyethersulfone membrane with a 1.6 m2 surface area). The blood flow rate was 200 mL/min and dialysate flow rate was 2500 mL/hr (2000 mL/1.73 m2/hr). The albumin dialysate was created by adding 125 g of 25% albumin to a 5 L dialysis bag to create a final dialysate albumin concentration of 2.5%. No changes were made to systemic heparin antiocoagulation.

The patient’s hemodynamic status stabilized several hours after SPAD initiation and escalation of insulin to 7 units/kg/hr. After receiving 16 hours of SPAD, a hospital shortage of albumin forced the albumin dialysis concentration to be decreased to 1.25%. Despite maintaining other supports, the patient’s hemodynamic worsened with MAP’s in the low 40’s for approximately 18 hours. After emergent request from another facility, the albumin dialysate concentration was increased back to 2.5% at approximately 40 hours of SPAD resulting in subsequent improvement in clinical status. Between hospital day 5 and 9, all her vasoactive agents were able to be stopped, along with the glucagon, insulin, and calcium infusions. The patient received a total of 117 hours of SPAD the patient followed by an additional 23 hours of conventional CVVHD.

On day 11, she was decannulated from ECMO, weaned off all inotropes, and extubated on day 12. She was transferred out of the ICU on day 16 and discharged on day 26 to an acute rehabilitation center for ongoing management. The only known medical complication is a stroke with multiple small infarcts resulting in right-sided visual defects. Figure 1 shows her vasoactive agent dosing and blood pressure related to therapeutic interventions.

Methods Use of MARS and SPAD on CCB Ingestion

The choice of therapy for removing a toxic substance depends on its molecular size, charge, binding characteristics, volume of distribution, patient size, and availability of extracorporeal techniques. As CCBs are highly protein bound and have a large volume of distribution, they are poorly removed by conventional hemodialysis. Molecular absorbent recirculation system (MARS) has been shown to be beneficial in cases of overdose of highly protein-bound CCBs, with decrease in vasopressor requirements noted in many cases shortly after initiation. Pinto et al reported the case of a pediatric patient treated with MARS in tandem with ECMO12. They demonstrated reduction in CCB levels and improvements in hemodynamic instability after each procedure. However, levels were noted to rise between MARS treatments due to rebound effect as blood-tissue drug equilibration occurs. Unlike MARS which utilizes specialized circuit and filters to recycle albumin, SPAD is a modification of the standard CRRT circuit where albumin is added to dialysate. Free drug crosses the dialyzer membrane, binding to albumin causing a diffusion gradient allowing more drug to be eliminated. This method has been used for protein-bound drugs in cases pediatric overdoses of phenobarbital, carbamazepine, valproic acid, acetaminophen, and methotrexate. Yeşilbaş et al described a case where SPAD was used efficaciously in a pediatric patient with severe verapamil intoxication. SPAD offers multiple benefits over other extracorporeal therapies. Compared to MARS, it can be provided with less technical and infrastructure support. As it does not require the use of specialized circuits or filters, it can be performed at any pediatric center with an established critical care nephrology program with CRRT capabilities. As MARS and charcoal hemoperfusion are not available at many pediatric institutions, SPAD may be the only therapy available for patients critically unstable to transfer to another center. In addition, for critical patients, we have shown that SPAD can safely be performed in adjunct with extracorporeal life support.

Pharmacologic Issues Several challenges were encountered from a pharmacy perspective, including dosing and concentration challenges and managing the albumin dialysis workload. As a pediatric hospital, safety parameters are in place on infusion pumps to minimize risk by restricting inappropriate dosing inputs for certain medications. The maximum norepinephrine concentration at our facility is 16 mcg/mL, whereas norepinephrine concentrations up to 64 mcg/mL have been shown safe in adults. Additionally, use of nonstandard concentrations of medications allows for errors at the bedside, including miscalculation in drip rates, manually entering rates on the pump for every titration, and the possibility that an old titration sheet prepared by the pharmacist which is no longer...
applicable based on changing clinical variables. These possibilities for error were identified early in the patient's course, and it was determined not to use a higher concentration of vasoactive agents and insulin which contributed to her significant fluid overloading (totaling over 50 liters). Given the rising obesity epidemic in the US, we routinely see pediatric patients that are adult size. This will continue to be a challenge as adult dosing and concentrations may be necessary to avoid excessive fluid administration for high dose medications, such as insulin and vasoactive agents.

Finally, the preparation of albumin dialysate is labor-intensive and large the amount of albumin required can be costly. The optimal concentration of albumin necessary to achieve benefit while limiting unnecessary excess albumin is currently unknown. Churchwell et al. showed a relationship between the albumin concentration and the clearance of valproic acid and carbamazepine, but not phenytoin. Although drug levels were not directly measured in our study, we saw a strong correlation in hemodynamic status and albumin concentration, with increased need for vasoactive support after decreasing albumin concentration from 2.5% to 1.25%. The supply of albumin became a barrier as we were only able to prepare 24 hours' worth of the 2.5% albumin dialysis solution. To temporarily extend the inventory, the albumin dialysis solution was changed to 2.5% after 24 hours resulting in further hemodynamic instability. Once adequate supply was obtained, the albumin dialysis was increased to 2.5%, with subsequent improvement in hemodynamics, weaning of vasoactive infusions, and decannulation from ECMO.

Conclusion To our knowledge, this is the first description of the use of SPAD in tandem with ECMO. For our patient, SPAD improved hemodynamic parameters and did not add any additional burden. The use of albumin dialysis in the management of CCB is controversial and is not currently recommended by expert groups due to the lack of clinical pharmacokinetic data. Although multiple studies have shown clinical improvements in CCB following albumin dialysis, it has also been suggested that hemodynamic improvements may be due to removal of endogenous vasodilatory substances, such as nitric oxide and inflammatory cytokines, rather than directly through clearance of toxins and acid-base balance correction. Although plasma and dialysate drug concentrations were not measured in our study, we saw a correlation between albumin concentration and hemodynamic improvement. Although albumin dialysis is not the current standard practice in the treatment of CCB toxicity, we have demonstrated use as a salvage therapy in cases of life threatening hemodynamic compromise and that SPAD may constitute an adjunctive treatment to extracorporeal life support.

REFERENCES
Neurology/neurodegeneration

**BIOPHYSICAL ANALYSIS OF TREM2 INTERACTIONS REVEALS A COMMON BINDING SITE FOR ALZHEIMER’S DISEASE LIGANDS APOE AND AMYLOID BETA**

Jessica Graven, Daniel Kober, Colin Kluender, Jennifer Alexander-Brett, Thomas Brett. Washington University

10.1136/jim-2022-MW.75

**Introduction/Background** There were 5.8 million people living with Alzheimer’s disease (AD) in the U.S. in 2020, and this number will increase to 12 to 16 million by 2050 unless effective treatments are developed to address the underlying causes of the disease. The development of new innovative treatments to prevent and ameliorate AD requires knowledge of molecular mechanisms that are critical to neuronal health. The triggering receptor expressed on myeloid cells 2 (TREM2) receptor is part of a signaling complex that modulates inflammatory responses, phagocytosis and cell survival in microglia, resident immune cells in the brain that play a critical role in clearing misfolded aggregates. Examples include neurotoxic aggregates consisting largely of amyloid beta (Abeta) and apolipoproteinE (apoE). Both molecules have emerged as important signaling ligands for TREM2. Although TREM2 signaling in microglia is generally associated with beneficial outcomes, intense or prolonged signaling may produce overactivated microglia leading to neuronal damage. Such events may also contribute to other diseases such as Parkinson’s or cancers. Furthermore, rare TREM2 variants, most notably R47H and R62H, have been identified that are associated with a significantly increased risk of developing AD. Given these significant roles, TREM2 has emerged as an important yet challenging therapeutic target for AD. Although a number of ligands for TREM2 with relevance to AD have been identified, little is known regarding the molecular details of how TREM2 engages them. Detailed knowledge of the molecular mechanisms underlying TREM2 signaling in microglia is urgently needed to facilitate the development of specific, potent, safe and efficacious therapies for AD that target the TREM2 signaling pathway.

**Objective(s)** To identify the critical surfaces on TREM2 that mediate interactions with both apolipoproteinE (apoE) and oligomeric amyloid beta1–42 (oAbeta42) using rigorous structural and biophysical methods.

**Methods** We used structure-based mutations and comprehensive biolayer interferometry (BLI) analysis to investigate TREM2 interactions with apoE and oAbeta42.

**Results** We found that TREM2 utilizes a distal hydrophobic surface, consisting of the CDR1, CDR2, and CDR3 loops, to engage apoE. Surprisingly, we found that this same surface is utilized to engage oAbeta42.

**Conclusion** Our results indicate that the hydrophobic site on TREM2 (consisting of the CDR1, CDR2, and CDR3 loops) is the critical ligand-engaging surface on TREM2. They also indicate that therapeutics that either directly bind or allosterically alter the hydrophobic site on TREM2 should modulate TREM2 signaling as potential AD treatments.


**Abstracts**

Introduction/Background Chronic diseases are a significant problem in aging population causing immense economic burden to healthcare systems around the world. Alzheimer’s disease (AD) is the most common form of dementia, affecting as many as 5.8 million Americans who are aged 65 and older and is the sixth leading cause of death in the United States. As age is the greatest risk factor in developing AD, there is great interest in the possibility of targeting AD through interventions that slow or delay aging. Dietary protein restriction (PR) has been shown to be beneficial in improving overall health span in both humans and mice. However the effect of PR in delaying the symptom progression of AD is largely unknown.

**Objective(s)** In this study we sought to determine the effects of PR in improving metabolic dysfunction, cognitive deficits and AD pathology along with examining the role of mTORC1 and its downstream targets in the 3xTg mouse model of AD.

**Methods** Six-month-old male and female 3xTg-AD mice were placed on either 21% protein (control) or 7% protein (PR) diets starting from six months and continued until 15 months to determine their effects on cognition, metabolic health and AD neuropathology. Cognitive functioning was analyzed via Novel Object Recognition (NOR) test, a measure of recognition memory; and Barnes maze, a measure of spatial learning and memory. Following behavioral testing the mice were sacrificed and tissues were harvested for molecular and histopathological analysis of the progression of AD markers.

**Results** Female 3xTg-AD mice on PR diet showed improved long-term memory (LTM), but no significant improvement in short-term memory test (STM), and males showed a positive trend in improved cognitive function compared with their age matched controls. Based on latency measurements in Barnes maze, we found that a PR diet substantially improved spatial memory in both male and female 3xTg mice. Female and male mice on low protein diets exhibited improvements in glucose tolerance, however females showed a stronger effect in glycemic control than males following a glucose tolerance test (GTT). Histopathological analysis of the hallmarks of AD showed that mice on PR had decreased tau phosphorylation...
and Abeta plaques. Phosphorylation of the mTORC1 substrate S6K1 was decreased in PR fed 3xTg mice which suggest that reduced mTORC1 signaling may be mediating the beneficial effects of PR on AD pathology. We also found that levels of p62 protein, the major autophagy cargo receptor, is increased in 3xTg AD mice, which suggests that autophagic flux is impaired and following PR, decreased p62 expression was observed, suggesting that PR activates autophagy. These results suggests the molecular interplay between mTORC1, autophagy and AD pathology.

Conclusion Our results are promising and demonstrates the use of dietary interventions as therapies for AD has significant potential, and may also provide additional insights into the molecular mechanisms by which diets can affect the development and progression of AD.

**Abstract 77 Figure 1**

**ACARBOSE REDUCES TAU PHOSPHORYLATION AND mTORC1 SIGNALING IN THE BRAIN OF THE 3XTG MOUSE MODEL OF ALZHEIMER’S DISEASE**

Michelle Sonsalla, Reji Babygirija, Yang Yeh, Mariah Calubag, Michaela Murphy, Victoria Flores, Cara Green. University of Wisconsin-Madison

**Introduction/Background** Alzheimer’s disease (AD), a neurodegenerative disease in which patients exhibit impaired memory, motor function, and language due to neuronal damage, is rapidly growing in prevalence as the population grays. As AD is a disease of aging, and other diseases of aging including diabetes and obesity are risk factors for AD, geroprotective interventions may be of use in the prevention and treatment of this disease. The geroprotector acarbose is an anti-diabetic drug which extends the lifespan of UM-HET3 mice.

**Objective(s)** We hypothesized that acarbose would improve metabolic health in 3xTg-AD mice and as a result of improvements in glucose homeostasis and insulin signaling, would lead to improvements in cognition and overall ameliorated Alzheimer’s pathology. We predicted that these improvements would be more dramatic in diet-induced obese mice as obesity has been shown to coincide with more severe Alzheimer’s symptoms.

**Methods** We tested the effect of acarbose on cognition and disease pathology in the 3xTg-AD mouse model of AD. We treated six-month-old male and female 3xTg-AD and B6129SF2/J mice with acarbose for 3–6 months to determine effects on AD pathology, metabolic health and cognition. We performed glucose and insulin tolerance tests, measured cognition via novel object recognition and Barnes Maze, and determined AD pathology via ex vivo western blotting of brain tissues. We repeated all experiments and analyses with six-month-old diet-induced obese mice and administered acarbose in conjunction with continued western diet.

**Results** We found that acarbose-treated male and female 3xTg mice had decreased tau phosphorylation (which is a marker for AD progression) and reduced mechanistic target of rapamycin complex 1 (mTORC1) signaling in the brain. Surprisingly, acarbose did not promote glucose tolerance or insulin sensitivity, suggesting the effects of acarbose may be independent from its effects on glucose homeostasis. Acarbose treatment also did not improve cognition in 3xTg-AD mice, which may be due in part to a lack of cognitive impairment at the timepoints tested. In diet-induced obese mice, acarbose treatment resulted in weight loss of ~20% in males and ~35% in females after 20 weeks of treatment. Glucose and insulin tolerance were not changed by acarbose treatment, but female mice did exhibit decreased fasting blood glucose during short fasts.

**Conclusion** Our results suggest that the beneficial effects of acarbose on metabolic health may vary widely based on genotype, but that improvements and tau phosphorylation and mTORC1 signaling are present independent of changes in metabolism or cognition. Acarbose regulates body weight in both male and female mice when administered with a western diet, but has a much less pronounced effect in a normal chow diet. Further analyses in diet-induced mice are ongoing. As a whole, acarbose does not appear to be beneficial in the treatment of Alzheimer’s disease, but further results in diet-induced obese mice may show a more pronounced benefit when the Alzheimer’s phenotype is exacerbated by obesity.

**Social defeat alters the firing rate distribution of medial amygdala neurons**

Alexandra Ritger, Maxine Loh, Jeremy Rosenkranz. Rosalind Franklin University of Medicine and Science

**Introduction/Background** Depression is a highly prevalent and debilitating psychiatric disorder and can emerge after exposure to a social stressor. The medial amygdala (MeA) regulates social behaviors and responds to social cues. Additional evidence of reduced MeA volume and connectivity in depressed patients suggests MeA activity may regulate social symptoms of depression. Repeated social defeat stress in rodents induces long term effects consistent with depression symptoms and results in increased MeA immediate early gene expression, an indirect marker of neuronal activity. However, neuronal activity in the MeA following social defeat has not been measured directly. A better understanding of the MeA’s sensitivity to...
social stressors can further elucidate mechanisms underlying depression, which can aid the development of novel therapeutics.

**Objective(s)**
The goal of this study was to determine the effect of repeated social defeat stress on MeA neuronal activity in rats. We hypothesized that repeated social defeat would increase the spontaneous firing rate of neurons in the MeA.

**Methods**
Fifty-six adult (postnatal day 71–83) male Sprague Dawley rats underwent five days of social defeat with a retired breeder Long Evans rat using the resident-intruder paradigm or control procedures. Control rats were placed in a transport cage for the same amount of time. Within 10 days of social defeat or control procedures, we performed in vivo extracellular single-unit electrophysiology in anesthetized rats and recorded the firing rate (Hz) of spontaneously active neurons in the posterodorsal (MeApd) and posteroventral (MeApv) nuclei of the MeA.

**Results**
MeA neurons trended towards firing faster in socially defeated rats relative to controls (Control-MeA: 1.1 ± 0.3/n=38 neurons, Stress-MeA: 2.4 ± 0.4/n=47 neurons, data expressed as mean ± SEM). The number of attacks a stressed rat experienced per day trended towards a positive correlation with their average MeA neuronal firing rate (R² = 0.3, n=10), suggesting a dose-dependent effect of the intensity of the stress on MeA firing. The increase in MeA activity after stress is likely driven by neurons in the MeApd subnucleus (Control-MeApd: 0.9 ± 0.3/n=21 neurons, Stress-MeApd: 2.1 ± 0.3/n=29 neurons) whereas MeApv firing rate was similar between groups (Control-MeApv: 1.2 ± 0.5/n=17 neurons, Stress-MeApv: 0.7 ± 0.2/n=18 neurons). Subsequently, cumulative frequency distributions of MeA, MeApd, and MeApv firing rates revealed significant differences in firing rate distribution between treatment groups. This suggests that there may be distinct populations of neurons in the MeApd and MeApv that respond differently to social stress.

**Conclusion**
These results suggest that the MeA is sensitive to prolonged social stressors and that social defeat may differentially affect the activity of MeApd and MeApv subnuclei. Furthermore, the differences in the distribution of MeA, MeApd, and MeApv neuronal firing rates between socially defeated and control rats may point to differences in MeA neurons that project to different downstream regions. Collectively, these findings point to dysregulated MeA activity as one possible mechanism for social stressors to drive depression-related symptoms.

**Abstract 80 Figure 1** A/B pre-operative X-ray of historical C3-C6 posterior spinal fusion

**Abstract 80 Figure 2** Post-operative CT scan of CAPDF consisting of posterior spinal fusion revision (A) and C3-C6 ACDF (B)

---

**Multi Stage Combined Anterior-Posterior Decompression and Fusion as Corrective Intervention in Octogenarian Population with Prior Spinal Fusion Attempt and Pseudarthrosis**

Matt Porter, Miguel Schmitz, Washington State University Elson S. Floyd College of Medicine

**Introduction/Background**
Cervical spondylotic myelopathy (CSM) is a spinal degenerative disorder that can ultimately lead to compression of the vertebral column with neurological sequelae. Although CSM is the most common spine pathology in the elderly American population, it remains a challenging disorder to treat among older patients.

**Objective(s)**
CASE PRESENTATION: We report an 86-year-old female patient with CSM with a history of posterior cervical fusion attempt on C3-C6 that progressed to C3-C6 nonunion with loose instrumentation. The patient had severe osteoporosis. With these indications, the patient underwent a combined anterior-posterior decompression and fusion (CAPDF) consisting of anterior cervical discectomy and fusion (ACDF) of the C3-C5, corpectomy of C6 and C7 with off FDA label use of polymethyl methacrylate augmentation (PMMA) fixation of T1 screws anteriorly for C3-T1 plate fixation and second stage instrumented posterior spinal fusion (PSF) of C3-T3. The patient had a successful fusion and reduction of her cervical spine pain with preservation of her neurological status.

**Methods**
We report this case of multi-stage combined anterior and posterior fusion as a corrective measure for pseudarthrosis of a prior posterior cervical spinal fusion attempt. In the event of posterior spinal fusion instrumentation failure in patients with severe osteoporosis, combined multi-stage anterior-posterior fusion is a viable corrective intervention in octogenarians. This case also illustrated the utility of using PMMA for anterior cervical plate and screw stabilization in osteoporotic bone. The authors are not aware of the prior use of PMMA for screw fixation augmentation in the anterior cervical spine.
Introduction/Background
With the increased frequency of antidepressants use in clinical practice, an increased number of cases of Serotonin Syndrome (SS) is being reported more than before. Treatment of SS mainly focuses on withdrawal of the offending agent, supportive care and use of benzodiazepines. Literature on cyproheptadine - a serotonin receptor antagonist - for the treatment of SS is limited with questionable evidence.

Objective(s)
A 48-year-old female with a psychiatric history significant for depression, presented to our hospital for confusion and lethargy that started 24 hours before admission. Upon arrival patient had altered mental status with Glasgow Coma Scale (GCS) of 13, significant clonus and muscle rigidity on exam in addition to hyperreflexia of the lower extremities. Vitals were significant for tachycardia of 130 beat/minute, Temp 38.3, blood pressure: 175/83 mm Hg, respiratory rate: 28 breaths/minute.

Blood work-up including CBC, kidney and liver function tests, TSH, T4 and urine drug screen were within normal limits. Two sets of blood cultures were negative, chest X-ray and head CT scan were normal.

Reviewing patient’s medication history revealed that patient takes duloxetine, escitalopram, tizanidine, eszopiclone for more than a year in addition to a recent use of promethazine and a scopolamine patch. A diagnosis of SS was established based on Hunter’s criteria and after exclusion of other differential diagnoses. Supportive treatment was started, all serotonergic medications were stopped, IV fluids and lorazepam 2 mg IV were given every 30 minutes, patient remained tachypneic, tachycardic, agitated and experienced visual hallucinations.

Cyproheptadine 12 mg orally was given and a mild improvement in agitation and hallucinations was noticed. Few hours later, patient developed agitation and hallucination again, another three doses of lorazepam 2 mg IV were given every 30 minutes, patient remained tachypneic, tachycardic, agitated and experienced visual hallucinations.

Cyproheptadine 12 mg orally was given and a mild improvement in agitation and hallucinations was noticed. Few hours later, patient developed agitation and hallucination again, another three doses of lorazepam 2 mg IV was given with no clinical improvement, patient then received another dose of cyproheptadine 4 mg after which agitation markedly improved within an hour with improved alertness and orientation.

Symptoms of agitation recurred again, cyproheptadine was restarted with 2 mg for two doses and patient had the same response to the previous dose with improved mental status within two hours of the given dose. Patient continued to show gradual improvement, was observed for 24 hours and then was discharged after she made full recovery. Patient continued to do well at one week follow-up after discharge.

Methods
Our case demonstrated response to treatment with cyproheptadine observed as improved agitation, alertness and orientation that was seen on more than one occasion with repeated doses. Knowing to have a good safety profile, we believe that it is reasonable to have a low threshold starting cyproheptadine early in the course of the treatment of this potentially life threatening syndrome.

Further large scale prospective studies is needed to better assess the indications, dosing and timing of cyproheptadine in the treatment of SS.

---

Abstract 82 Figure 1  Pulse sequence diagram
Conventional Protocol with two separate scans:

- Scan Prep duration = ~20 sec.
- Cine Breath-Hold = ~6 seconds

Proposed Protocol with prescan bypassing for the second scan:

- Total Preparation = ~20 sec.
- Cine → Tagging = ~14 seconds

Abstract 82 Figure 2  Timing diagram

Abstract 82 Figure 3  Cine and tagging pre-scan calibration sensitivity
This initial approach is demonstrated in single-breath-held cardiac MRI, which is known to benefit from matched spatio-temporal acquisition of multiple parameters.

**Methods** Figure 1 shows the schematic of our proposed combined pre-scan bypassing approach at the pulse sequence level; where bSSFP (sensitive) + SPGR (less sensitive) pulses can be achieved by simply inverting the bSSFP readout refocusing pulse for pseudo-SPGR contrast and minimizes the differences in calibration parameters. This scheme further enables pre-scan bypassing (figure 2) on a standard clinical hardware with minimal disruption to the MRI systems architecture. bSSFP-cine CMR was obtained with (n=2) and without (n=6) full bSSFP calibration, followed by SPGR-Tag with both cartesian and spiral (figure 2) readouts. Experiments: The proposed pre-scan bypass approach was examined on a Philips 3T system using phantoms on which calibration duration benchmarks were acquired. Three sets of n=3 swine subjects with ~30kg (pediatric control), ~70kg (adult control); and two pediatric/adult (1x each) validation subjects were imaged under an IACUC approved study; where varied off-resonance conditions were introduced by subject size, as well as by manual suppression of bSSFP-cine calibration to examine the 'worst-case' resultant image quality. The validation cohort optimized for the bSSFP-cine calibration while tuning the SPGR’s ‘main-magnetic field drift calibration’ to that of the first bSSFP-cine calibration. Timing benchmarks for realistic ‘bypassed’ multicontrast scan feasibility, and resultant image quality were assessed.

**Results** Calibration timing performances were toggled to 1.8 seconds from a full ~18 second calibration for which F0 off-resonance (coarse + fine ~7–8 sec total) and shimming (5.5–8.5 sec) were bypassed. The second of the scan sequence was deliberately chosen to be the pulse sequence that is less sensitive to this calibration (i.e. SPGR), which only required a consistent 0.8–1.2 second toggling after the first sequence play out. After accounting for any trigger delays, the second of the dual acquisition commenced within three heart beats after the first scan readout. All dual-sequence scans therefore completed within a single breath-hold within 14 seconds. In figures 3 and 4 we show that the latter image (known as SPGR-TAG) maintained diagnostic image quality with clearly...
distinguishable striped ‘tags’ in the myocardium throughout the cardiac cycle. The high quality validation cines demonstrates pre-scan bypassing robustness. Figure 5 shows an example of a combined hybrid single breath-held scan that combines cine and tag. This allows for additional depiction of cardiac function under a single breath-hold.

Conclusion We demonstrate the initial feasibility of achieving scan-time reduction by means of a pulse sequence manipulation to allow for deliberate pre-scan bypassing. Such approach is particularly effective for further improving cardiac MR exams that may benefit from single-breath-held acquisitions of several under matched geometric conditions. Acknowledgements: Pritzker Fellowship at IIT (Goes); NIH K25 HL141634 (Kawaji).

Abstract 83 Figure 1* Inpatient Day 5 – First administration of doxycycline therapy • ** Inpatient Day 9 – Final administration of doxycycline therapy • Outpatient Day 4- First follow up after hospital discharge • Marked increase in serum creatinine 24 hours after first dose of doxycycline. Serum creatinine begins to downtrend 48 hours after final dose of doxycycline

Abstract 83 Figure 2 Marked decrease in GFR 24 hours after doxycycline administration with near threefold increase in BUN. GFR begins to recover 48 hours after final dose of doxycycline. BUN levels begin to decline after GFR exceeds 20 mL/min

Abstract 83 Figure 3 Diffuse lymphocytes, monocytes and eosinophils infiltrate between the tubules and are associated with lymphocytic tubulitis. (H&E stain, 20x magnification)

Abstract 83 Figure 4 Tamm-Horsfall protein casts are found within tubules and show extravasation into the interstitium associated with an inflammatory infiltrate. (PAS stain, 20x magnification)
worsened. Doxycycline was discontinued, and 48 hours after the last dose, renal function began to steadily improve. Electron microscopy findings from renal biopsy exhibited severe acute interstitial nephritis likely from antibiotics (figures 3 & 4).

Methods Discussion: Pathology findings confirm acute interstitial nephritis, ruling out other potential causes including contrast-induced nephropathy and vancomycin-induced tubular necrosis. The patient experienced a decline in renal function less than seven days from introduction of an offending agent, which would indicate a repeat exposure. The patient received doxycycline in the week prior to admission. Drug-induced acute interstitial nephritis characteristically improves after withdrawal of the offending drug. Doxycycline was the only agent for which kidney function improved after withdrawal.

Results There were 81 candidates who passed preliminary filtering thresholds to qualify for further testing; 13 of these were selected for functional in vitro analysis based on their safety profile in a pediatric population. We proceeded to measure the IC50 of these compounds via an MTT assay and identified three classes of drugs with effective cytotoxicity in G3 MB cell lines: selective serotonin reuptake inhibitors, tricyclic antidepressants, and statins. Specifically, these compounds included fluoxetine (72h IC50 ~16μM), sertraline (72h IC50 ~20μM), and simvastatin (72h IC50 ~4μM). Selecting nortriptyline (NT) for further study, we report a clear anti-neoplastic effect on wound healing and clonogenicity in HDMB03. Moreover, NT induced a dramatic dose-dependent increase in apoptosis (2% to 30%) by flow cytometry. Western blotting confirmed apoptosis with increases in cleaved caspases 3 and 9, cleaved PARP, and Bcl-2. Additionally, NT induced oxidative stress through mitochondrial O2- and cytosolic H2O2 generation by MitoSOX and DCFDA staining, respectively.

Discussion Malignant brain tumors of childhood, accounting for 20% of pediatric brain tumors. With the advent of high throughput sequencing, international consensus has identified four molecular subgroups of MB: wingless (WNT), sonic hedgehog (SHH), group 3 (G3), and group 4 (G4). Each subgroup is characterized by unique methylation and molecular profiles, cytogenetic aberrations, histology, and prognosis. Current treatment protocols consist of surgical resection followed by craniospinal radiation and chemotherapy, but fail to capitalize on these ‘molecular grades,’ guided only by histologic tumor grade and stage. However, molecular subgroup-specific prognoses vary widely, from >95% five-year survival in WNT MB to <50% five-year survival in G3 MB. As such, there is a great need to address these outcome disparities, specifically in G3 MB, the most aggressive subgroup.

Objective(s) By comparing patient-derived gene expression signatures with transcriptomic drug signature databases, we aim to identify FDA-approved compounds with promising cytotoxic effects against G3 MB.

Methods Differential expression analysis was performed with two cohorts of RNA-seq data: a local cohort of pediatric medulloblastoma samples with normal cerebellum (NC) samples as control (GSE148389; MB n=26, G3 n=7, NC n=14), as well as an external validation cohort (GSE164677; MB n=63, G3 n=14, NC n=4). These data were analyzed in parallel against the LINCS database, containing expression signatures of cell lines treated with over 42,000 perturbagens. This identified discordant compounds in both cohorts, with the potential to reverse the disease state expression signature to a control-like state. Next, compounds were filtered with a modified version of Lipinski’s Rules of 5, serving as an estimate of blood-brain barrier permeability using molecular characteristics. Additionally, compounds were filtered for FDA-approval status through the DrugBank database. Functional assays were then used to quantify drugs’ effect(s) with respect to cytotoxicity, clonogenicity, wound healing, cell cycle progression, and apoptosis in vitro in HDMB03, a G3 MB cell line.

Results A total of 120 patients (n=33 Immediate; n=43 Early; n=44 Delayed) were included in the final analysis. Immediate and early extubation patients were similar in presence of post-
operative cyanosis (42% vs. 37%, p=0.57), while delayed extubation patients were more likely to be cyanotic (70%, p=0.005). When only comparing the immediate and early groups, there was no difference in time to first enteral feed [1.3 days (IQR 1.0–3.4) vs. 2.3 days (IQR 1.1–3.3), p=0.27]. There was also no difference in time to first oral feed [2.0 days (IQR 1.1–4.5) vs. 3.1 days (IQR 1.8–4.4), p=0.34], and time to goal feed [6.0 days (IQR 3.2–8.3) vs. 6.9 days (IQR 5.0–9.0), p=0.15)]. Length of hospital stay was similar [15.0 days (IQR 11.6–19.8) vs. 14.0 days (IQR 12.3–18.2), p=0.30]. There was no difference in all oral feeds at one year: 88% vs. 98%, p=0.16. The delayed extubation group did worse on all measures.

**Conclusion** There was no difference in feeding patterns and hospital length of stay in children extubated in the OR vs. those extubated within three days of surgery for congenital heart disease. Children with delayed extubation were likely had a higher severity of illness and prolonged time to achieve feeding goals. Additionally, there was no difference in oral feeding at one year of age between the immediate and early extubation groups, pointing towards a lack of long-term impact in this patient population. Due to the lack of difference between these two groups, physicians should emphasize extubation within three days post-surgery rather than immediate extubation. Ensuring safety and preventing possible complications from failed extubation should be prioritized.

### Pulmonary/critical care

**EXAMINING THE ROLE OF SOCIAL DETERMINANTS OF HEALTH ON QUALITY OF LIFE IN URBAN PULMONARY HYPERTENSION PATIENTS**

Cat Humpal, Dustin Fraidenburg, Rebekah Anguiano. University of Illinois at Chicago

**Introduction/Background** Pulmonary hypertension (PH) is a debilitating condition with no known cure, yet with appropriate and timely care, treatments are clearly effective. Preliminary research has identified differing PH health outcomes when stratified by age, race, and sex but few studies have elucidated the role of social determinants of health (SDH). Utilizing SDH, researchers may identify interventions which can address patient financial, social, and health outcomes as a means of improving overall quality of life (QoL). Following diagnosis, the estimated annual healthcare costs associated with group 1 PH in the US is $100,000 per patient. In urban environments with marked socioeconomic segregation, health care costs are further compounded by inadequate insurance coverage and access to pulmonary specialists.

**Objective(s)** By utilizing available epidemiological data, we may contextualize reported QoL data from urban PH patients and determine public health measures that may improve clinical outcomes and QoL for PH patients in areas of increased hardship.

**Methods** Patients at UI Health with a diagnosis of PH from 2017 to 2021 who visited a pulmonologist were included. To be included in the final study sample, patients must have completed the Emphasis-10 questionnaire. EmPhasis-10 scores were analyzed using multivariate analysis to determine trends when stratified by Chicago community area. Demographic and clinical data was used to identify associations among clinical characteristics and QoL measures.
Results Initial data in a subset of Group 1 PH identified sociodemographic status as having important association with PH disease severity. Median income of patients was inversely correlated with pulmonary vascular resistance (p< 0.05) and directly correlated with cardiac output (p < 0.05) on right heart catheterization. This led to collection of QoL data on 103 PH patients to further determine the effects of SDH on this group. 52.4% (SD=8.49) of patients reported lack of confidence in public places/crowds because of their PH, 23.3% (SD=2.83) felt PH controlled their life, 19.4% (SD=1.41) felt highly dependent, and 9.7% (SD=2.31) of patients reporting both feeling like a burden and frustrated by their breathlessness.

Conclusion Patients living with PH are subject to both physical and social disadvantages due to their diagnosis. These disadvantages are compounded when individuals face barriers to healthcare access, lack of independence, and increased hardship. Understanding how SDH affect PH patients will require careful consideration of the disadvantages and barriers our patients face daily, but with the expectation that this understanding will allow for innovation in healthcare delivery and outcomes.

Introduction/Background Acute chest syndrome (ACS) causes lung injury and respiratory failure in patients with sickle cell disease and remains the leading cause of intensive care unit admissions and mortality within this population. The pathophysiology of ACS is incompletely understood; however, pulmonary vascular leak due to acute intravascular hemolysis and release of extracellular hemin is a well-defined mechanism in preclinical models.

Objective(s) We hypothesize that hemin leads to endothelial dysfunction via necroptosis in pulmonary artery endothelial cells, and that this effect is downregulated by hypoxia. The hypoxia-inducible factor (HIF) pathway is thought to play an important role in the balance of apoptosis and necroptosis.

Methods A cell culture subchamber (C-chamber, Biospherix) was used to create hypoxic conditions with identical temperature, humidity, and carbon dioxide concentration to normal culture conditions. Human pulmonary artery endothelial cells (HPAECs) were exposed to hypoxia with 24-hour incubation in 1% oxygen or pretreated with cobalt chloride (250 µM) for four hours, a known HIF inducer. Western blot analysis was used to measure mixed lineage kinase domain-like (MLKL), cleaved caspase 3, and HIF1α protein expression. ELISA assay (LifeSpan BioSciences, Inc) was used to measure receptor interacting protein kinase 3 (RIPK3) activity as a measure of necroptosis.

Results HPAECs treated with 40 µM hemin for four hours demonstrated increased necroptosis by increased MLKL expression and an approximately 30% increase in RIPK3 activity when compared to control (p< 0.001). Pretreatment with necrostatin-1 (Nec-1) inhibitor nearly eliminated the increased MLKL expression and RIPK3 activity seen in hemin-treated cells (p< 0.001). Hemin-treated HPAECs exposed to hypoxia had decreased MLKL expression and more than 30% decrease in RIPK3 activity when compared to hemin-treated cells in normoxic conditions (p< 0.001). In addition to decreased necroptosis, hemin-treated HPAECs in hypoxia show increased apoptosis with increased cleaved caspase 3 expression when compared to hemin-treated cells in normoxia. Cobalt chloride treatment was also associated with a decrease in hemin-induced necroptosis with decreased MLKL expression and RIPK3 activity as compared to control.

Conclusion Hemin exposure induces necroptosis in HPAECs, and hypoxia exposure downregulates this effect. These findings combined with similar findings after cobalt chloride treatment, suggest an interaction between HIF and RIPK3 signaling in hemolysis-induced lung injury, such as ACS. The downregulation of necroptosis induced by hypoxia is coupled with an upregulation of apoptosis, highlighting the known overlap of these two cell death pathways. Focusing on this balance in hemolysis-induced lung injury could lead to a novel therapeutic target for this deadly complication.
induced by MRSA in vivo was significantly reduced with ABO treatment as measured by BAL fluid total protein, cell counts and cytokine levels as well as changes on lung histology.

Conclusion Our data support ABO as highly effective in attenuating vascular inflammation and permeability induced by MRSA via inhibition of ITGB4 phosphorylation and strongly support a protective effect of ABO administered in vivo in a MRSA-ALI model. These findings add to growing evidence that ABO is a potentially novel and effective therapeutic molecule for ALI in general and warrants further investigation for this purpose.

CHARACTERIZATION OF CORTACTIN-MLCK PROTEIN-PROTEIN INTERACTION BY IN VITRO AND IN SILICO ANALYSES

Mounica Bandela, Yulia Epsteint, Patrick Belvitch, Steven Dudek. The University of Illinois at Chicago
10.1136/jim-2022-MW.89

Introduction/Background Cortactin (CTTN) is an actin binding and barrier regulatory protein that is activated by Src-mediated tyrosine phosphorylation to promote actin rearrangement. Prior work has demonstrated that tyrosine phosphorylation of CTTN increases association with myosin light chain kinase (MLCK), a critical regulator of contractility. MLCK-cortactin interaction plays a critical role in endothelial cell (EC) permeability and other cellular functions, but detailed structural information about this interaction is lacking. The major tyrosine phosphorylation sites of human CTTN are 421, 466, and 486, and we previously described a human genetic variant (S484N) that alters CTTN phosphorylation at the functionally important Y486 site to affect lung EC actin dynamics. We hypothesize that CTTN-MLCK interaction may be a promising therapeutic target for reversing lung EC dysfunction

Objective(s) The goal of this current project is to study the protein-protein interactions between cortactin-MLCK—and the effects of S484N on their binding.

Methods WT human CTTN and S484N cortactin 3D structures were built using advanced homology modeling techniques, including the MODELLER9.19 protein structure modeling tool. Molecular docking of CTTN-MLCK interaction was performed by the ClusPro web server to identify the number of residues involved. Duolink assay was used to characterize the association between CTTN and MLCK in cultured lung EC. The role of CTTN expression and function in this process was explored using plasmid overexpression in EC with or inhibition ameliorates MRSA-induced lung EC barrier dysfunction.

RESULTS After MRSA exposure, CYP1A1 mRNA expression was increased by 4-fold in HLMVEC and by 12-fold in HPAEC. Protein expression of CYP1A1 also was significantly increased in MRSAtreated lung EC (both HLMVEC and HPAEC) compared to control cells. Treatment of cells with Tys, which is an S1P analog and S1PR1 agonist. CYP1A1 protein and mRNA expression were assessed by western blotting and qPCR respectively. In separate experiments, prior to MRSA treatment, lung EC were either transfected with CYP1A1 siRNA (or control siRNA) or treated with a CYP1A1 inhibitor (Rhapontigenin). Lung EC barrier function was then evaluated using the electric cell-substrate impedance sensing (ECIS) system.

Conclusion Our findings demonstrate that CYP1A1 is upregulated in MRSA-exposed lung EC, possibly via mechanisms that involve S1PR1 signaling. Moreover, CYP1A1 down-regulation or inhibition ameliorates MRSA-induced lung EC barrier dysfunction.
disruption. This study identifies CYP1A1 as a novel mediator of EC barrier-disrupting events underlying MRSA-induced sepsis and ARDS.

**THE ROLE OF NADPH OXIDASE 4 IN HYPEROXIC ACUTE LUNG INJURY**

Panfeng Fu, Li Jiang, Feng Xu, Feng Guo. The Affiliated Hospital of School of Medicine, Ningbo University; Ningbo Medical Center Lihuili Hospital

Introduction/Background Oxygen therapy is uniformly used in emergency and intensive care medicine. However, excessive oxygenation causes acute lung injury, which is characterized by hyperpermeability of the pulmonary vasculature. The underlying mechanism of hyperoxia-induced endothelial permeability has not been well established.

Objective(s) The objective of this study is to determine the role of NADPH oxidase 4 (Nox4) in hyperoxia-induced endothelial permeability.

Methods Human lung microvascular endothelial cells (HLMVECs) were cultured in the presence of 95% oxygen for various time points. The expression of Nox4 was assessed by western blot and real-time PCR. Phosphorylation of Nox4 was determined by co-immunoprecipitation. Immunofluorescent staining of intracellular Nox4 was performed to localize Nox4 in response to hyperoxia. The role of Nox4 in endothelial permeability was determined by FITC-conjugated dextran permeability assay and immunofluorescent staining of VE-cadherin and filament actin. In vivo, wild-type and Nox4 knock-out (KO) mice were exposed to normoxia (21% O2) or hyperoxia (100% O2) for 72 hrs. Bronchial alveolar lavage (BAL) was examined for total proteins and Evans Blue dye (EBD) extravasation to assess vascular leakiness.

Results Hyperoxia up-regulated Nox4 expression at both mRNA level and protein level. Meanwhile, hyperoxia-induced Nox4 serine phosphorylation, which was blocked by PKCδ inhibition. In contrast to normoxia-challenged cells, hyperoxia-challenged cells showed accumulation of Nox4 in Golgi. Downregulation of intracellular Nox4 by Nox4 siRNA significantly attenuated hyperoxia-induced endothelial permeability in vitro. Finally, Nox4 KO mice showed significantly less pulmonary permeability compared with wild-type mice exposed to hyperoxia.

Conclusion Hyperoxia induced significant Nox4 expression and intracellular translocation, which resulted in hyper-permeability of the endothelial barrier. Inhibition of Nox4 represents a potential therapeutic target for hyperoxia-induced acute lung injury.

**THE INFLUENCE OF HISTAMINE-2 RECEPTOR ANTAGONISTS ON SEPSIS MORTALITY**

Tarek Firzli, Sunil Sathappan, Daniel Antwi-Amoabeng, Bryce Beutler, Mark Ulanja, Farah Madhani-Lovely. University of Nevada Reno School of Medicine; Christus Ochsner St. Patrick Hospital; University of Southern California, Keck School of Medicine; Renown Health

Abstract 93 Figure 1 Multivariable model of predictors of 28 day mortality. Ordered forest plot of the predictors, including H2RA group, of mortality in our cohort of sepsis-3 patients
Introduction/Background Sepsis is a life-threatening inflammatory dysregulation defined by organ dysfunction in the setting of infection that contributes to extremely high mortality among patients who are admitted to the hospital and intensive care unit (ICU). Treatment modalities include antibiotics to treat underlying infection, fluid resuscitation and vasopressor agents to maintain mean arterial pressure (MAP) >65, and life supporting modalities as required. Additional therapies have been used, researched, or suggested, such as corticosteroids, cocktails including vitamin C and even statins. Research has demonstrated that sepsis is associated with increased plasma histamine, which has vasodilatory effects at the capillary level. Studies in mice have further suggested that activation of Histamine 1 and 2 receptors contributed to development of major end organ damage which was protected against with famotidine administration. This therapy, which is often used for other indications in admitted patients, has not yet been studied in humans with sepsis.

Objective(s) Our primary aim is to evaluate whether sepsis patients admitted to the ICU receiving Histamine 2 receptor antagonists (H2RAs) influence mortality. Future research using this dataset will evaluate other outcomes such as mechanical ventilation, and markers of organ function in these patients.

Methods We queried the MIMIC-4 ICU database, identifying all patients admitted to the ICU meeting sepsis-3 criteria. We excluded patients who were mechanically ventilated prior to ICU admission or patients who received H2RAs (famotidine, ranitidine, or cimetidine) after one day into ICU admission. Patients were then grouped into patients who received H2RAs prior to or within 24 hours of ICU admission and those who never received H2RAs. This left a cohort of 12,908 in the H2RA group and 17,683 in the non H2RA group. We also extracted age, gender, risk scores (APSiii, SAPSii, SOFA and OASIS), the Charlson Comorbidity Index and subcategories, first ICU or hospital admission indicators, mechanical ventilation, PaO2/FiO2 (PF) ratio, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), Creatinine, length of hospital and ICU stay and 28-day mortality. Univariate analysis was performed between these factors using appropriate statistics tests. Multivariable logistic regression was utilized to evaluate odds of mortality between these groups controlling for any univariate covariates which differed significantly.

Results Mortality at 28 days was 15.1% in the no H2RA group compared to 12.6% in the H2RA group (p< 0.01). In a multivariable model, the odds of mortality of receiving H2RA prior to or within 24 hours of ICU admission compared to not receiving H2RAs was 0.82 [0.75, 0.89] (p< 0.001).

Conclusion Patients meeting sepsis-3 criteria who received H2RA therapies for any reason displayed a significantly lower odds of mortality in this cohort. We posit that this may be due to decreased systemic vasodilatory (SVR) and vascular permeability which may prevent decrease in SVR and fluid leak in capillary beds of various organs. We cannot rule out that this effect was due to unknown confounder(s) and cannot conclude causation based on this retrospective study, however as H2RAs have been demonstrated safe in sepsis patients and are low-cost medications, we believe more research is worthwhile. Our continued work using this dataset will evaluate associations between other outcomes such as mechanical ventilation, and length of stay. As mouse research suggests H2RAs had differential protective effects on organs, the lung, kidney, and liver will also be examined via commonly obtained lab values and hemodynamic parameters.

Abstracts

94 IMPACT OF TIME FROM ADMISSION TO NOREPINEPHRINE USE ON MORTALITY IN SEPSIS 3 PATIENTS IN THE ICU: A RETROSPECTIVE STUDY USING THE MIMIC-4 DATABASE

Tarek Firzli, Amneet Rai, Mark Riddle, Faisal Siddiqui. University of Nevada Reno School of Medicine; VA Sierra Nevada Health Care System

Introduction/Background Sepsis and septic shock are leading causes of mortality in hospitalized patients. Integral to treatment of sepsis and septic shock has been maintaining mean arterial pressure (MAP)>65 mmHg and treatment of underlying pathogens. Often, fluid resuscitation is not enough to maintain MAP and vasopressors (VPs) are required. It has been suggested from prior research and in clinical guidelines that earlier use of VPs such as norepinephrine (NE) provides a short-term mortality benefit to these patients, however few larger studies exist examining this. Furthermore, it is uncertain what level of fluid resuscitation is ideal prior to the administration of VPs. Current practice is to ‘fill the tank before squeezing the pipes’, however it remains an open question to what level of fluids should be given prior to VP use.

Objective(s) Our primary objective is to examine the impact of early (less than 600 minutes from admission) and late (more than 600 minutes from admission) NE use in sepsis patients admitted to the intensive care unit (ICU). In future analyses of this dataset, we seek to identify if early vs late VP use has any mortality benefit depending on volume of fluid received prior to VP use.

Methods The MIMIC 4 ICU database was queried to identify all patients admitted to the ICU meeting sepsis-3 criteria and who received NE, the most common first line agent used in in MAP maintenance. Patients were excluded if they received other VPs prior to NE use, died within 72 hours, did not have recorded fluids, or were missing covariates. Our cohort consisted of 4606 patients, with 1870 patients in the early NE group and 2736 in the late NE group. Variables queried for each patient consisted of time to first NE use, total volume of fluids received prior to NE use, Charlson Comorbidity Index (including individual disease indicators), age, gender, ethnicity, SAPSii, APSiii, OASIS and SOFA scores. 28-day mortality was also obtained for each patient. Univariate statistical tests were performed on each variable, and those that differed significantly were selected for use in a multivariable model. Multivariable logistic regression was applied to the entire cohort and future analysis will apply this to subgroups of patients based on quartile of fluids received.

Results In a multivariable logistic regression model applied to all patients, it was found that mortality was 1.205 (1.022–1.42) times greater in the late NE group when compared to the early NE group when controlling for covariates which differed between groups in univariate analysis.

Conclusion These results lend additional support for the mortality benefit of starting vaspressors early in septic patients, although we are limited by the observational study design. The mechanism for this effect is likely due to one or a combination of factors such as maintenance of perfusion, decreased vascular permeability and lower risk of fluid...
overload. What is not known and is of utmost importance is how a patient's fluid status impacts this effect, which could contribute to precise guidelines on when to administer NE. In the full analysis of this work, we will examine subgroups of patients based on total volume of fluids received, as well as examine other outcomes such as mechanical ventilation, length of stay in ICU and hospital, organ failure based upon SOFA score, and total volume of fluids received at 24, 48 and 72 hours.

CARMIL1 EXPRESSION ALTERS PULMONARY ENDOTHELIAL BARRIER FUNCTION FOLLOWING INFLAMMATORY INJURY

Patrick Belitch, Cat Hampl, Regina Dementie, Joe GN Garcia, Steven Dudek.
University of Illinois at Chicago; University of Arizona
10.1136/jim-2022-MW.94

Introduction/Background The acute respiratory distress syndrome (ARDS) can be caused by lung or systemic inflammation and results in severely impaired gas exchange and high mortality. Loss of pulmonary endothelial barrier integrity is a common pathologic hallmark of ARDS. Cytoskeletal regulatory protein activity and interaction are responsible for changes in actin structure and membrane-associated actin polymerization which alter endothelial cell (EC) shape to determine barrier function. Variations in the gene encoding the cytoskeletal regulator capping protein Arp2/3 complex myosin-I linker (CARMIL1) have been implicated in human ARDS outcomes through preservation of platelet count (Wei, et al. AJRCCM 2017). CARMIL1 is also known to function at the periphery of motile cells and regulate membrane protrusion. We have previously demonstrated that CARMIL1 is expressed in pulmonary endothelial cells and contributes to barrier regulation. Objective(s) In the current study we investigate the effects of altered CARMIL1 expression on pulmonary endothelial responses to inflammatory stimuli and investigate interactions with other EC cytoskeletal regulatory proteins. Methods EC barrier function was assessed by transendothelial electrical resistance (TER). Human pulmonary artery ECs were transduced with lentiviral particles containing CARMIL1 or control (2374+/-42 vs 1981+/-24 Ohm; p< 0.01). Resistance measurements were normalized at t=0 and observed for 12–20 hours. The response to inflammatory stimuli (thrombin 1U/ml) or methicillin resistant staph aureus (MRSA; 3 x 108 CFU) was determined. Protein immunoprecipitation studies were conducted following treatment with barrier enhancing sphingosine-1-phosphate (S1P 1µM x 15 min) and protein interaction was measured by western blot. Results ECs transduced with CARMIL1 lentivirus demonstrate significantly increased electrical resistance compared to vector control (2374+/-42 vs 1981+/-24 Ohm; p< 0.01). Resistance increased an additional 2-fold over the subsequent 15 hrs. CARMIL1 siRNA knockdown exacerbates the percent reduction in TER compared to scramble siRNA following thrombin (-30% v. -15%) and MRSA (-49% v. -37%). Immunoprecipitation revealed an interaction between CARMIL1 and the actin regulatory protein cortactin which increased following S1P treatment. Conclusion CARMIL1 expression regulates pulmonary endothelial barrier function at baseline and following inflammatory stimuli. CARMIL1 interacts with known regulators of EC cytoskeletal rearrangement. These results suggest an important role for endothelial CARMIL1 in ARDS pathologic mechanisms.

POST VACCINATION TRANSCRIPTOMIC PROFILING IN SARCOIDOSIS YIELDS PATHWAYS ASSOCIATED WITH DECREASED IMMUNE RESPONSE

Christen Vagts, Yi-Shin Chang, Jessica Lee, Kai Huang, Yue Huang, Christian Ascoli, Nadera Sweiss, David Perkins, Patricia Finn. University of Illinois at Chicago
10.1136/jim-2022-MW.95

Introduction/Background Sarcoïdosis is a T cell mediated systemic disease of unknown etiology that results in granulomatous inflammation and multiorgan dysfunction. Individuals with sarcoidosis have been shown to be at increased risk for infection arguing the importance of vaccination as a primary prevention strategy. However, current knowledge as to how individuals with sarcoidosis respond to vaccination is limited. Furthermore, proteomic and transcriptomic profiling post vaccination will offer integrated insight into the immune mechanisms that drive sarcoidosis disease. Objective(s) The objective of this study is to determine the quantitative antibody response to COVID-19 vaccination to correlate to the unique proteomic and transcriptomic profiles underlying the immune response. Methods With local institutional review board approval, a prospective case control study was conducted to compare the proteomic and transcriptomic profiles of subjects with and without sarcoidosis before and after vaccination with the BNT162b2 mRNA vaccine. Recruited subjects included individuals ≥18 years who received two doses of the vaccine at the University of Illinois (UIC). Sixteen subjects with biopsy proven sarcoidosis were recruited, six of whom were not on any treatment while 10 were on immunosuppressive therapy, while 23 age-gender matched healthy controls were recruited. Blood was sampled prior to each vaccine dose as well as one and seven days after vaccination. Anti-spike protein IgG titers and serum cytokine profiles were quantified with ELISA while bulk RNA sequencing was performed on peripheral blood mononuclear cells (PBMCs). Results Sarcoïdosis subjects had significantly less antibody production after two doses of the BNT162b2 mRNA vaccine than controls (p-val 0.0040). A multivariate regression analysis indicated that a sarcoidosis diagnosis (p-val 0.026) was significantly and independently predictive with lower follow up antibody titers, which was more pronounced if subjects were on immunosuppressive therapy (p-val 0.00013). Differential gene expression will compare temporal individual variation after vaccination and identify group differences to identify transcriptomic pathways associated with the diminished antibody response. Weighted gene co-expression analysis will identify likely expressed genes to determine distinct profiles that may be predictive of sarcoidosis disease. Conclusion Subjects with sarcoidosis mount a decreased antibody response to the BNT162b2 mRNA COVID-19 vaccine supporting a dysregulated immune response inherent to sarcoidosis pathogenesis. Correlated transcriptomic and proteomic profiling offers a unique opportunity to comprehensively study the genes and pathways underlying the immune response to vaccination in sarcoidosis.
Introduction/Background
Respiratory involvement after acute coronavirus disease 2019 (COVID-19) infection is its most common severe manifestation. Hypoxemia associated with the acute illness is often prolonged and many patients are discharged with home oxygen regardless of their initial level of care needs. Standardized oxygen re-assessment guidelines, as well as the expected trajectory of hypoxemia, have previously been published for other chronic hypoxemic lung diseases but this data is essentially lacking for post-COVID-19 related prolonged hypoxemia.

Objective(s) In this study, we report features of the U.S. military veterans who were discharged on new home oxygen therapy after surviving a COVID-19 hospitalization. Additionally, we report the incidence of post-acute symptoms related to COVID (PASC) in these patients.

Methods We conducted a retrospective study of 285 patients admitted to our Veterans Affairs (VA) medical center between March 2020 to Feb 2021 for an acute COVID-19 related illness. Exclusion criteria included: death during hospitalization, no home oxygen needs on discharge, and those with prior home oxygen use. Out of these, 65 patients (23%) that were discharged with new domiciliary supplemental oxygen were included in the analysis.

Results These patients were predominantly African American (69%) men (93%), with a mean age of 67 years ±11 standard deviation (SD). Common comorbidities included hypertension (83%), hyperlipidemia (61%), obesity (59%) with a mean body mass index (BMI) of 31 kg/m (±6SD), type-2 diabetes (49%) and obstructive sleep apnea (40%). Most of these patients did not undergo a formal six-minute walk test to reassess ongoing ambulatory supplemental oxygen requirements post-discharge. By eight weeks post-discharge, only 6% of these patients had a formal oxygen prescription assessment which increased to 23% by end of six months. Nonetheless, home oxygen was discontinued in most patients (52%) within eight weeks of discharge and up to 15% by end of six months. In addition, a large proportion of patients (46%) who were on home oxygen for at least eight weeks thereafter developed PASC.

Conclusion We conclude that prolonged hypoxemia after acute COVID-19 related illness though prevalent is infrequently reassessed in veterans. We recommend that healthcare providers be appraised about proper monitoring and evaluation of new domiciliary oxygen use in patients for persistent hypoxemia after discharge from a COVID-19 hospitalization. Whether the patients that survived COVID-19 hospitalization and were treated with home oxygen after discharge have an elevated risk of developing PASC remains to be determined in larger, prospective studies.

Abstract 97 Table 1 Characteristics of patients who reported PASC ≥8 weeks after hospital discharge

<table>
<thead>
<tr>
<th>Characteristics of patients with PASC (n=65)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median [IQR], yr.)</td>
<td>70 (65-76)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 30 (100)</td>
</tr>
<tr>
<td>Race: African American</td>
<td>21 (70)</td>
</tr>
<tr>
<td>Caucasians</td>
<td>6 (20)</td>
</tr>
<tr>
<td>Others</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Smoking history</td>
<td>Current smoker 8 (24)</td>
</tr>
<tr>
<td>Previous smokers</td>
<td>17 (56)</td>
</tr>
<tr>
<td>Unknown</td>
<td>5 (18)</td>
</tr>
<tr>
<td>Co-morbidity conditions</td>
<td>Hypertension 20 (60)</td>
</tr>
<tr>
<td></td>
<td>Hyperlipidemia 20 (60)</td>
</tr>
<tr>
<td>Obesity (BMI ≥30 kg/m²)</td>
<td>18 (60)</td>
</tr>
<tr>
<td>Diabetes mellitus, type 2</td>
<td>14 (40)</td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
<td>12 (40)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>10 (33)</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>10 (33)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>6 (20)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>5 (16)</td>
</tr>
<tr>
<td>Non-small lung cancer</td>
<td>4 (13)</td>
</tr>
<tr>
<td>COPD</td>
<td>3 (9)</td>
</tr>
<tr>
<td>CVA</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Asthma</td>
<td>2 (6)</td>
</tr>
<tr>
<td>History of venous thromboembolism</td>
<td>2 (6)</td>
</tr>
<tr>
<td>TIA/ILE</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Intestinal lung disease</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Todd organ transplant</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>
Abstract

Results In order to assess the effect of asthma itself on changes in epithelial gene expression, we compared asthmatic donor cells to healthy donor cells at baseline (without MC-LR exposure) and found that 25.5% of all protein-coding genes detected were upregulated (log2 fold change (log2FC) > 0.25), in the pre-existing asthma donor epithelium. Importantly, when comparing MC-LR exposed vs unexposed asthma derived epithelium, MC-LR exposure further upregulated (log2FC > 0.25) a subset (~10%) of genes that were upregulated by asthma alone including inflammation mediators, such as toll-like receptor 2 (TLR2) (log2FC = 0.31); TLR3 (log2FC = 0.26); and TLR4 (log2FC = 0.31) (figure 1). Protein interaction analysis found a significantly large number of predicted interactions among these genes suggesting a biological connection. An ontology analysis revealed a significant association of these genes with pathways, such as ‘regulation of cytokine production involved in immune response’ (FDR = 0.04); ‘cytokine binding’ (FDR = 0.015); ‘cellular response to chemical stimulus’ (FDR = 0.0008); and ‘defense response to virus’ (FDR = 0.0017). When comparing asthmatic donor cells to healthy donor cells we also found 23.3% of all protein-coding genes detected were downregulated (log2FC < -0.25), in the pre-existing asthma state. Again, when comparing MC-LR exposed vs unexposed asthma derived epithelium, MC-LR exposure further downregulated a subset (~9%) of genes that were downregulated (log2FC < -0.25) by asthma alone including extracellular matrix (ECM)-related and cadherin signaling-related mediators, such as PCDHGA7 (log2FC = -1.46); MMP3 (log2FC = -0.37); and COL6A1 (log2FC = -0.44). Protein interaction analysis of these genes also found a significantly large number of predicted interactions. An ontology analysis revealed a significant association of these genes with localization to ‘extracellular matrix’ (FDR = 0.004).

Conclusion Airway epithelium of asthmatic patients demonstrates a gene transcriptional profile that is distinguishable from its healthy counterpart. Importantly, the results of this study show that aerosolized MC-LR further amplifies these differences leading to the exacerbation of inflammatory mediators of asthma such as toll-like receptors and decreases in ECM proteins, suggesting a potential for MC-LR exposure to worsen asthma severity.

99 A NOVEL EB3 INHIBITOR TO COMBAT VASCULAR LEAKAGE AND SYSTEMIC INFLAMMATION IN AN ACUTE LUNG INJURY MODEL

Martin Chan, Xinyan Qu, Jonathan Le, Ryan Kowk, Shuangping Zhao, Yulia Komarova. University of Illinois at Chicago

Objective(s) This study aims to test the beneficial effects of the inhibitor of end binding protein 3 (EB3) in endotoxemia and sepsis-induced ARDS.

Methods The inhibitor of the microtubule-associated factor End Binding protein 3 (EB3) termed 109 was administered to mice challenged with endotoxin lipopolysaccharide (LPS) or underwent a cerclage ligation and puncture (CLP) surgery to induce ARDS. 109 therapeutic benefits were also tested in ARDS induced with a two-hit approach: a combination of CLP with normal tidal volume mechanical ventilation (NVMV). Mice survival, lung microvessel permeability to albumin, pulmonary edema, lung mechanics, and levels of chemokines were assessed. Bulk RNA-sequencing was also performed on endothelial cells isolated from control or 109-treated mice to determine the underlying mechanism of 109 effects.

Results Administration of 109 in mice challenged with lethality dose 90 (LD90) of LPS showed dose-dependent improvement in survival rate with EC50 30 nmol/kg. 250 nmol/kg (maximal response dose) of 109 improved survival rate by more than seven-fold when compared to the control mice post-LPS challenge. In mice that underwent CLP surgery, a single dose of 500 nmol/kg of 109 improved the survival rate by up to 75% when compared to control. A lower dose of 109 (250 nmol/kg) had similar results when combined with antibiotics. A single maximal response dose of 109 also restores lung compliance of mice challenged with an LD90 of LPS. Furthermore, 109 reduces pulmonary vascular leakage of Evans Blue-labeled albumin and neutrophil infiltration when administered in both early and late stages of lung injury; 109 also blocked vascular hyperpermeability induced by CLP with and without NVMV. Chemokine analysis of mice subjected to CLP showed reduced concentrations of MCP-1, CXCL2, IL-6, and TNF-α in bronchoalveolar lavage and blood plasma but did not change bacteria count in blood. Additionally, 109 reduced levels of blood urea nitrogen, creatinine, bilirubin, and alanine aminotransferase in blood plasma of mice post-CLP surgery. Bulk RNA-seq performed on isolated pulmonary endothelial cells revealed the downregulation of the inflammatory NF-kB and NFAT signaling and activation of repressive FOXM1 pathways.

Conclusion Our studies showed therapeutic benefits of EB3 inhibitor in treating acute lung injury and lung inflammation. These results suggest that 109 could provide a novel and significant clinical use in treating ARDS patients.
OSELTAMIVIR AND REMDESIVIR AS A TARGETED COMBINATION THERAPY FOR A YOUNG AND PREVIOUSLY HEALTHY ADULT WITH ACUTE RESPIRATORY DISTRESS SYNDROME SECONDARY TO FLURONA

Saf-Eddin Malhas, Azizullah Beran, Waleed Khokher, Omar Sour, Mohammed Mhanna, Ziad Abuhelwa, Wasef Sayeh, Mohammed Khalifah, Ragheb Assaly. University Of Toledo

10.1136/jim-2022-MW.99

Introduction/Background COVID-19 and influenza typically present in a very similar clinical picture. The co-infection of influenza among COVID-19 patients (i.e., flurona) can occur in the fall and winter of the year. The prevalence of flurona was estimated to be 0.4% and 4.5% in America and Asia, respectively. The damage of respiratory ciliated cells by the influenza virus can facilitate COVID-19 infection. Few studies reported COVID-19 co-infection with influenza virus. The majority of flurona cases affected older patients with co-morbidities. The co-infection of influenza among COVID-19 patients was associated with more severe disease, especially among older patients with co-morbidities. Young and healthy adults are less likely to develop severe COVID-19 leading to ARDS even with co-infection. However, severe COVID-19 can still occur regardless of age and co-morbidities. Herein, we report a case of severe ARDS in a young and previously healthy adult secondary to flurona that was successfully treated with targeted combination therapy with oseltamivir and remdesivir.

Objective(s) A 21-year-old Caucasian male patient without significant past medical history presented the ED with a chief complaint of fatigue, cough, and generalized body aches. The patient mentioned that symptoms started a few days before his presentation. He suspected it was the flu, so he did not seek medical care initially. However, his symptoms continued to worsen, to the point that he could not move without getting severely out of breath. He was tachycardic, tachypneic in the emergency department (ED). His COVID-19 swab returned positive, and a respiratory pathogen panel was also positive for influenza A infection. Initial CTA was negative for PE but showed extensive multifocal bilateral infiltrates consistent with viral pneumonia. He was started on a high-flow nasal cannula. Still, his oxygen was peaking around 85% with increased work of breathing. The patient also did not tolerate BiPAP. Therefore, the patient was intubated in the ED and admitted to the intensive care unit (ICU). He was started on a five-day course of oseltamivir, remdesivir, and intravenous methylprednisolone. The patient remained intubated and mechanically ventilated on the next day, and PaO2/FIO2 ratio was 100. He was started on ARDS treatment protocol, and daily prone positioning was initiated. Gradually the patient started to improve. On day nine, he successfully passed a CPAP trial and was extubated. His ICU stay was complicated by the development of a small segmental PE that was treated with IV heparin. He also had upper GI bleeding, and esophagogastroduodenoscopy revealed a bleeding gastric ulcer, which was successfully managed with endoscopic clipping. The patient gradually improved, and his oxygen requirements decreased significantly over the next few days. He was discharged home with no supplemental oxygen on apixaban and pantoprazole.

Methods Our study highlights the importance of screening for co-infecting influenza virus in COVID-19 patients, which could be the leading cause of disease severity. Early detection of flurona can play an important role in managing these patients, especially if they develop ARDS. Targeted combination therapy against influenza and COVID-19 with oseltamivir and remdesivir may effectively mitigate the morbidity and mortality of these patients. Improving compliance with flu vaccination is highly recommended to reduce influenza virus transmission during this long COVID-19 pandemic and reduce the risk of COVID-19 severity.

ACUTE THROMBOSIS OF A LONGSTANDING UNRETRIEVED INFERIOR VENA CAVA FILTER PRESENTING AS A CASE OF ORTHOSTATIC SYNCOPE

Saf-Eddin Malhas, Azizullah Beran, Waleed Khokher, Omar Sour, Ziad Abuhelwa, Wasef Sayeh, Mohammed Mhanna, Abdulaziz Aldhafeeri, Ragheb Assaly. University Of Toledo

10.1136/jim-2022-MW.100

Introduction/Background Inferior vena cava (IVC) thrombosis has been reported in 3–30% of patients following IVC filter (IVCF) placement. However, the true incidence of IVC thrombosis, especially with the longstanding unretrieved IVCFs, may be underestimated due to the lack of standardized ways of its detection. IVCF thrombosis can occur acutely, resulting in severe hemodynamic collapse/shock secondary to an abrupt decrease in the preload. It can also develop chronically over the years, allowing collateral circulation to develop. The chronic form is usually incidentally found on imaging studies but with minimal to no clinical effect. To our knowledge, we report the first case of acute IVCF thrombosis presenting as orthostatic syncope but with normal resting vitals.

Objective(s) A 71-year-old Caucasian male with a history of heterozygous factor-V Leiden mutation and multiple venous thrombotic events status post unretrieved Greenfield IVC filter placement 15 years prior to presentation. The patient presented to the emergency room for evaluation of a syncopal episode. The patient fell and lost consciousness after feeling dizzy when he stood up out of bed. The episode lasted for almost a minute, followed by a complete regain of consciousness. The episode was not witnessed. He has also been light-headed without vertigo or tinnitus over the past few days. On arrival, his vital signs were as follows: temperature of 36.7 °C, heart rate of 81 bpm, blood pressure of 132/74 mmHg, respiratory rate of 15 breaths/min, and oxygen saturation of 100% on room air. Initial labs including CBC, BMP Troponin, TSH, ethanol, and urine drug screen were unremarkable. EKG revealed a right bundle branch block without QT prolongation. CT brain without contrast was unremarkable. Orthostatic vital signs were positive with a drop of blood pressure to 72/40 mmHg and severe lightheadedness. The patient was started on intravenous fluids. On day two, D-dimer was significantly elevated at 3100. Lower extremity venous duplex revealed acute left femoropopliteal, posterior tibial, peroneal, and deep calf vein thrombosis. Intravenous heparin infusion was initiated. Shortly, the patient developed worsening swelling in his left lower extremity with involvement of the right lower extremity. Vascular surgery was consulted. Venogram revealed IVC occlusion at the inferior vena cava filter level with a free-floating thrombus cephalad to the tip of the filter into the decompressed suprarenal IVC. There was no impressive collateral vascularity to suggest a chronic IVC occlusion, making acute thrombotic occlusion the likely cause. Catheter-directed thrombolytics was done by vascular surgery, followed...
by IR-guided mechanical thrombectomy. The patient’s lower extremity swelling, and orthostatic symptoms significantly improved following the procedure. Repeat orthostatic measurements two days following the procedure were negative.

**Methods** The presentation of patients with thrombotic occlusion of IVC filters mainly depends on the chronocity and size of the occlusion, whether it is acute vs. chronic, total vs. near-total occlusion. Unlike previously described cases of acute occlusion that presented as an obstructive shock, our patient presented with a more subtle hemodynamic instability that requires a high level of suspicion (i.e., considering his normal resting blood pressure). In conclusion, IVCF thrombosis can rarely present with orthostatic hypotension and syncope. This case contributes to the growing literature on this rare presentation of IVCF thrombosis. It highlights the risks associated with IVCFs and illustrates the importance of removing IVCFs as soon as they are no longer needed to reduce long-term complications.

**Introduction/Background** Microscopic polyangiitis (MPA) is one of the three ANCA-associated vasculitides (AAVs). It is a multi-organ, necrotizing vasculitis predominantly affecting the small-sized arteries, mainly kidneys and lungs. MPA most often affects individuals in their 50s-60s, and is more commonly seen in Asian population. MPA can present with a multitude of signs and symptoms. Up to one-third of patients with MPA develop diffuse alveolar hemorrhage. Rapidly progressive glomerulonephritis (RPGN) is a common renal manifestation of MPA. Concurrence of alveolar hemorrhage with RPGN is termed as pulmonary-renal syndrome which can be treated with immuno-suppressants. We present a case of an 83-year-old Caucasian female who developed pulmonary-renal syndrome due to MPA leading to death within one month of onset of symptoms.

**Objective(s)** Patient was an 83-year-old white female with a past medical history of chronic kidney disease (CKD) stage III, hypothyroidism, and obesity who presented with worsening dyspnea on exertion two weeks prior to her presentation. Patient was functionally independent at her baseline and was living by herself. She was tachypneic on examination and was in respiratory distress. She was started on two liters of oxygen via nasal cannula. Rest of the vitals were within normal limits. Additionally, her examination revealed crackles bilaterally. Arterial blood gases were notable for respiratory acidosis. Labs were significant for blood urea nitrogen (BUN) of 31.2, creatinine of 2.20, and white cell count of 16.3. Chest X-ray showed bilateral interstitial alveolar airspace opacities. Patient was started on furosemide for possible new onset congestive heart failure, and antibiotics for suspected multifocal pneumonia. However, her oxygen requirement increased over the following days. Repeat imaging studies showed increasing bilateral pulmonary infiltrates. Patient underwent bronchoscopy with bronchoalveolar lavage which showed gross alveolar hemorrhage. Autoimmune etiology was considered given her renal and pulmonary decline. Serological studies showed positive antinuclear antibody (ANA), positive peripheral antineutrophil cytoplasmic antibodies (p-ANCA), positive anti-myeloperoxidase (anti-MPO) and positive anti-proteinase 3 (pR3) antibody. Her kidney function continued to worsen and she developed severe oliguria. She underwent CT guided renal biopsy which revealed focal, necrotizing, crescentic glomerulonephritis, pauci-immune type. She received cyclophosphamide and was started on high dose steroids. However, she was unable to tolerate hemodialysis due to cardiopulmonary instability. She remained on HHFNC for two weeks without any improvement of pulmonary function. Given poor prognosis due to rapid renal decline and pulmonary failure, family decided to make patient comfort care.

**Methods** This case has many unique aspects. MPA is common in Asian population with age of onset between 50–60 years. Given that our patient was an 83-year-old Caucasian, MPA was not initially considered. Before patients develop RPGN, there is usually a long prodromal phase which can last up to months. Our patient was functionally independent prior to her presentation and as per daughter she was ‘normal, driving, shopping and getting her hair done’. It is unclear why she developed rapid onset of pulmonary renal syndrome. Our case highlights that physicians should consider autoimmune vasculitis with renal and pulmonary failure, even in atypical age group and ethnicities. Atypical patients can present with rapid decline. Early recognition of signs and symptoms is important to start treatment as disease process is often fatal.

---

**Abstracts**

**102 83-YEAR-OLD FEMALE WITH FATAL PULMONARY-RENAL SYNDROME DUE TO MICROSCOPIC POLYANGIITIS**

Amana Hasnain, Kashif Mukhtar, Natalie Warda, Trung Hua, Zarak Khan, Nandish Ban athally. St. Mary Mercy Hospital, Livonia

**Introduction/Background** Microscopic polyangiitis (MPA) is one of the three ANCA-associated vasculitides (AAVs). It is a multi-organ, necrotizing vasculitis predominantly affecting the small-sized arteries, mainly kidneys and lungs. MPA most often affects individuals in their 50s-60s, and is more commonly seen in Asian population. MPA can present with a multitude of signs and symptoms. Up to one-third of patients with MPA develop diffuse alveolar hemorrhage. Rapidly progressive glomerulonephritis (RPGN) is a common renal manifestation of MPA. Concurrence of alveolar hemorrhage with RPGN is termed as pulmonary-renal syndrome which can be treated with immuno-suppressants. We present a case of an 83-year-old Caucasian female who developed pulmonary-renal syndrome due to MPA leading to death within one month of onset of symptoms.

**Objective(s)** Patient was an 83-year-old white female with a past medical history of chronic kidney disease (CKD) stage III, hypothyroidism, and obesity who presented with worsening dyspnea on exertion two weeks prior to her presentation. Patient was functionally independent at her baseline and was living by herself. She was tachypneic on examination and was in respiratory distress. She was started on two liters of oxygen via nasal cannula. Rest of the vitals were within normal limits. Additionally, her examination revealed crackles bilaterally. Arterial blood gases were notable for respiratory acidosis. Labs were significant for blood urea nitrogen (BUN) of 31.2, creatinine of 2.20, and white cell count of 16.3. Chest X-ray showed bilateral interstitial alveolar airspace opacities. Patient was started on furosemide for possible new onset congestive heart failure, and antibiotics for suspected multifocal pneumonia. However, her oxygen requirement increased over the following days. Repeat imaging studies showed increasing bilateral pulmonary infiltrates. Patient underwent bronchoscopy with bronchoalveolar lavage which showed gross alveolar hemorrhage. Autoimmune etiology was considered given her renal and pulmonary decline. Serological studies showed positive antinuclear antibody (ANA), positive peripheral antineutrophil cytoplasmic antibodies (p-ANCA), positive anti-myeloperoxidase (anti-MPO) and positive anti-proteinase 3 (pR3) antibody. Her kidney function continued to worsen and she developed severe oliguria. She underwent CT guided renal biopsy which revealed focal, necrotizing, crescentic glomerulonephritis, pauci-immune type. She received cyclophosphamide and was started on high dose steroids. However, she was unable to tolerate hemodialysis due to cardiopulmonary instability. She remained on HHFNC for two weeks without any improvement of pulmonary function. Given poor prognosis due to rapid renal decline and pulmonary failure, family decided to make patient comfort care.

**Methods** This case has many unique aspects. MPA is common in Asian population with age of onset between 50–60 years. Given that our patient was an 83-year-old Caucasian, MPA was not initially considered. Before patients develop RPGN, there is usually a long prodromal phase which can last up to months. Our patient was functionally independent prior to her presentation and as per daughter she was ‘normal, driving, shopping and getting her hair done’. It is unclear why she developed rapid onset of pulmonary renal syndrome. Our case highlights that physicians should consider autoimmune vasculitis with renal and pulmonary failure, even in atypical age group and ethnicities. Atypical patients can present with rapid decline. Early recognition of signs and symptoms is important to start treatment as disease process is often fatal.

---

**Rheumatology/immunology/allergy**

**103 REVIVIFY® GEL STIMULATES THE IMMUNE SYSTEM VIA T-CELL ACTIVATION EVALUATED IN VITRO JURKAT CELLS: POTENTIAL ROLE IN THE PREVENTION/TREATMENT OF COVID-19 INFECTION**

1Ahmed Pantho, 2Syeed Afroz, 3Zauidinn Ahmed, 1Liaquat Hossain, 1Thomas Kuehl, 2Muhammad Uddin, 1Orion Institute for Translational Medicine; 2Emergent Biotechnologies; 3Temple University, Philadelphia; 4Advance Pharmaceutical Inc

**Introduction/Background** REVIVIFY® pro-vitality antioxidant gel composed of primary antioxidant superoxide dismutase [SOD], probiotic fibers, diverse polyphenols from various fruits juice. SOD diminishes the superoxide anion that is produced due to normal cellular activity. Polyphenols are phenolic compounds act as antioxidant, anti-inflammatory, anti-viral agent. It repairs damaged cells due to reactive oxygen molecules of ROS/RNS. Dietary probiotic fibers modulate beneficiary gut eco microbiomes and provide many health benefits including immunity. Combination of these three components stimulate the immunity via T-cell activation and antioxidative and anti-inflammatory pathway.

**Objective(s)** The objective of this study is to evaluate the effect of REVIVIFY® Gel on in vitro T cell Model.

**Methods** The JURKAT CELL LINE is an immortalized T lymphocyte cell line that has most often been used as a prototype T cell line to study multiple events in T cell biology, including T cell signaling. JURKAT cells were seeded on six well plates. Prior to treatment, cells will be incubated in serum free media for 24 hours. Cells will be treated with following agents: 1. Superoxide Dismutase only; 2. Probiotic fiber only; 3. Fruit juice only; 4. superoxide Dismutase + Probiotic
FIBRINOGEN DUALLY MODIFIED WITH MALONDIALDEHYDE-ACETALDEHYDE (MAA) AND CITRULLINE (CIT) MODIFIED UPREGULATES PEPTIDYLARGININE DEIMINASE IN HUMAN MACROPHAGES

Nozima Aripova, Michael Duryee, Spencer Jones, Andrew Gerber, Austin Ragland, Bryant England, James O’Dell, Ted Mikulas, Geoffrey Thiele. University of Nebraska Medical Center

Introduction/Background The discovery of circulating anti-citrullinated protein antibody (ACPA) as a highly diagnostic tool implicates a potential role for citrullinated antigens in rheumatoid arthritis (RA) pathogenesis. Citrullination is a post-translational modification (PTM) that is associated with chronic inflammation and is catalyzed by peptidyl arginine deiminase (PAD), a group of calcium-dependent enzymes that convert arginine to citrulline on many proteins. MAA is another type of PTM that is formed in the process of lipid peroxidation from malondialdehyde (MDA) and acetaldehyde (AA). Recently, antibodies to malondialdehyde-acetaldehyde adducts (MAA) have been shown to present at higher concentrations in the serum of RA patients and are strongly associated with disease activity markers. Additionally, MAA protein adducts co-localize with citrullinated proteins in RA synovium.

Objective(s) Macrophages are critical cells shown to play a role in the citrullination of extracellular matrix proteins via PAD enzymes and are implicated in RA pathogenesis. The objective of our study is to determine whether fibrinogen modified with MAA and/or CIT, characteristic of RA-impacted tissues, further influences citrullination remains unknown.

Methods The human monocytic cell line (U-937) were differentiated to macrophages using phorbol 12-myristate 13-acetate (PMA) treatment, and stimulated with; fibrinogen (FIB), FIB-MAA, FIB-CIT, and FIB-MAA-CIT. RNA was collected at 24 hours for RT-qPCR experiments, and the following markers were quantified: CAMKK2, ORA1, PAD2, and PAD4. At 48 hours, stimulated cell lysates were collected for protein analysis using Western Blot, and the following antibodies were used as probes: anti-CIT, anti-PAD2, and anti-β-actin antibodies. The relative expression of the protein was normalized to β-actin (endogenous control).

Results In comparison to unmodified fibrinogen, U-937 cells stimulated with FIB-MAA-CIT demonstrated the highest mRNA levels for CAMKK2 (1.6-fold increase, p<0.05 vs. unmodified FIB), ORA1 (2-fold, p<0.001), PAD2 (6-fold, p<0.001), and PAD4 (2.5-fold, p<0.001). In comparison, FIB-CIT treatment of U-937 cells significantly decreased mRNA levels of both PAD2 (3-fold decrease, p<0.05 vs. unmodified FIB) and PAD4 (2.5-fold, p<0.05) (figure 1). For Western Blot experiments, FIB-MAA-CIT demonstrated the highest amount of citrullinated sites at a 75kDa protein (8-fold increase, p<0.001 vs. unmodified FIB) and the highest PAD2 protein expression (6-fold, p<0.001) in comparison to unmodified fibrinogen. We chose 75kDa band for evaluation of citrullinated sites since it appeared as the most predominant band on Western blot and is thought to be PAD2.

Conclusion These studies demonstrate that FIB dually modified with MAA and CIT upregulates key intracellular calcium-binding proteins (CAMKK2, ORA1), potentially affecting calcium-dependent PAD2 and PAD4 enzymes, which further catalyze citrullination of proteins. The increase of citrullinated sites in
macrophages after stimulation with FIB-MAA-CIT is highly suggestive of increased PAD enzyme activity. The citrullination of the 75kDa band potentially implicates the autocitrullination of PAD (a 75kDa molecular weight protein) in the process, which in the broader scheme is implicated in the formation of new citrullinated antigens that may be involved in RA pathogenesis.

Introduction/Background The characterization of anti-citrullinated protein immune responses represents a seminal advancement in our understanding of rheumatoid arthritis (RA) pathogenesis. Autoantibodies to citrullinated (CIT) proteins are highly disease specific and are associated with heightened disease activity, which is characterized by joint erosion and lung disease. There are several autoantibodies to modified proteins currently under investigation; the focus of our laboratory is on autoantibodies to the malondialdehyde-acetaldehyde adduct (MAA). MAA is one of the byproducts of oxidative stress, shown to be strongly immunogenic. Our laboratory has shown that MAA adducts are highly expressed in RA patient joint/lung tissue and co-localize with CIT-modified proteins. Antibodies to MAA also correlate with heightened RA disease activity. We believe CIT and MAA post-translational modifications act synergistically driving the immunological response involved in RA pathogenesis. As lung disease is a common comorbidity of RA, we sought to determine if airborne
exposures induce commodification of proteins (potentially implicated in the inflammatory pathogenesis of RA) with MAA and CIT. We hypothesized that a mouse model of exposure to CIA (collagen induced arthritis model) and LPS (lipopolysaccharide) will lead to increased co-modification of self-proteins.

Objective(s) The objective was to determine if airborne exposure induces co-modification of proteins with MAA and CIT.

Methods DBA1/J male mice (n=5/group) were assigned to either: sham (saline injection/saline inhalation), CIA (CIA/saline inhalation), LPS (saline injection/LPS inhalation) or CIA+LPS for five weeks. Hind paws were observed and given an arthritis inflammatory score of 0–4 based on swelling and redness of the hind paws. Serum and lung tissues were collected. An antigen capture ELISA was developed by coating plates with polyclonal rabbit anti-MAA antibody overnight. Tissue homogenates were then plated and incubated. The modified protein was removed and plates blocked with casein. The wells were then incubated with a monoclonal mouse anti-CIT IgM antibody. Plates were then incubated with goat anti-mouse IgM tagged with HRP. A second capture ELISA (#2) was run with identical parameters except the secondary antibody used was anti-Fibrinogen (Fib) CIT instead of simply anti-CIT. A third ELISA (#3) was run using serum to detect antibodies to both MAA, CIT and the combination of MAA-CIT.

Results The highest arthritis inflammatory scores were seen in CIA+LPS mice at five weeks, followed by CIA and LPS treatment alone compared to sham (figure 1). Figure 2 represents assay #1, where the combination of CIA with LPS had the highest yield of MAA-CIT co-modified protein. Figure 3 shows Fib as a target of co-modification by MAA and CIT adduction (assay #2). Interestingly, the group with the highest inflammatory score has the highest amount of co-modified protein as well. Figures 4–6 illustrate that mice serum contain the highest concentrations of antibodies to MAA adducts, CIT and co-modified MAA-CIT proteins when treated with both LPS and CIA.

Conclusion The co-modified capture assay was successful in retrieving co-modified proteins from the lung homogenates. This is the first report confirming commodification with MAA and CIT. There appears to be a correlation between LPS and CIA exposure and co-modification of proteins. This unique capture assay can be utilized to advance our understanding of inflammatory diseases characterized by the co-localization of MAA and CIT modified proteins by identifying the specific in vivo antigens that are co-modified potentially driving the autoimmune responses in RA.

106 EFFECTS OF PROTEIN MODIFICATION WITH MALONDIALDEHYDE-ACETALDEHYDE AND/OR CITRULLINE ON HUMAN MACROPHAGES IN A MODEL OF RA SYNOVIAL PATHOGENESIS

Madison Bierman, Nozima Aripova, Michael Duryee, Bryant England, Ted Mikuls, James O’Dell, Geoffrey Thiele. University of Nebraska Medical Center

10.1136/jim-2022-MW.105

Introduction/Background Malondialdehyde (MAA) is an immunogenic protein modification that forms from the lipid peroxidation byproducts malondialdehyde and acetaldehyde. MAA protein adducts co-localize with citrillinated (CIT) proteins in rheumatoid arthritis (RA) synovium, and anti-MAA antibodies are significantly increased in RA patient serum compared to controls.

Objective(s) When stimulated with antigens, immature macrophages (M0) can differentiate into M1 (pro-inflammatory) or M2 (pro-fibrotic) phenotypes. Macrophage responses to modified proteins and their release of corresponding soluble factors potentially affects other cells to exacerbate the disease process. Currently, the cellular response of macrophages to MAA and/or CIT antigens in the context of RA disease pathogenesis is not well delineated in the RA synovium. As such, the objective of our study is to provide further insight into the RA disease process by determining the responses of immature macrophages to these modified antigens.

Methods The human monocytic cell line (U-937) was matured to a macrophage cell line (M0) using phorbol 12-myristate 13-acetate (PMA), and stimulated with the following antigens: human serum albumin (HSA), MAA modified HSA (HSA-MAA), CIT modified HSA (HSA-CIT), and MAA-CIT modified HSA (HSA-MAA-CIT). Macrophages were cultured and then stimulated with the antigens for different time periods. The cells were then harvested and RNA was extracted. Real-time PCR was performed to determine the mRNA expression levels of M1 and M2 marker genes.

Abstract 106 Figure 1 PCR for mRNA-fold increase from stimulated U-937 macrophages
MAA), citrullinated HSA (HSA-CIT), or co-modified HSA (HSA-MAA-CIT). Cells were isolated and RNA was extracted at the following points: 4, 8, 12, 24, 48, and 72 hours. Differentiation to either the M1 or M2 phenotype was determined using RT-qPCR to measure mRNA levels of M1 (CD14, CX3CR1, CD192) and M2 (CD163, CD206) markers. The data was normalized to M0 stimulated with unmodified HSA. In additional experiments, 48-hour stimulated supernatants were collected and evaluated for several M1 (IL-12, IL-23, IL-6, TNF-α, IL-1β, MCP-1) and M2 (IL-10, IL-13, M-CSF, MCD) cytokines using ELISA.

**Results**

HSA-MAA stimulated M0 cells upregulated mRNA levels of CD14 (p< 0.001 vs. unmodified HSA for all time points) and CD163 (p< 0.001 for 48h), signifying population of M1 and M2 macrophages. HSA-MAA-CIT stimulation induced upregulation of CXCR3 (p< 0.001 for all time points, except 24h), CD192 (p< 0.001 for 48 and 72h), CD163 (p< 0.001 for 24–72h), and CD192 (p< 0.001 for 4–24h).

Abstract 106 Figure 2  ELISA for M1- associated cytokines from stimulated U-937 macrophages

Abstract 106 Figure 3  ELISA for M2- associated cytokines from stimulated U-937 macrophages
signifying distinct M1 and M2 macrophage populations. Stimulation of M0 with HSA-CIT did not upregulate mRNA levels of any markers, suggesting undifferentiated M0 population (figure 1). For the cytokine analysis, HSA-MAA stimulation yielded significant increase in release of both M1 cytokines (figure 2): IL-12 (p < 0.001 vs unmodified HSA), IL-23 (p < 0.001), IL-6 (p < 0.001), IL-1β (p < 0.001); and M2 cytokines (figure 3): IL-10 (p < 0.001), M-CSF (p < 0.001), and MDC (p < 0.05). Similarly, HSA-MAA-CIT stimulation of M0 yielded significant increase in release of both M1 cytokines: MCP-1/CCL2 (p < 0.001), IL-6 (p < 0.001), TNF-α (p < 0.001), and IL-1β (p < 0.001); and M2 cytokines: IL-13 (p < 0.001) and MDC (p < 0.001). In contrast, HSA-CIT stimulation of M0 upregulated the release of MCP-1/CCL2 (p < 0.001) and IL-1β (p < 0.05); and did not upregulate the release of any M2 cytokines.

Conclusion These experiments show that there is a differential effect on macrophage differentiation following stimulation with MAA-, CIT-, or MAA-CIT-adducted HSA. Overall, mixed and distinct M1 and M2 macrophage populations were present for M0 cells stimulated with HSA-MAA or HSA-MAA-CIT. Additionally, HSA-CIT stimulation induced the release of few M1 cytokines. These cellular effects vary both in overall magnitude and over time. There is heterogeneity in which and to what extent either pro-inflammatory or pro-fibrotic markers and cytokines are produced between antigen groups, which plays a potential pathogenic role in inflammatory state of RA synovium.

Objective(s) This study aims to characterize the relationship of community-level environmental factors and poverty rate with high-acuity presentation settings in patients with sinonasal disease. In particular, increased community-level particulate matter and traffic intensity exposure were associated with high-acuity visits among these patients. These observations need to be studied in a prospective, more rigorous fashion and may have wide-reaching public health implications, underscoring a need to mitigate these exposures in the public.

Introduction/Background Exposure to particulate matter and traffic-related air pollutants has been linked to the exacerbation of upper respiratory symptoms at both an individual and community level. Additionally, lower socioeconomic status has been associated with increased prevalence and severity of sinonasal disease. While limited, community-level studies have linked environmental exposures and low-income status to high-acuity health care presentation settings in patients with respiratory conditions, they have largely excluded sinonasal diseases.

Methods A retrospective analysis based on City of Chicago Health Atlas data (community-level) and medical records (individual-level) of 6,095 adult patients presenting with sinusitis, allergic rhinitis, or sinus/nasal polyps to an urban academic medical center from 2015 to 2019 was conducted. Zip code of residence was used to match individual patients with community-level data on environmental exposures (particulate matter and traffic intensity) and poverty rate, derived from Chicago Health Atlas data covering corresponding years. Particulate matter exposure was defined as the annual average concentration of particulate matter (measured in μg/m3) in each zip code, while traffic intensity was defined as a ratio of the annual average of the daily vehicle count divided by distance from the center of each census block within a zip code. Poverty rate was defined as percentage of residents in each zip code belonging to households below the Federal Poverty Level. Chi-square analysis was used to assess bivariate associations of environmental factors and poverty rate with high-acuity presentation settings – including emergency department and inpatient visits. Multivariable binary logistic regression was performed to examine the adjusted associations between environmental factors and poverty rate with high-acuity presentation settings. Variables adjusted for included demographic factors (age, race/ethnicity, sex, employment status, insurance type) as well as comorbid conditions (gastric reflux, allergy, depression, body mass index).

Results From 2015 to 2019, the average particulate matter exposure in the City of Chicago was 9.43 μg/m3, and the average traffic intensity index was 1458. In adjusted models, the odds of high-acuity visit presentation was significantly higher in patients residing in zip codes with above average exposure to particulate matter in the City of Chicago compared to those at or below average (OR:1.46; CI:1.20–1.76). Additionally, patients from zip codes with above average traffic intensity index in the City of Chicago were significantly more likely to present to high-acuity settings compared to those at or below average (OR:1.20; CI:1.002–1.43). There was no significant association witnessed with poverty rate.

Conclusion In this study, environmental exposures were found to impact health care presentation settings in patients with sinonasal disease. In particular, increased community-level particulate matter and traffic intensity exposure were associated with high-acuity visits among these patients. These observations need to be studied in a prospective, more rigorous fashion and may have wide-reaching public health implications, underscoring a need to mitigate these exposures in the public.
provide a novel preventative and/or therapeutic strategy for MC-LR exposure and hepatotoxicity.

Objective(s) The objective of the study was to determine the effect of microcystin (MC) degrading bacteria on MC-LR induced toxicity under in vivo and in vitro conditions.

Methods First, to determine if MC degrading bacteria protect the hepatocytes from cellular injury, we performed an in vitro experiment in which human Hep3B hepatocytes were treated with various ratios of hepatocyte: bacterial cells- 1:10, 1:50, and 1:100 for 30 minutes prior to exposure with 10 μM MC-LR. The cells were incubated with the MC-degrading bacteria and MC-LR for 24 hours at 37°C with 5% CO2. The cells were then collected to perform quantitative PCR (qPCR) analysis for markers of hepatocyte injury. For the in vivo experimental set-up, age-matched Balb/c female mice were either given a mix of MC degrading bacteria at 105 CFU/ml in drinking water (n=3–8 mice each) or normal drinking water for a period of four weeks. Mice in the treated group (n=5) were then gavaged with 500 μg/kg of MC-LR and those in the vehicle control group (n=3) were gavaged with an equivalent amount (300 μl) of water. The mice were then euthanized two or 24 hours post-exposure to MC-LR. qPCR was performed on target organs (liver and kidney) and liquid chromatography-mass spectrometric (LC-MS) analysis, to quantify the toxin levels, was performed using urine from mice euthanized after 24 hours.

Results In the in vitro experiments, to determine if the MC degrading bacteria survive the in vitro conditions, the bacteria from the spent media were plated onto nutrient agar plates and incubated at room temperature for three to five days. The presence of MC degrading bacterial colonies confirmed the presence of live bacterial strains and no contaminating bacterial colonies were observed. qPCR analysis of the treated hepatocytes for markers of hepatotoxicity (OSMR) and inflammation (Tgf-β) showed a significant increase in the gene expression (p ≤ 0.01 for OSMR and p ≤ 0.0001 for Tgfβ) on exposure to MC-LR but was significantly lowered in the presence of MC degrading bacteria indicating that the bacteria are capable of alleviating MC-LR induced hepatotoxicity. For in vivo experiments, LC-MS analysis of the 24-hour urine samples revealed significant reduction (p ≤ 0.05) in the MC-LR levels in the urine of mice that were pretreated with MC-LR degrading bacteria as compared to the untreated group indicating a reduction in toxin levels after exposure to the toxin. qPCR analysis of KIM-1 expression to assess the kidney injury caused by exposure to MC-LR revealed significant KIM-1 upregulation (p ≤ 0.001) within two hours of exposure in the control mice that was significantly attenuated in mice that received MC degrading bacteria. MC-LR exposure significantly increased markers of hepatotoxicity (OSMR) and inflammation (CD36) in the liver in the control mice at 24 hours while mice receiving MC degrading bacteria displayed significant downregulation of both OSMR (p ≤ 0.01) and CD36 (p ≤ 0.0001). Finally, genes related to MC-LR induced apoptosis, DNA damage, ER stress, and fatty acid metabolism were significantly downregulated in mice treated with MC degrading bacteria compared to control mice exposed to the toxin alone.

Conclusion These results indicate that acute exposure to MC-LR induces significant hepatotoxicity and inflammation that is alleviated by treatment with MC degrading bacteria. This suggests a potential novel therapeutic approach that can be developed for MC-LR-induced toxicity.
interactions in the TargetScan database (v7.21). Interestingly, among unestablished interactions, we found that signature miRNAs (hsa-miR-150-3p, hsa-miR-342-5p, hsa-miR-22-5p, hsa-miR-92a-1-5p) from our prior study have significant correlations to significant transcription factors.

**Conclusion** Though further investigation is warranted, in sarcoidosis, a dysregulated monocyte-driven transcriptional network is associated with lymphopenia. Transcription factors within this module significantly correlate with miRNAs and their relationships may influence their regulatory activity and impact lymphocyte survival and function.

**Abstract 109 Figure 1**

---

**Abstract 110**

**RECURRENT BILATERAL PRE-PATELLAR BURSITIS: A RARE PRESENTATION OF CALCIUM PYROPHOSPHATE DIHYDRATE CRYSTAL DEPOSITION DISEASE (CPPD)**

Yeohan Song, Sheryl Mascarenhas. The Ohio State University

10.1136/jim-2022-MW.109

**Introduction/Background** Pre-patellar bursitis is a common presentation of synovial inflammation of the knees, with an estimated annual incidence of 10/100,000. Calcium Pyrophosphate Dihydrate Crystal Deposition Disease (CPPD) is a highly prevalent condition also often involving the knees, though estimates are difficult to ascertain due to the definitive diagnosis requiring confirmation by aspiration. More recently, musculoskeletal ultrasound has been increasingly utilized, with reported sensitivity of 85% and specificity of 87% in detecting CPPD. This report describes the rare presentation of recurrent bilateral pre-patellar bursitis due to CPPD confirmed on ultrasound-guided bursal fluid aspiration, which should be considered in the differential diagnosis, as appropriate identification can guide targeted treatment interventions.

**Objective(s)** A 42-year-old Caucasian female with history of seropositive (rheumatoid factor 19 international units/milliliter [mL] and cyclic citrullinated peptide antibody 396 units [U]/

---

**Abstract 110 Figure 1** Ultrasound images of bilateral pre-patellar bursitis
mL) well controlled on sulfasalazine 1500 mg twice daily and ibuprofen 400 mg twice daily as needed for pain for over five years reported gradual onset of bilateral anterior knee pain with mild swelling over three months, not associated with traumatic injury or repetitive kneeling.

On initial assessment by a previous provider in rheumatology clinic, the patient had a temperature of 36.3 degrees Celsius, with blood pressure of 110/70 mm Hg, heart rate of 100 beats per minute, and respiratory rate of 16 breaths per minute. Anterior knee effusions were noted on physical examination. Laboratory analysis showed white blood cell (WBC) count of 5.73 thousand/μL, hemoglobin of 13.6 g/dL, and platelets of 243 thousand/μL. Creatinine was 0.66 mg/dL.

Hydroxychloroquine was added to her existing medication regimen, but was stopped due to associated lightheadedness. Consideration was also given to the potential addition of methotrexate, but the patient reported significant alcohol intake, so this was not pursued. Three months later, a non-image guided aspiration was attempted, with 15 mL of yellow fluid from the left pre-patellar bursa but unsuccessful aspiration of the right. Examination of this fluid aspirate showed 1,627 WBC/μL, 2,440 red blood cells (RBC)/μL, with negative crystal analysis, no organisms detected on Gram stain, and no growth on culture.

Four months later, the patient returned to clinic with persistent atraumatic bilateral anterior knee pain and recurrent swelling, undergoing an ultrasound-guided diagnostic aspiration and therapeutic methylprednisolone 20 mg injection of the bilateral pre-patellar bursae by the first author, with aspiration of 3 mL yellow fluid from the left and 1 mL yellow fluid from the right pre-patellar bursae. Interestingly, hyperechoic margins alongside the synovial lining of the pre-patellar bursae were observed during sonographic assessment (figures 1 and 2). Examination of the fluid aspirates from the bilateral pre-patellar bursae showed (left and right, respectively): 6,463 and 1,784 WBC/μL; 32 and 2,492 RBC/μL; no organisms detected on Gram stain; and no growth on culture. Crystal analysis was positive for calcium pyrophosphate crystals.

Four months after the above procedure, the patient reported sustained alleviation of pain related to bilateral pre-patellar bursitis. She has also not required the addition of any further immunosuppressive therapy.

Methods This case describes the identification of a rare presentation of CPPD in the form of recurrent bilateral pre-patellar bursitis using ultrasound assessment and diagnostic aspiration. The appropriate identification of this condition will allow for targeted medical interventions while potentially minimizing addition of systemic therapies.

REFERENCES
Introduction/Background Eosinophilic fasciitis (EF) is a rare disease characterized in its early phase by symmetrical and full circumferential erythema with nonpitting edema involving the limbs or trunk, and in the late phase by collagenous thickening of the subcutaneous fascia of the involved area.

Objective(s) A 41-year-old male with past medical history remarkable for Asthma, plantar fasciitis, and bilateral carpal tunnel syndrome, presented to the rheumatology clinic with two months history of right forearm swelling, warmth, and induration. Prior to the onset of symptoms, patient was camping in Michigan, he did not experience tick bite, myalgia, chills, or fever after returning from the camp. Physical exam was remarkable for right forearm swelling extending to the elbow, tenderness, skin tightening and warmth. He had positive Tinel’s sign on the right hand. CBC with differential unremarkable except for increased Eosinophils at 9% and basophils at 1.6%, absolute eosinophils count at 0.6 x103/μL and absolute basophils count was at normal limit. Erythrocyte sedimentation rate slightly elevated at 12 mm/HR (normal range 0–10). C-reactive protein elevated at 12.3 mg/L (normal range 0–7). ANA negative. Cyclic citrullinated peptide antibody, rheumatoid factor and Lyme IgG and IgM were negative. Patient scheduled for skin and subcutaneous incisional biopsy and started on Prednisone 40 mg daily with taper to 20 mg daily over three weeks. On follow up, patient symptoms improved on Prednisone 40 mg daily but once the patient taper to 20 mg daily his symptoms started to worsen. After one month of Prednisone treatment his Peripheral eosinophilia normalized. Skin and subcutaneous incisional biopsy demonstrate a predominantly deep reticular dermal, subcutaneous, and fascial inflammatory infiltrate composed of lymphocytes, histiocytes, plasma cells, and scattered eosinophils. Given the patient clinical history, physical examination, peripheral eosinophilia, and biopsy findings, he was diagnosed with eosinophilic fasciitis. He was started on methotrexate 12.5 mg weekly that was increased gradually to 25 mg weekly because of lack of clinical improvement on steroid therapy. Over the
next three months, patient’s symptoms didn’t resolve, and the decision was made to continue Prednisone 10 mg daily, stop methotrexate and start mycophenolate 1000 mg twice daily that was subsequently increased to 1500 mg twice daily. Upon follow up, the swelling and induration were markedly improved.

**Methods** Eosinophilic fasciitis is a challenging diagnosis of unknown etiology. In one study, 79% of patients with EF were misdiagnosed as having systemic sclerosis, DVT, hypereosinophilic syndrome or cellulitis. Clinical picture overlaps significantly with scleroderma-spectrum conditions but the main distinguish feature of EF is absence of visceral involvement as well as absence of Raynaud’s phenomenon. Skin biopsy involving the fascia and MR image are essential to establish the diagnosis. Several case reports had noticed an association of EF and hematological diseases, strenuous physical activity, autoimmune conditions, infectious diseases, medications, and checkpoint inhibitors. Majority of patients respond well to steroids and considered as the mainstay therapy of EF. Several case reports of steroid resistant cases were responded well to the addition of Methotrexate or Mycophenolate Moefit. In a retrospective study of patients diagnosed with EF, mycophenolate moefit was added due to failure or poor tolerance to prior treatment, steroid. In the 13 patients treated concomitantly with systemic corticosteroids, and mycophenolate moefit, mycophenolate moefit allowed for corticosteroid discontinuation in nine patients after a median of 13 months of treatment.

**Abstract 112** A RARE CASE OF SUPERIOR MESENTERIC ARTERY VASCULITIS PRESENTING WITH ABDOMINAL PAIN


**Introduction/Background** Isolated mesenteric vasculitis, involving the vessels of the gastrointestinal tract without involvement of other organ systems, is considered a rare disorder. Isolated mesenteric vasculitis poses a diagnostic challenge, and delays in therapy can be associated with significant morbidity and mortality by causing intestinal ischemia with necrosis, bleeding, or perforation. Herein, we describe a rare case of isolated superior mesenteric artery (SMA) vasculitis that was managed medically with corticosteroids.

**Objective(s)** A 19-year-old Caucasian male with no known past medical history presented to the emergency department with epigastric abdominal pain of three months duration that became severe in the past week. Pain was burning in nature, non-radiating, intermittent, and worsened with food. He denied other gastrointestinal symptoms including melena, hemeatocrhea, or hematemia. He denied any shortness of breath, chest pain, fevers, night sweats or weight loss. He denied joint pain, swelling, skin rash, or mouth ulcers. He did not abuse alcohol, smoke, or use illicit drugs. Family history was negative for gastrointestinal tumors or rheumatological disorders. Physical exam was remarkable for mild epigastric tenderness. Initial laboratory evaluation showed normal blood counts, comprehensive metabolic panel, and serum lipase.

A computed tomography (CT) scan of the abdomen with intravenous contrast revealed a 4 mm stricture at the origin of the superior mesenteric artery (SMA) followed immediately by a 1.5 cm aneurysm dilation. This dilation was spanning over a segment of 5 cm and was associated with fat stranding around the artery wall (figure 1A). These findings were concerning for medium vessel vasculitis. Patient was admitted to the hospital for further evaluation. Extensive workup was done to evaluate for etiologies of vasculitis and signs of systemic involvement. This workup included the following: Erythrocyte sedimentation rate and C-reactive protein were elevated (25 mm/hr and 1.5 mg/dl, respectively). The antinuclear antibody, antineutrophil cytoplasmic antibodies, myeloperoxidase antibody, anti-Pr-3 antibody, complement levels, and cryoglobulins were within normal range. Screening for Viral hepatitis, human immunodeficiency virus, and drugs (via urine sample) were negative. Urinalysis was negative for microscopic hematuria or proteinuria. Further testing for antiphospholipid antibodies, cardiopin antibody, and beta-2-glycoprotein antibodies was unremarkable. Additionally, CT angiotherapy of the chest was performed to evaluate for vasculitis in medium or large vessels of the thorax. With all of the aforementioned tests being negative, a diagnosis of isolated SMA vasculitis was presented.

Rheumatology and vascular surgery were consulted to assist with management. Surgical intervention was deferred due to the relatively small size of the SMA aneurysm and lack of signs of bowel edema or ischemia on imaging. Patient was started on daily prednisone 60 mg and over the following weeks, reported improvement of his abdominal pain. Follow-up repeat CT angiogram after two months showed resolution of the inflammation surrounding the SMA along with slight improvement of the aneurysm size to 1.3 cm (figure 1B). Prednisone was tapered over a four-month period. Patient continues to follow with vascular surgery and surveillance CT scans continue to show stable size of the SMA aneurysm two years later.

**Methods** Isolated mesenteric vasculitis can be defined as vasculitis involving blood vessels of the GI tract in the absence of a systemic inflammatory illness. The cause of isolated vasculitis is unknown. One theory suggests that local exposure to antigens or infectious agents may lead to local stimulation of the immune response. The most common presenting symptom is abdominal pain; however, a diagnosis based solely on gastrointestinal symptoms is challenging, as these can be nonspecific. The diagnosis of isolated mesenteric vasculitis requires imaging studies or histopathological examination of surgical specimens.

**Abstract 112 Figure 1** CT scans showing the sagittal sections of the SMA artery before (A) and after (B) two months of treatment with steroids.
In the reported cases, conventional catheter-based angiography was used to diagnose most cases; however, more recently, CT or MR angiography is being increasingly utilized for the evaluation of medium- and large-vessel vasculitis with findings of circumferential arterial wall thickening, luminal narrowing, and aneurysms.

Effective treatment of isolated mesenteric vasculitis requires close collaboration between surgical and medical specialties. Surgery and/or endovascular treatment might be required for perforations, fistulas, ischemia or severe stenoses and aneurysms not responding to medical therapy. Glucocorticoids are the corner stone medical treatment for isolated mesenteric vasculitis as opposed to systemic vasculitis which usually requires the addition of other immunosuppressant therapies.

This case highlights the unique condition of isolated SMA vasculitis. High index of suspicion is key to achieve timely diagnosis and management to avoid life-threatening complications related to mesenteric vasculitis.

REFERENCES

HISTOPLASMOSIS IN A PATIENT WITH SARCIOIDOSIS

Omar Hussein, Aseel Alkhader, Mahmoud Mansour, Baraa Saad, Mohammad Al Bataineh.
1University of Missouri Columbia; 2Jordan University of Science and Technology

Introduction/Background Sarcoidosis is an inflammatory multinodular granulomatous. The lung is the most frequently involved organ, but any other organ can be involved. Infection with histoplasmosis in the setting of sarcoidosis has been described in a few case reports and represents a diagnostic challenge.

Objective(s) We present a case of a 36-year-old male with remote history of sarcoidosis who presents to the emergency department for shortness of breath for four weeks with fevers. Patient was on chronic maintenance steroids (10 mg prednisone daily). Initially found to be hypoxemic requiring five liters of oxygen via nasal cannula. Chest X-ray showed bilateral interstitial infiltrates. COVID PCR and influenza A and B antigen swap were negative, laboratory workup demonstrated leukocytosis WBC 17 x10^9/L with neutrophilic predominance 95%. Patient was initially started on piperacillin/tazobactam in addition to methylprednisolone 80 mg three times per day. Bronchoscopy with bronchoalveolar lavage (BAL) showed no organisms on gram and acid fast stains (AFP), cystology exam revealed no evidence of dysplastic or neoplastic process. Fluid cultures and transbronchial biopsies were obtained.

On day five, blood and respiratory cultures obtained on the first day remained negative, respiratory status improved and patient required 2 L O2 through nasal cannula. Patient was discharged on levofloxacin and prednisone 60 mg daily.

Two days after discharge, patient returned to the ED with subjective fevers and worsening hypoxia requiring oxygen through high flow nasal cannula of 60 L/min and FiO2 60% and was admitted to the ICU. Nasal swap PCR for common respiratory viruses was negative. Chest CT angiography was negative for pulmonary embolism but showed diffuse worsening bilateral reticulonodular opacities with minimal bilateral perihilar consolidation. Urine histoplasma capsulatum antigen was elevated at >15.0 ng/mL and a diagnosis of severe pulmonary histoplasmosis was suggested. Patient was started on amphotericin B 450 mg IV daily with high dose of methylprednisolone 80 mg three times daily and treatment was continued for five days. Transbronchial biopsies and PAS fungal stains obtained in the first admission resulted and showed rare intracellular structures highly suggestive of Histoplasma. Patient demonstrated clinical recovery and required 2 L O2 on day five of hospitalization. Patient was discharged with plan to complete a course of 14 days of amphotericin B followed by 12 weeks of oral itraconazole.

Methods Sarcoidosis patients have dysregulated cell mediated immunity due to reduced number of T-cells, steroid treatment can further cause immunosuppression, infections with endemic mycosis such as histoplasmosis should be excluded carefully in these patients. Clinicians should be aware of the similarities in clinical and radiological presentations between sarcoidosis and histoplasmosis, misdiagnosis and inappropriate treatment can lead to significant mortality and morbidity.
were included, representing brief suicide prevention intervention outcomes for 3,960 participants.

In the 12 eligible studies, brief suicide prevention interventions (i.e., single session intervention delivered to patients with identified suicide risk) were delivered in healthcare settings.

We compare the number of implementation strategies reported in the publications to those endorsed by authors using two-sided, paired t-tests, correcting for unequal variances. We also describe of the most frequently used implementation strategies.

**Results** On average, authors endorsed using 26 implementation strategies (SD=3.15) to embed their brief interventions into healthcare settings—a large and statistically significant difference from the average of 4 described in publications (SD=18.41, CI: -9.98, -33.69). The most frequently endorsed implementation strategies by authors were ‘provide clinical supervision’ (n=10 studies), ‘develop academic partnerships’ (n=9 studies), ‘build a coalition’ (n=8 studies), ‘conduct ongoing training’ (n=8 studies), ‘develop educational materials’ (n=8 studies), and ‘develop and implement tools for quality monitoring’ (n=8). However, these strategies were infrequently reported in their publications.

**Abstracts**

**115 EVALUATING THE RELATIONSHIP BETWEEN SOCIAL VULNERABILITY AND MISSED APPOINTMENTS FOR OPHTHALMOLOGY OFFICE VISITS AT AN URBAN TERTIARY CARE REFERRAL CENTER**

Angelica C Scanzera, Sasha Kravets, Sage J Kim, Hugh Musick, Paul Chan, Jerry A Krishnan. University of Illinois at Chicago

10.1136/jim-2022-MW.114

**Introduction/Background** Vision loss disproportionately affects individuals with limited socioeconomic resources. While social determinants of health are known to affect health outcomes, little is known about the association between social vulnerability and missed appointments for ophthalmology office visits.

**Objective(s)** To examine the association between the Centers for Disease Control and Prevention Social Vulnerability Index (CDC SVI) and missed appointments for ophthalmology office visits at an urban tertiary care referral center.

**Methods** Single center retrospective cohort study in an academic health center in Chicago, Illinois. The study was approved by the UIC IRB.

This study was conducted at the Illinois Eye and Ear Infirmary, an urban tertiary care referral center.

All individuals 18 years and older scheduled for an ophthalmology office visit between September 12, 2020, and February 8, 2021 were included.

No intervention was administered. We assessed each individual’s CDC SVI (possible range 0 to 1; higher SVI indicates greater vulnerability) based on the census tract of residence. The CDC SVI ranks each census tract on 15 social factors, including poverty, lack of vehicle access, and crowded housing.

The number of scheduled office visits per patient for ophthalmology can vary substantially. For the purposes of this study, we classified individuals as ‘missed appointments’ (primary outcome) if they missed more than 25% of scheduled appointments.

**Results** A total of 8,322 unique patients (41% black, 24% Hispanic, rest another) had scheduled appointments during the five-month study period (range 1 to 23 scheduled appointments). Just over 1 in 4 (28%) had missed appointments; the mean CDC SVI was higher in patients with missed appointments (0.69) compared to patients without missed appointments (0.58; p=0.01). Percentage of missed appointments varied by race/ethnicity: Blacks (36%) followed by Hispanics (30%), other (27%), Asian (18%), and White (13%), p-value <0.01. The mean CDC SVI was higher among Blacks (0.73) followed by Hispanics (0.69), other (0.54), Asian (0.47), and White (0.36); p-value<0.01.

**116 IMPLEMENTATION EVALUATION OF NORTHWESTERN MEDICINE’S HEALTH-RELATED SOCIAL NEEDS SCREENING AND REFERRAL PROGRAM**

1Sabira Taher, 2Teresa Pollack, 1Cindy Barnard, 1Stephen Persell. 1Northwestern University Feinberg School of Medicine; 2Northwestern Medicine

10.1136/jim-2022-MW.115

**Introduction/Background** Social determinants of health (SDOH) continue to negatively affect patient health. Some U.S. health systems have adopted social needs screening and resource referrals to assist patients with disease management. Nevertheless, a lack of demonstrated evidence-based implementation strategies impedes upscale and dissemination of potentially effective practices within diverse clinical settings.

**Objective(s)** We used implementation science to evaluate implementation of an EHR-integrated social needs screening and referral intervention in outpatient clinics in urban and suburban Cook County, IL. The purpose was to identify the feasibility of implementation within a specific health system as well as implementation factors generalizable for other clinical settings.

**Methods** We used a mixed-methods approach to evaluate implementation processes/outcomes. EHR data were analyzed to measure process outcomes. Clinician interviews, guided by the Consolidated Framework for Implementation Research, were used for data interpretation. Our study was IRB exempt, protected under the Medical Studies Act 735 ILCS 5/8 on October 3, 2022. A mix of suburban and urban outpatient clinics (N=12) from the Northwestern Medicine health system, participated in the intervention over the course of seven months. Three diverse primary care clinics (two suburban, one urban) volunteered to participate in the qualitative interviews.

The total number of patients that participated in the intervention was N=12,195.

The total number of primary care clinicians interviewed was N=9. Individuals that were actively involved in implementation were recruited using an iterative process starting with practice managers that subsequently recruited physicians, residents, and medical assistants for interviews.

Patients responded to an electronic SDOH screening questionnaire in a self-administered, pre-visit questionnaire received via email or in the waiting room before their appointment via iPad/tablet. Responses were populated into the EHR. Clinicians could review and generate a community resource list curated by the platform NowPow if patients requested assistance.
Assessment occurred in month seven. Primary outcomes were: 1) Number of patients screened; 2) Number of patients screened positive for one or more SDOH; 3) Social needs identified most; 3) Number of patients that requested assistance. Secondary outcomes were implementation factors identified from one-on-one semi-structured interviews with primary care clinicians.

**Results**
The number of patients screened was $N=12,195$; 22.3% screened positive ($N=2,778$). Mental health was identified most (26%), followed by a need for a regular doctor (n=26%) and medication affordability (11%). Patients that requested resources was 21%. Implementation barriers were: 1) Physician lack of time to refer patients; 1) Resource list outdated; 2) Limited awareness about existing community organizations and services; 3) positively screened patients lost to follow-up. Implementation facilitators were: 1) The EHR integrated intervention ensured every patient may be screened; 2) Medical assistants (MA) screened patients to ensure completion of questionnaire; 3) Existing medical teams assisted physicians with referrals.