DEVELOPMENT OF SUSTAINABLE EX-VIVO NORMOTHERMIC LIVER PERFUSION PLATFORM FOR RESEARCH PURPOSES

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Introduction/Background Ex vivo perfusion (EVP) has continued to emerge as a viable alternative to cold storage (CS) for transplant organs, particularly livers, given EVP’s demonstrated ability to improve marginal organ quality. This usage of marginal donor organs would significantly expand the donor pool and help decrease the burden of transplant organ shortage. Ex vivo perfusion of pre-transplant organs creates a window of time where an organ at near physiologic conditions may be pharmacologically or immunologically manipulated with minimal effect on the graft recipient due to washout of the agents prior to transplant. This ability has been used to date in resuscitating organs, improving steatosis, and has potential in reducing graft rejection rates and necessity for life-long recipient immunosuppression. However, a significant hurdle in development of novel protocols using EVP has been the single-use cost per organ using commercially available platforms (£4000-£7000 ($5700-$9800) per use for OrganOx metra device). In this project, we develop a low-cost reusable liver perfusion platform indicated for research purposes to develop protocols for organ resuscitation and conditioning.

Objective(s) The objective of this project is to establish a research platform for ex-vivo perfusion of livers that maintains near-physiological parameters that allows for pharmacological or immunological manipulation while maximizing reusability and efficiency.

Methods A normothermic ex-vivo perfusion circuit was assembled with single-use items of RotaFlow pump head ($500), cardiotomy reservoir with oxygenator ($450), and discarded unused ECMO tubing kit ($500). Reusable items including a Centrimag pump and heater/cooler were borrowed from the Department of Perioperative Services at the University of Chicago. Initial perfusions were completed on donor after cardiac death (DCD) pig livers and subsequent perfusions were performed on human livers declined by all regional transplant centers and obtained through Gift of Hope, IL. Perfusions were completed for 6 hours using DMEM (ThermoFisher Scientific, Waltham, MA) and expired pRBCs from the University of Chicago Blood Bank. Perfusion parameters were measured each hour and included inflow/outflow flow rates and pressures, bile production, lactate clearance, perfusate glucose, pH, and liver transaminases.

Results The circuit achieved near-physiological parameters in the third iteration with an overall flow rate of 1.5 L/min with 1.1 L/min through the portal vein (PV) and 0.4 L/min through the hepatic artery (HA), at average pressures of 0 mmHg and 43 mmHg, respectively. Clearance of lactate was seen with a concentration of 57 mmol/L at 1 hour and subsequent maintenance of 0.8 mmol/L from hour 2 to 6. A total of 7.5 mL of bile was produced with maximum production of 3 mL/hr at hour 2.

Conclusion This projected demonstrated the ability to establish an ex-vivo perfusion platform for livers in a research setting while minimizing cost and resources per organ. This platform is reproducible and allows for development of protocols using extant and novel mechanisms for manipulation of organs to improve transplant outcomes when adapted to commercial devices approved for patient use. Finally, a sustainable platform as developed here can be adapted more widely for the isolated study of any organ system at physiologic conditions.
Bone marrow transplant

A Rare Case of Pericardial Effusion Due to Primary Mediastinal Large B-Cell Lymphoma

Sudeepthi Bandikatla, Apara Dadlani, Mohamed Hegazi. University of Louisville

Introduction/Background Pericardial effusion, unlike pleural effusion, is a very rare presentation of Non-Hodgkin’s lymphomas (NHL). When present, pericardial effusion in NHL is usually a late manifestation. Only very few cases are reported in the literature with cardiac effusion concurrently present during the initial diagnosis of NHL. We present a rare case of cardiac effusion present during the initial diagnosis of primary mediastinal large B cell lymphoma (PMBL). PMBL is a rare variant of diffuse large B cell lymphomas and represents 2.4% of all NHLs.

Case Presentation A 30-year-old female was admitted to medicine initially with pain abdomen and was found to have acute cholecystitis. She was in her usual state of health 3 months ago, at which time she developed a persistent cough. She underwent extensive imaging for her acute and persistent chronic symptoms during the hospitalization which revealed an incidental large anterior mediastinal mass as well as small pericardial effusion on CT chest as seen in Image A and B respectively. The patient had concurrent cholecystitis and underwent percutaneous pericystostomy tube placement. Her pericardial effusion did not cause any symptoms and she remained hemodynamically stable. She underwent a biopsy of her anterior mediastinal mass and was discharged. The pathology confirmed PMBL. Shortly after discharge, within a week, the patient had increasing dyspnea, fatigue and began noticing increasing swelling of bilateral extremities for which she presented to the emergency department. She was tachycardic with a heart rate of 120 beats/minute, otherwise hemodynamically stable. 2D Echo revealed a large dramatically increased pericardial effusion from one week ago with tamponade physiology for which she had a percutaneous pericardial drain placement which resolved the tamponade. Pericardial fluid microscopy showed predominantly neutrophils, small lymphoid cells, and rare larger cells. Flow cytometry of the fluid showed no definitive immunophenotypic evidence of involvement by T or B non-Hodgkin lymphoma. She was then transferred to the bone marrow transplant team for emergent initiation of chemotherapy. She was started on DA-R-EPOCH therapy. Repeat 2D-Echo at 1st month, 2nd month and 6th month showed no evidence of recurrent pericardiac effusion.

Discussion Pericardial effusion due to malignancy is more often present with solid malignancies (lung, breast carcinoma)
but may occasionally occur in hematological malignancies. It can be caused by seeding of pericardium by tumor or hematoegenous spread. It can be also caused by a mass effect from mediastinal lymphadenopathy blocking drainage of lymphatic ducts which we think was the mechanism of serous effusion in our patient. Pericardial effusion progressed significantly within one week in our patient. This emphasizes that physicians should be vigilant when a patient presents with asymmetrical pericardial effusion due to malignancy and closely monitor for signs of cardiac tamponade. The management of pericardial effusion has two components; acute management to alleviate any hemodynamic compromise in patients with cardiac tamponade (fluid is typically removed by percutaneous pericardiocentesis) and chronic management to prevent fluid from re-accumulating (includes prolonged catheter drainage or creation of a permanent pericardial window which allows fluid to drain into the pleural or peritoneal cavity). Patients who remain hemodynamically stable without evidence of cardiac tamponade are usually managed with careful monitoring, serial 2D-Echo, and therapy aimed at the underlying cause of the pericardial effusion. Treatment is guided by the patient’s overall medical status, goals of care, the prognosis of the underlying malignancy, and availability of local expertise. In Conclusion, prompt diagnosis and treatment of underlying malignancy is therefore imperative to prevent the progression of pericardial effusion to cardiac tamponade which could otherwise be life-threatening.

A RARE CASE OF PANCYTOPENIA DUE TO COPPER DEFICIENCY IN PATIENT WITH GRAFT VS HOST DISEASE

Apaar Dadhani, Sudeepthi Bandikatla, Kristine Krueger, University of Louisville

Introduction/Background Acquired copper deficiency in adults is rare. It leads to hematological and neurological alterations such as pancytopenia, peripheral neuropathy and myelopathy. Copper supplementation allows prompt normalization of the hematological disturbances and the copper balance, but neurological improvement takes longer and is commonly irreversible. We present a rare case of copper deficiency associated pancytopenia.

Case Presentation 67-year-old female with acute lymphoblastic leukemia status post stem cell transplant complicated by graft versus host disease of the digestive tract (GVHD-DT) presented with generalized weakness and poor oral intake. Her laboratory work-up was significant for pancytopenia (hemoglobin 6.1 g/dL; mean corpuscular volume 93 fl; leukocytes 2.4 × 10^3/μL; and platelets 24× 10^3/μL). Workup of pancytopenia revealed reticulocyte production index of 0.08 suggestive of hypo proliferative marrow, and low haptoglobin at <15 mg/dL. Normal tests included: total bilirubin 0.9 mg/dL, vitamin B12 level 1000 pg/mL, folate 18 mg/mL, lactate dehydrogenase 193 U/L, and a normal iron panel. Serum electrolytes and liver function tests were unremarkable. Periperal smear showed moderate anemia, mild leukenopia and thrombocytopenia and few lobed neutrophils, however no blasts or schistocytes were seen. HIV and hepatitis panel were negative. She was not on any medications typically known to cause decreased platelets, including heparin. The work-up for pancytopenia was broadened and copper levels were ordered, which showed markedly low plasma copper level of 14 μg/dL (normal 70–175 μg/dL), and ceruloplasmin of 7.4 mg/dL (normal 19–39 mg/dL). Zinc level was normal at 67 μg/dL (normal range 60–130 μg/dL).

The patient was diagnosed with pancytopenia secondary to hypocupremia. She was started on copper chloride 3mg intravenous daily, given her poor oral intake. After 3 doses her copper levels improved to 31 μg/dL, and after an additional 3 doses the levels normalized to 77 μg/dL. Her complete blood counts improved to hemoglobin 8.3 g/dL; leukocytes 6.1 × 10^3/μL; and platelets 114 × 10^3/μL after copper supplementation.

Discussion Copper deficiency is an extremely rare cause of pancytopenia. Copper deficiency has been associated with gastric bypass surgery, intestinal resection, excessive zinc intake or prolonged total parenteral nutrition. Malnutrition has been rarely reported as a cause. In a study by Jacobsohn et. al., >40% of GVHD patients had concurrent malnutrition. In our patient we suspect malnutrition due to graft versus host disease of the digestive tract (GVHD-DT) as the main cause of our patient’s copper deficiency. Evidence shows that GVHD-DT is often associated with severe malnutrition, with both macronutrient and micronutrient malabsorption secondary to mucosal inflammation and loss of microvilli, leading to profound gastrointestinal symptoms such as vomiting and diarrhea. Copper deficiency may interfere with iron transport and utilization and, therefore, with heme synthesis, causing anemia. The mechanism of leukopenia and thrombocytopenia remains unclear. In Conclusion, it is important to keep copper deficiency as a possible etiology of pancytopenia, particularly in patients with GVHD-DT, as it is easily treatable and can prevent further complications. To our knowledge, ours is the first case highlighting the association between copper deficiency and graft vs host disease to our knowledge, further studies are required to better understand this association.

Cardiology/Cardiovascular disease

DEVELOPMENT AND VALIDATION OF A DIAGNOSTIC MODEL AND SCORING SYSTEM FOR TRANSTHYRETIN CARDIAC AMYLOIDOSIS

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Introduction/Background Transthyretin cardiac amyloidosis (ATTR-CA) is a fatal disease, caused by the misfolded protein aggregation in the heart, leading to restrictive cardiomyopathy. Once considered to be a rare disease, the emergence of Tc-99m pyrophosphate (PYP) scintigraphy has unleashed the high community prevalence of ATTR-CA and has circumvented the need for endomyocardial biopsy. However, ATTR-CA continues to be misdiagnosed and under-diagnosed. There are potential ‘red flag’ features that could raise suspicion for ATTR-CA, however these features individually are non-specific.

Objective(s) We aimed to use a combination of these ‘red flag’ features to develop a diagnostic model and clinical score to timely diagnose ATTR-CA. We hypothesized that a combination of these ‘red flag’ features could be used to predict the Results of a Tc-99m PYP study.
Methods

Demographic, clinical, ECG and echo data were recorded for patients who underwent Tc-99m PYP imaging between 06/2015 to 06/2020. Positive Tc-99m PYP study was defined as Perugini grade ≥ 2 on planar image and a diffuse myocardial tracer uptake on the SPECT. Patients were randomly divided into derivation (n=500) and validation (n=300) cohorts. Independent predictors of a positive PYP study were identified from the derivation cohort by multivariable regression analysis. Presence/absence of these variables was assigned a score of 1/ -1 respectively, which was then weighted by the regression coefficient (RC). Weighted values were summed to derive an Amyloidosis Prediction Score (APS). Receiver operating characteristics (ROC) curve was used to describe the predictive value of the APS for a positive Tc-99m PYP study in the validation cohort.

Results

Among the 800 patients studied (age=75 ± 11 years, 71% men, 81% Caucasian) a positive Tc-99m PYP was present in 206 (25.8%). Bilateral carpal tunnel syndrome (RC=0.48), lumbar spinal stenosis (RC=0.15), atrial fibrillation (RC=0.08), low QRS voltage (RC=0.14), pseudo-infarct pattern (RC=0.13) and left ventricular hypertrophy ≥ 1.4 cm (RC=0.14) were independent predictors of a positive Tc-99m PYP study in the derivation cohort. APS ranged from -1.2 to +1.2 and predicted a positive PYP in the validation cohort with an area under the curve of 0.96 (figure 1). An APS value of ≥-0.31 conferred a sensitivity and specificity of 95% and 91% for predicting a positive Tc-99m PYP study, with a positive likelihood ratio of >10. A score of <-0.68 had a negative predictive value of 100%.

Conclusion

A combination of clinical, ECG and echo features can be used to derive an APS which has high predictive accuracy for a positive Tc-99m PYP study. The utility of this prediction score for improving the yield of Tc-99m PYP scintigraphy needs to be evaluated prospectively.
However, the incidence of thromboembolic events was higher in AF-ATTR compared to AF-controls (37.3% vs. 19.5%, p=0.02). AF-ATTR was associated with increased risk of ischemic stroke, TIA or systemic embolism (OR 2.46, 95% CI 1.16–5.21, p=0.02) compared to AF-controls. On multivariable logistic regression analysis adjusting for CHA2DS2-VASc, oral anticoagulation use and LAVI, ATTR-CA was an independent predictor of thromboembolism (OR 6.5, 95% CI 2.33–18.08, p<0.001). The incidence of hemorrhagic stroke (p=0.3), intracranial hemorrhage (p=0.9), major bleeding (p=0.7), and all-cause death (p=0.4) did not differ between the 2 groups.

Conclusion ATTR-CA cardiomyopathy is a strong predictor of thromboembolism in patients with AF, independent of CHA2DS2-VASc score or left atrial size.

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**INTESTINAL DYSBIOSIS IN CONGENITAL HEART DISEASE IS EXACERBATED AFTER CARDIOPULMONARY BYPASS**

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**Introduction/Background** The gut flora has a complex relationship with the human body. Systemic inflammation can change the microbiome resulting in dysbiosis and select for pro-inflammatory bacteria. These microbial changes can disrupt the intestinal barrier and perpetuate the inflammatory process. Patients receiving cardiopulmonary bypass (CPB) have cytokine secretion and clinical findings similar to other forms of systemic inflammation. We hypothesize patients with congenital heart disease (CHD) will have dysbiosis exacerbated by CPB and evidence of intestinal epithelial barrier dysfunction (EBD).

**Objective(s)** To determine the microbial composition and EBD of patients with CHD undergoing cardiac surgery with CPB.

**Methods** We included a prospective cohort of patients; 1 month to 18 years of age assigned in 2 arms: surgery with CPB and surgery without CPB (control). A pre-surgical stool sample (S) was obtained in the hospital prior to surgery. A second stool sample was obtained 3–5 days post-surgery (PS).

Stool DNA extraction performed via Qiagen DNA extraction kit. A library prep for all samples was created and bacterial DNA was then sequenced and analyzed using Past Software. Pro-inflammatory metabolites evaluated in the stool using mass spectroscopy. Serum was collected pre- and post-surgery and evaluated for markers of barrier dysfunction.

**Abstract 20 Figure 2** Study scheme and initial results

**Abstract 20 Table 1** Patients’ characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>AF-ATTR</th>
<th>AF-Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>61 (90)</td>
<td>57 (74)</td>
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<tr>
<td>Serum creatinine (mg/dl), mean ± SD</td>
<td>1.4 ± 0.63</td>
<td>1.9 ± 1.15</td>
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<td>Coronary disease, n (%)</td>
<td>32 (47)</td>
<td>57 (74)</td>
<td>0.001</td>
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<td>BNP (pg/ml), mean ± SD</td>
<td>4.7 ± 1.4</td>
<td>5.4 ± 1.2</td>
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<tr>
<td>CHADS-VASc, mean ± SD</td>
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<tr>
<td>ECHO Parameters</td>
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<tr>
<td>LVEF (%), mean ± SD</td>
<td>50.8 ± 13.1</td>
<td>53.6 ± 11.4</td>
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<tr>
<td>LAVI (ml/m²), mean ± SD</td>
<td>46.4 ± 16.8</td>
<td>61.3 ± 34.7</td>
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<td>IVSD (cm), mean ± SD</td>
<td>1.67 ± 0.27</td>
<td>1.50 ± 0.15</td>
<td>&lt;0.001</td>
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<tr>
<td>Global longitudinal strain (%), mean ± SD</td>
<td>-10.1 ± 3.35</td>
<td>-18.9 ± 3.70</td>
<td>&lt;0.001</td>
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<tr>
<td>AF Management</td>
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<td></td>
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<tr>
<td>Anticoagulation</td>
<td>65 (95.6)</td>
<td>72 (93.5)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

**Outcomes**

| Thromboembolic events, n (%) | 25 (37) | 15 (20) | 0.02 |
| Major Extracranial Bleeding, n (%) | 5 (7.3) | 7 (9.1) | 0.7 |
| All-cause death, n (%)        | 15 (22) | 12 (16.6) | 0.4 |

**Abstract 45 Figure 1** Bacterial Richness and Diversity
Panel A shows the number of operational taxonomic units (OUT) or bacterial richness present in each sample. Panel B shows the alpha diversity, a representation of bacterial richness and evenness of bacterial species within each sample. A statistically significant reduction in bacterial richness (p<0.001) and alpha diversity (p<0.001) exist in the CPB group compared to the control group.
Results 29 patients enrolled in the study, CPB (n=17) and Control (n=12). In S samples, the CPB group showed reduced bacterial richness and diversity vs controls (p< 0.001). Relative abundance of pro-inflammatory bacteria, Proteobacteria, was elevated in CPB vs controls (p< 0.001) and increased 17% in PS samples within CPB group (p=0.008). Significant

Abstract 45 Figure 2  Taxonomy of Bacteria
Panel 2A shows the bacteria at the phylum level in each sample pre- and post-surgery for the control group and the CPB group. There is a significant difference in the pro-inflammatory bacteria (red bars) between the CPB group and the control group in both pre- and post-surgery samples, p<0.001. Panel B shows the genus level bacteria in each sample. Red bars indicate pro-inflammatory bacteria. Blue, green, yellow, and tan bars indicate healthy gut-promoting bacteria.

Abstract 45 Figure 3  Beta diversity in CPB and controls
A shows the Bray-Curtis beta-diversity similarities between CPB and Controls. Figure 3B shows the Jaccard beta-diversity similarities between CPB and Controls. Red indicates CPB and Black indicates Controls. Closed circles represent pre-surgery samples for each group and open circles represent post-surgery samples for each group.

Abstract 45 Figure 4  Changes in Markers of Intestinal EBD
A) Significant increase of FABP2 in CPB vs Controls (p=0.001). B) Significant increase of claudin-3 in CPB vs Controls (p<0.001). C) Significant reduction of citrulline in CPB vs Controls (p=0.001). Independent t-test for means at each time point. FABP2, Intestinal Fatty Acid Binding Protein 2; EBD, Epithelial Barrier Dysfunction. * p<0.05; ** p<0.01; *** p<0.001

Abstract 45 Figure 5  Principle Component Analysis for Stool Eicosanoids in CPB group
Principle component analysis was performed with pre-CPB (red, n=6) and post-CPB (green, n=12). Two-dimensional PC score plot, are separated from other groups, indicating a distinct metabolite composition between the two groups. Component 1 indicates the degree of variation between the groups based upon their total metabolite content. Component 2 indicates the differences within groups. Measuring distances between samples with partial least squares discriminate analysis revealed p=0.09.
LONG-TERM PROGNOSTIC VALUE OF RIGHT VENTRICULAR DYSFUNCTION ON CARDIOVASCULAR MAGNETIC RESONANCE IMAGING IN ANTHRACYCLINE-TREATED CANCER SURVIVORS

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Introduction/Background Cancer survivors treated with anthracycline-based chemotherapy are at risk for long-term adverse cardiovascular outcomes. Clinical and imaging risk factors for these outcomes are unknown. Right ventricular (RV) systolic dysfunction has been described in small series to have prognostic relevance in these patients.

Objective(s) We aimed to determine the prevalence on cardiovascular magnetic resonance imaging (CMR) of RV systolic dysfunction and its influence on long-term adverse outcomes in a large cohort of cancer survivors treated with anthracycline-based chemotherapy.

Methods Consecutive cancer survivors treated with anthracycline-based chemotherapy who underwent clinical CMR for known or suspected anthracycline-related cardiomyopathy were studied. The primary endpoint was a composite of death or major adverse cardiac events (MACE): aborted cardiac arrest, heart transplantation, left ventricular assist device implantation, or heart failure hospitalization.

Results Among 249 survivors who underwent CMR at a median of 2.9 years after cancer treatment, RV systolic dysfunction - defined as an RV ejection fraction (RVEF) < 51% - was present in 54 (21.7%). Of these, 50 (92.6%) were in survivors with an abnormal left ventricular ejection fraction (LVEF), defined as < 57%. At a median follow-up time after the CMR of 2.7 years, 105 survivors experienced the composite endpoint of all-cause death or MACE. There were 89 deaths, 41 heart failure hospitalizations, 2 heart transplantations, 2 left ventricular assist device implantations, and 1 resuscitated asystolic cardiac arrest. On Kaplan-Meier analyses, there was no difference in the cumulative incidence of death or MACE when survivors were stratified by the median value of RVEF (log rank p=0.10). On Cox proportional hazards regression univariable analyses, RVEF was associated with death or MACE (hazard ratio (HR) 1.37 per 1 standard deviation (SD); 10.6% decrease; 95% CI 1.13–1.66; p=0.001). However, on multivariable analyses, RVEF was not associated with death or MACE (HR 1.09 per 1 SD decrease; 95% CI 0.86–1.39; p=0.46) after adjustment for age, type of cancer, time between anthracycline treatment and CMR, cumulative anthracycline dose, chest radiation therapy, trastuzumab, heart failure diagnosed before the CMR, and LVEF.

Conclusion In anthracycline-treated cancer survivors undergoing CMR for suspected cardiotoxicity, RV systolic dysfunction was present in 22% and accompanied LV systolic dysfunction in 93% of cases. However, it was not independently associated with the long-term incidence of death or MACE.

Abstract 47 Table 1

<table>
<thead>
<tr>
<th></th>
<th>All, n=90 (%)</th>
<th>AS-Present, n=19 (%)</th>
<th>AS-Absent, n=71 (%)</th>
<th>P-value</th>
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<td>Age, years</td>
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<td>Gender (female)</td>
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<td>G Erd</td>
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<td>7 (36.8)</td>
<td>29 (40.8)</td>
<td>0.80</td>
</tr>
</tbody>
</table>

*Statistically significant at p<0.05, the unpaired t-test with Welch’s correction was used for continuous variables and the Fischer-exact test was used for categorical variables. Variance= standard error.
transcatheter aortic valve replacement (TAVR) in patients with WHO group I PAH on advanced pulmonary vasodilator therapy.

Objective(s) To report the prevalence of AS and TAVR associated hemodynamic, imaging and long-term outcomes among a cohort of patients with SSc-PAH.

Methods Retrospective cohort study among 90 patients with SSc-PAH evaluated at a tertiary PAH center. The SSc-PAH cohort was stratified by the presence or absence of aortic stenosis to identify differences in baseline characteristics, hemodynamics, and long-term outcomes.

Abstract 47 Table 3

<table>
<thead>
<tr>
<th></th>
<th>All (n=90)</th>
<th>AS-Present (n=19)</th>
<th>AS-Absent (n=71)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASP (mmHg)</td>
<td>67.1 ± 2.1</td>
<td>72 ± 3.4</td>
<td>65.7 ± 2.5</td>
<td>0.14*</td>
</tr>
<tr>
<td>PAPD (mmHg)</td>
<td>26.3 ± 0.9</td>
<td>29.1 ± 1.3</td>
<td>25.6 ± 1.1</td>
<td>0.048**</td>
</tr>
<tr>
<td>MPAP (mmHg)</td>
<td>42.1 ± 1.2</td>
<td>45.3 ± 1.8</td>
<td>41.3 ± 1.4</td>
<td>0.09</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>9 (7–11.3)</td>
<td>10 (7–11)</td>
<td>9 (7–13)</td>
<td>0.49</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>12 (9–15)</td>
<td>13 (9–16)</td>
<td>11 (8–14)</td>
<td>0.19</td>
</tr>
<tr>
<td>Cardiac Output (L/min)</td>
<td>4.1 (3.3–5.4)</td>
<td>4.4 (3.7–5.5)</td>
<td>4 (3.2–5.4)</td>
<td>0.18</td>
</tr>
<tr>
<td>Cardiac Index (L/min/m²)</td>
<td>2.3 (1.8–2.9)</td>
<td>2.4 (2.2–3.9)</td>
<td>2.3 (1.8–2.9)</td>
<td>0.51</td>
</tr>
<tr>
<td>PVR (dynes/s/cm⁵)</td>
<td>512 (356–841)</td>
<td>528 (368–789)</td>
<td>504 (344–856)</td>
<td>0.97</td>
</tr>
</tbody>
</table>

*Statistically significant at p<0.05, a unpaired t-test with Welch’s correction, b Mann-Whitney U test, Variance= standard error or IQR.

AS, aortic stenosis; RVSP, right ventricular systolic pressure.

Right heart catheterization hemodynamic data at pulmonary arterial hypertension diagnosis.
Results The prevalence of AS was 21.1% (19/90 patients, 95% CI: 13.2–30.1%) with mean age of AS diagnosis of 66.3 ± 2.2 years. SSc-PAH patients with AS presented with a higher pulmonary artery diastolic pressure, 29.1 ± 1.3 mmHg vs 25.6 ± 1.1 mmHg, p-value=0.048, at time of PAH diagnosis. Among AS patients, 31.6% (6/19) progressed to severe AS, five of which underwent TAVR (median age: 70 years) while on advanced PAH therapy. The five-year survival rate from AS diagnosis date was 37.2%.

Conclusion Aortic valve stenosis was highly prevalent in our cohort of patients with scleroderma associated pulmonary arterial hypertension, with an age onset of severe stenosis that is younger than patients with non-bicuspid aortic valve stenosis. We have reported the largest series of patients with SSc-PAH on advanced pulmonary vasodilator therapy who underwent TAVR with acceptable peri-procedural and early outcomes.

Baseline characteristics, medical comorbidities, and systemic sclerosis manifestations at pulmonary arterial hypertension diagnosis

Introduction/Background New left bundle branch block (LBBB) and advanced degree atrioventricular block are complications of transcatheter aortic valve replacement (TAVR), and the latter often necessitates permanent pacemaker implantation.

Case Presentation An 80-year-old lady with severe aortic stenosis presented for a TAVR. Prior to the procedure, her ECG (figure 1.A) showed sinus rhythm with a right bundle branch block (RBBB) and left anterior fascicular block (LAFB). The patient underwent implantation of a 26 mm Edwards SAPIEN 3 valve (figure 1.B) with a deployment depth of 80% aortic and 20% ventricular. Transient complete heart block for less than three minutes was noted after valve deployment.

ECG after the TAVR procedure (figure 1.C) demonstrated sinus rhythm with RBBB and a left posterior fascicular block (LPFB). The patient was monitored in the intensive care unit overnight. No recurrent complete heart block was noted, and the patient was discharged home the following day. An ECG done during follow-up with her outpatient cardiologist two days after discharge demonstrated LAFB akin to that from her pre-TAVR ECG (figure 1.D). A 30-day event monitor was ordered for additional surveillance.

Discussion New LBBB, complete heart block, nonspecific intraventricular conduction delay, and LPFB are common following TAVR. Regardless of the nature of the conduction abnormality, close monitoring for these complications and symptomatic bradycardia following TAVR is essential.

Abstract 52 Figure 1 A ECG before TAVR revealing sinus rhythm, right bundle branch block, and left anterior fascicular block. B. Cineangiography still of the 26 mm Edwards SAPIEN 3 valve after deployment. C. ECG after TAVR revealing sinus rhythm right bundle branch block, and a new left posterior fascicular block. D. ECG performed three days after TAVR showing sinus rhythm, right bundle branch block, and a left anterior fascicular block akin to the pre-TAVR ECG.
manipulation. Therefore, a cardiac computer tomographic (CT) angiogram was recommended to rule out any concomitant coronary artery disease. With an unremarkable cardiac CTA, the patient underwent aortic valve replacement with a #21 mm Saint Jude mechanical prosthesis. The patient was discharged with appropriate antibiotics and started on Warfarin with INR goal of 2.5–3.5 as per guidelines.

Discussion

Infective endocarditis (IE) is a microbial infection of the endocardial surface of the heart, mainly involving the heart valves. Early detection and accurate diagnosis are important for the care of patients with IE who will often require surgery along with prolonged antibiotic therapy.

Prior to open heart surgery, it is necessary to conduct a coronary angiogram to detect presence of coronary artery disease that can be intervened on simultaneously with valve replacement. Patients who have aortic valve vegetation, close attention must be paid to the size and mobility of the vegetation due to high risk of embolism in the setting of catheter manipulation during diagnostic angiography. Our patient did not undergo an angiogram due to high risk of vegetation manipulation secondary to its large size and extremely mobile nature. Although coronary angiography is mainstay of evaluation, coronary CTA is a reasonable substitute for patients with low- to intermediate-risk for coronary artery disease. Several reports including one done by Erba et. al discuss about the use of cardiac CT as a complement to the diagnosis of IE and perivalvular complications such as abscess as well as concurrent CAD.1

REFERENCES


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Objective(s) This study evaluated the association of statin intensity with the development of ASCVD in a multi-ethnic population of adults at higher risk of cardiovascular disease.

Methods Total CVD and coronary heart disease (CHD) events were prospectively evaluated in MESA participants who were free from CVD at baseline, considered at higher risk for CVD, and on statin therapy at any point during the study (2000–2017). Mutually exclusive higher-risk groups were Diabetes Mellitus (DM), High-risk (Pooled Cohort Equation (PCE) estimated 10-year ASCVD risk ≥ 20%) without DM, and intermediate-risk (PCE estimated 10-year ASCVD risk 7.5–20%) without DM. The association of statin intensity (high versus moderate/low) with total CVD and CHD events was analyzed using Cox regression, accounting for time-varying covariates of cardiovascular risk factors, use of non-statin lipid lowering medications, and MESA field center. Cardiovascular risk factors included age, gender, race, physical activity, cigarette use, body mass index, blood pressure, fasting glucose status, lipid profile, and renal function.

Results We included 2,288 adults (53% female, 55% non-white), who were a mean (standard deviation) age of 68.5 years (9.1), in the analysis. At baseline, 31% had DM, 30% were High-risk, and 39% were Intermediate-risk. During follow-up, 235 participants used high-intensity statin therapy at any time point. High-intensity statin therapy was not associated significantly with lower risk of total CVD or CHD events in any higher-risk group as compared to moderate-/low-intensity statin therapy (figure 1).

Conclusion To our knowledge, this is the first study to evaluate the association of statin intensity with the development of ASCVD. Our Results indicate that in adults at higher risk of ASCVD, high-intensity statin use was not associated with lower risk of total CVD or CHD events, as compared to moderate-/low-intensity statin use. This study was limited by small numbers of events in all higher-risk groups. However, the direction of hazard ratios consistently suggests CVD benefit with high-intensity statin therapy. Further research, with a larger cohort, will help establish the association of intensity of statin therapy with development of ASCVD.
SEX DIFFERENCES IN LONG-TERM OUTCOMES OF CANCER SURVIVORS WITH SUSPECTED ANTHRACYCLINE-RELATED CARDIOTOXICITY ASSESSED BY CARDIOVASCULAR MAGNETIC RESONANCE IMAGING

1Chetan Shennoy, 2Andrew Hughes, 3Pal Satyajit Singh Athwal, 1Sanya Chikihara, 4Mohamed F Ismail, 1University of Minnesota; 2Vanderbilt University Medical Center

Introduction/Background Cancer survivors treated with anthracycline-based chemotherapy are at risk for long-term adverse cardiovascular outcomes. Some studies have found sex differences in the long-term outcomes while others have not. Most of these studies have not rigorously accounted for confounders.

Objective(s) We aimed to investigate sex differences in the long-term outcomes of a large cohort of cancer survivors with suspected anthracycline-related cardiotoxicity assessed by cardiovascular magnetic resonance imaging (CMR).

Methods Consecutive cancer survivors treated with anthracycline-based chemotherapy who underwent clinical CMR for known or suspected anthracycline-related cardiomyopathy were studied. The primary endpoint was a composite of all-cause death or major adverse cardiac events (MACE): aborted cardiac arrest, heart transplantation, left ventricular assist device implantation, or heart failure hospitalization. The secondary endpoint was all-cause death.

Results Among 249 survivors who underwent CMR at a median of 2.9 years after cancer treatment, 149 (59.8%) were female survivors and 100 (40.2%) were male survivors. The most common cancers among female survivors were breast cancer (55.7%), lymphoma (24.2%), and leukemia (14.8%). The most common cancers among male survivors were lymphoma (56.0%), leukemia (32.0%) and sarcoma (10.0%). At a median follow-up time after the CMR of 2.7 years, 105 survivors experienced the primary endpoint of all-cause death or MACE. There were 89 deaths, 41 heart failure hospitalizations, 2 heart transplantations, 2 left ventricular assist device implantations, and 1 resuscitated asystolic cardiac arrest. On Kaplan-Meier analyses, there was no difference in the cumulative incidence of all-cause death or MACE between female survivors and male survivors (p=0.11). Female survivors had a lower incidence of the secondary endpoint of all-cause death compared with male survivors (p=0.036). On Cox regression multivariable analyses, sex was not independently associated with the long-term incidence of the primary endpoint of all-cause death or MACE [hazard ratio (HR) for female sex 1.01; 95% confidence interval (CI) 0.64–1.61; p=0.95], or the secondary endpoint of all-cause death [HR for female sex 1.08; 95% CI 0.66–1.75; p=0.77].

Conclusion In a large cohort of anthracycline-treated cancer survivors undergoing CMR for suspected cardiotoxicity, after robust adjustment for confounders, sex was not independently associated with long-term outcomes.

INTRODUCTION TO PERSPECTIVE

ANTHRACYCLINE USE IN CANCER THERAPY

ANTHRACYCLINES ARE A CLASS OF ANTAGONISTS OF TOPOISOMERASE II. THEY ARE USED IN THE TREATMENT OF VARIOUS CANCER TYPES, INCLUDING BREAST CANCER, LYMPHOMA, AND LEUKEMIA. ANTHRACYCLINES ARE ASSOCIATED WITH A RANGE OF TOXIC EFFECTS, INCLUDING CARDIOTOXICITY.

CARDIOTOXICITY ASSESSED BY CMR

CARDIOVASCULAR MAGNETIC RESONANCE IMAGING (CMR) IS A POWERFUL TOOL FOR ASSESSING CARDIOTOXICITY IN CANCER SURVIVORS.

SEX DIFFERENCES

RECENT STUDIES HAVE SUGGESTED THAT SEX MIGHT PLAY A ROLE IN THE OUTCOMES OF CANCER SURVIVORS. MALE SURVIVORS OF CANCER COULD HAVE A HIGHER RISK OF CARDIOTOXICITY COMPARED TO FEMALE SURVIVORS.

METHODOLOGY

METHODS

RESULTS

CONCLUSION

LEFT VENTRICULAR DYSFUNCTION AT DIAGNOSIS IS AN INDEPENDENT PREDICTOR OF MORTALITY IN TRANSTHYRETIN CARDIAC AMYLOIDOSIS

1Syed Bukhari, 2Zubair Shahid, 3Syed Zamrak Khan, 1Dan Shipinsky, 1Ric Nieves, 1Yvonne Eisele, 1Prem Soman, 1University of Pittsburgh Medical Center; 2Cleveland Clinic

Abstract 80 Figure 1 Reduced EF is associated with worse prognosis in ATTR-CA

Introduction/Background Introduction: Transthyretin amyloid cardiomyopathy (ATTR-CA) is an increasingly recognized etiology of heart failure with preserved ejection fraction (HFpEF), which is non-invasively diagnosed with the help of Tc-99m pyrophosphate scintigraphy. Although ATTR-CA is known primarily to be associated with preserved ventricular function, these patients could also have reduced ventricular function. However, the exact prevalence of heart failure with reduced ejection fraction in ATTR-CA and its prognostic significance is unknown.

Objective(s) We sought to determine the prevalence of heart failure with reduced ejection fraction (HRxF) in ATTR-CA and its prognostic implications.

Methods We analyzed patients with the diagnosis of ATTR-CA in our prospective Tc-99m pyrophosphate (PYP) registry. The diagnosis was non-invasively established based on positive PYP (defined as Perugini grade ≥2 and diffuse myocardial tracer uptake on the SPECT) and negative serum studies for AL amyloidosis. The transthoracic echocardiogram (TTE) at the time of PYP was used to identify patients with reduced EF <50% (ATTR-rEF) and preserved EF ≥50% (ATTR-pEF). Kaplan-Meier curve for survival between the two groups and multivariable logistic regression models were generated.

Results Of the 124 ATTR-CA patients (mean age of 79.9 ± 7.4, 87% men, 90% Caucasians), 51 (41%) were ATTR-REF. Compared to ATTR-pEF, at the time of PYP, ATTR-rEF were more symptomatic ( NYHA-FC ≥ 3, 61% vs 26%, p<0.001), had lower prevalence of obstructive coronary artery disease (CAD)(37% vs 53%, p=0.05), worse mean diastolic dysfunction (3 vs 2.15, p<0.01), lower tricuspid annular plane systolic excursion (TAPSE <1.7, 59% vs 25%, p<0.001) and reduced renal function ( creatinine, 1.63 ± 0.85 vs 1.27 ± 0.55 mg/dl, p<0.01). There was no difference in terms of biomarkers (BNP, p=0.1 and troponin, p=0.3) and interventricular septal thickness (p=0.2). Over a mean follow up period of 1.5 years, 27 (22%) patients died. ATTR-rEF was associated with higher mortality compared to ATTR-pEF (35% vs 12%, p=0.002; HR 3.7, 95%CI 1.62–8.63, p<0.01). After multivariable logistic regression analysis adjusting for TAPSE and other covariates, ATTR-rEF was an independent predictor of mortality. Lower EF values were also associated with higher mortality, with each 1% decrease in EF associated with a 1.2-fold increased risk of mortality (p<0.001). Reduced EF was associated with worse prognosis in ATTR-CA.
Abstract 80 Figure 2  Increasing mortality with decreasing EF in ATTR-CA

and creatinine, reduced EF was an independent predictor of mortality (HR 3.02, 95% CI 1.30–7.10, p=0.01). When divided into EF \textless 50%, EF 41–49% and EF \textless 40%, there was stepwise increase in the risk of mortality (p<0.01).

Conclusion HFrEF is present in more than one-third of patients with ATTR-CA at the time of diagnosis, and is an independent predictor of mortality in ATTR-CA.

Abstract 86 Figure 1  EKG upon presentation to the emergency room

The EKG demonstrates atrial fibrillation in left bundle branch block.

Abstract 86 Figure 2  Axial (left) and sagittal (right) chest computed tomography with contrast

CT scan of the chest demonstrates enlarged left atrium with 1.6 cm round filling defect in the left atrial appendage, representing a thrombus (white arrow).
examinations were unremarkable. Initial blood workup was unremarkable. Serial troponin T remained negative, as did D-dimer. Electrocardiogram (EKG) was remarkable for left bundle branch block (LBBB) (figure 1). Previous EKG was not available for comparison.

He was admitted with a working diagnosis of unstable angina, for which he was started on aspirin, Clopidogrel and continuous heparin infusion. In view of the progressive deterioration of the back and chest pain, a computed tomography (CT) of the chest (figure 2) and abdomen (figure 3) was performed, which showed a left atrial thrombus and right ARI. The pain resolved with oral opioids and the patient was switched to Apixaban on discharge.

Discussion Cardioembolic ARI is rare, and patients may exhibit various non-specific symptoms, including fever, pain on the flank, upper abdomen or back, nausea, vomiting, hematuria, proteinuria, leukocytosis and elevated LDH, which can simulate other pathologies that lead to misdiagnosis and delayed intervention. The main precipitating factors for ARI are Afib, heart diseases and hypercoagulability. In our case, the patient has CAD and Afib without anticoagulation due to the borderline CHA2DS2-VASc score of 1, and was initially diagnosed with unstable angina pectoris, overlooking some of the physical signs and symptoms. Contrast CT of the chest and abdomen are recommended in case of suspected ARI, to investigate kidney and multiple organ involvement as well as an emboli source. Transthoracic and transesophageal echocardiograms are also recommended to investigate cardioembolic lesions and valve pathologies. Treatment of ARI is geared towards treating the underlying etiology like anticoagulation, management of valvular disease or systemic hypercoagulability. This case reminds physicians to include ARI in their differential diagnosis when the presentation of Afib or CAD is atypical and accompanied by other systemic symptoms. Thorough history, physical exam, and evaluation of other comorbidities are crucial for early identification and management of ARI.
brief stay, she remained chest pain free and was discharged to commence cardiac rehabilitation in an outpatient setting.

Discussion It is likely that in our patient, one who did not have EKG or cardiac enzyme abnormalities on presentation, suffered an event of ACS from the development of TCM due to the presence of mid-ventricular akinesis and basilar-apical hypercontractility on echocardiogram. It was important to note that the presence of basilar-apical hypercontractility indicated that there was no residual WMAs from her past ACS of the LAD which required PCI. Angiogram did not reveal any coronary disease in these segments as well suggesting non-coronary distributive disease. A possible mechanism of this presentation was proposed in a similar case reported by Mencer et. al, suggesting that development of TCM first would have led to a catecholamine surge, that ultimately could have led to coronary micro-vascular dysfunction and thrombus formation resulting in ACS of the RCA.2

On the other hand, atherosclerotic disease of the RCA, with the lack of echocardiographic regional WMAs corresponding to this lesion, was believed to be an innocent bystander in this case and not the true cause of her ACS. It is also possible that isolated coronary disease of the RCA could have led to a catecholamine surge, resulting in TCM and ultimately her presentation, a mechanism discussed in a similar Case Presentation by Chamount et. al.3

It can be a challenge to distinguish TCM from ACS in the same patient as they have similar presenting features both clinically and radiographically. A similar case reported by Alfonso et. al, suggested that although coronary angiography is indispensable in the diagnosis of TCM and differentiating it from ACS, non-invasive imaging modalities such as echocardiography plays a key role in the detection rate of TCM and differentiate it from true coronary artery disease and that ‘clean-coronaries’ are not always required for the diagnosis of TCM.4

In our case, the WMAs seen on echo in a non-coronary distributive manner extending beyond the distribution of a single coronary artery advocates for the development of TCM. Furthermore, the importance of TTE highlights other important factors such as the evaluation of LV function with hemodynamic assessment, variants and complications related to TCM.

REFERENCES
significant for Tetralogy of Fallot status post right Blalock-Taussig shunt, ventricular septal defect patch repair and right ventricular (RV) myectomy, + cleft palate repair (1996), pulmonary regurgitation and severe RV dilation status post stenting of the right pulmonary and main pulmonary arteries, and surgical pulmonary valve replacement (2018), who presented to our institution after suddenly developing palpitations, abdominal pain and vomiting for a 2 hour duration. Upon presentation, the triage nurse was unable to obtain a blood pressure in either of his arms, prompting a stat electrocardiogram to be performed, which showed a wide-complex tachycardia rhythm. Shortly after arrival, while conversing with the medical team, the patient went into ventricular fibrillation. He was immediately given 2 grams of magnesium and defibrillated with 200 Joules. He briefly returned to a wide-complex tachycardia but went back into ventricular fibrillation once again, and received a dose of epinephrine. Patient was then defibrillated a second time, this time resulting in sinus rhythm with bundle branch block. He was intubated for about 15 hours due to his inability to protect his airway. He was gradually weaned off of the ventilator over several days, and ultimately returned to baseline mentation. His left ventricular function was initially severely depressed; however, there was an improvement in function over the course of his admission. Patient was taken to the catheterization laboratory for diagnostic catheterization, electrophysiology study, and implantable cardioverter-deﬁbrillator implantation. He completed three doses of intravenous antibiotics and then got discharged home with oral antibiotics, Amiodarone, Aspirin, and pain medication in stable condition.

**Discussion** A multicenter, cohort study comprised of 793 patients (mean age of surgical repair being 8.2 years) investigated the correlation between collected data (surgical, hemodynamic, and electrocardiographic) and clinical arrhythmias with or without subsequent sudden cardiac death over a ten-year time span (Gatzoulis MA et al). This study found a statistically significant relation between prolonged QRS duration and ventricular arrhythmias as well as sudden cardiac death. Atrial tachyarrhythmias, on the other hand, were more closely associated with older age of repair. Of note, none of the patients who suffered sudden cardiac death had undergone later reoperation. This suggests there may be some value in pre-emptively performing screening electrocardiograms regularly, and perhaps even more frequently in the patient population containing older individuals at age of repair. Some consideration should also be given to defining guidelines, which govern candidacy for these repeat operations. In this particular study, it was also shown that pulmonary regurgitation was the predominant lesion, which precipitated sustained ventricular tachycardia and, in some cases, sudden cardiac death (Therrien J et al). Screening echocardiograms on a regular basis may serve to identify faulty pulmonic valves, altered hemodynamics, and prompt reoperation to prevent future fatal complications. To determine the exact intervals of time at which these screenings are to be performed would require additional studies.

In patients with several different surgically repaired congenital heart defects, it is imperative to put in place appropriate and adequate screening methodologies in order to risk stratify these patients based on the findings of the aforementioned studies. As exemplified by our patient, by the age of 31, it is possible that these patients encounter increased durations and burden of sustained life-threatening arrhythmias. With factors such as increasing age, age at repair, number of cardiac surgeries, presence of cardiovascular comorbidities such as hypertension, diabetes, hypercholesterolemia, and obesity, left ventricular end-diastolic function, an E/e’ ratio cutoff of 10 as evaluated by echocardiography, presence of pulmonic regurgitation, and QRS duration being known to increase the rate of cardiac complications including sudden cardiac death, we propose closer and more regular monitoring of these factors in patients with surgically repaired congenital heart defects.

**Introduction/Background** Congenital heart disease contributes to various unexpected structural & physiological phenomena, occasionally manifesting later in life.

**Case Presentation** 59-year-old male, with a history of cognitive impairment & hypertension, presented for elective closure of a large 26–29 mm secundum atrial septal defect (ASD). Echocardiogram (Echo) 2 years prior had demonstrated a left-to-right atrial shunt with an elevated Qp:Qs (pulmonary to systemic flow) 3.0–3.2; however, the family refused surgery. Subsequently, he developed worsening exertional dyspnea & bilateral lower extremity edema. Repeat Echo demonstrated Qp:Qs 2.5, moderate supravalvular pulmonary stenosis (peak velocity 3.4 m/s, peak gradient 46 mmHg) [figure 1] and normal left ventricular structure & function.

Coronary angiography demonstrated an anomalous origin of the left anterior descending (LAD) artery arising from the right coronary cusp superior to the right coronary artery.

**Abstract 89 Figure 1** A: Echocardiogram demonstrating pulmonary stenosis (peak velocity 3.4 m/s, peak gradient 46 mmHg); B: Echocardiogram demonstrating shunting between right and left atrium; C: AO: ascending aorta, BSA: body surface area, CI: cardiac index, CO: cardiac output, Hb: hemoglobin, IVC: inferior vena cava, LA: left atria, LV: left ventricle, PA: pulmonary artery, PCWP: pulmonary capillary wedge pressure, Qp: pulmonary flow, Qp:Qs: pulmonary to systemic flow, Qs: systemic flow, RA: right atria, RV: right ventricle, SaO2: oxygen saturation of arterial blood, SVC: superior vena cava; D: Coronary angiogram of left anterior descending (LAD)- anomalous origin from the right coronary cusp (*) superior to the origin of the right coronary artery. Angiographically normal large caliber vessel which gives off two diagonal branches (D1, D2) with disease.
AN UNUSUAL APPROACH TO TREATING VENTRICULAR TACHYCARDIA STORM WITH CHOLESTYRAMINE

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University of Missouri-Columbia

10.1136/jim-2021-MW.19

Introduction/Background Cholestyramine is a bile acid sequestrant and antilipemic agent with an off-label indication for adjunctive therapy for hyperthyroidism caused by Graves’ disease. Studies have shown that cholestyramine can be effective as an additional medication to treat hyperthyroidism. One case report in the literature showed how cholestyramine alone can be effective.

Hyperthyroidism is usually treated with either methimazole or propylthiouracil, and it is expected it will take 1-3 months for the patient to feel better. It has been suggested that cholestyramine could be used to speed up the secretion of thyroid hormones when necessary. This can be helpful in critical conditions such as ventricular tachycardia. In the literature there are rarely documented reports of hyperthyroidism in connection with ventricular tachycardia. We present a case of iatrogenic hyperthyroidism that contributes to ventricular tachycardia and has been effectively treated with cholestyramine as a monotherapy. This case is yet another example of hyperthyroidism causing ventricular tachycardia and providing additional support for using cholestyramine in the treatment of hyperthyroidism.

Case Presentation An 82-year-old male presented as a transfer from an outside hospital with recurrent sustained ventricular tachycardia (VT) of 1-day duration, for which he received recurrent electrical shocks via his cardiac resynchronization therapy defibrillator (CRT-D). The patient’s past medical history was remarkable for the history of ischemic cardiomyopathy, VT status post-ablation, and CRT-D placement, as well as pheochromocytoma. His antithyroid treatment (PTU) was stopped either 1 hour before or 4 days after his second dose of cholestyramine. The patient subsequently underwent successful catheter ablation of ventricular tachycardia and then levothyroxine was restarted at 100 mcg daily with plans to repeat TSH, levothyroxine, and free T3 in 4-6 weeks. He was only advised to take 100 mcg a day on discharge.

Discussion The indication for cholestyramine for the treatment of hyperthyroidism stems from the mechanism of cholestyramine that promotes the fecal elimination of T4. 50 mg of cholestyramine can bind to about 3000 mcg of T4. The half-life of levothyroxine is 7.5 days. One study which was done on Graves’ disease patients suggested using cholestyramine for a duration of 4 weeks. In our case, since it was iatrogenic, the patient’s free thyroxine level improved to a normal level after four days, which suggests that in iatrogenic cases, a few days should be sufficient to achieve the goal of speeding up the elimination process.

However, the use of cholestyramine may be complicated by diarrhea, which requires other oral medications to be administered either 1 hour before or 4-6 hours after. In our case, particular attention was taken with regard to timing of other oral medications and cholestyramine for mexiletine and metoprolol to be effective in the setting of ventricular tachycardia. Doctors should be aware of the potential benefits of cholestyramine for the rapid reversal of hyperthyroidism that causes a critical disease and the possibility that hyperthyroidism may contribute to ventricular tachycardia.

SPONTANEOUS CORONARY ARTERY DISSECTION: A RARE NON-ATHEROSCLEROTIC CAUSE OF ACUTE MYOCARDIAL INFARCTION

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10.1136/jim-2021-MW.20

Introduction/Background Spontaneous coronary artery dissection (SCAD) occurs in 0.1 to 4% of cases of acute coronary syndrome (ACS) and is seen in women of young age, devoid of atherosclerotic risk factors. We report a case of a patient with acute myocardial infarction (MI) caused by SCAD in diagonal 2 (D2) of the left anterior descending artery.

Case Presentation A 51-year-old female smoker and no significant past medical history, presented with severe and crushing chest pain with diaphoresis. There was no history of illicit drug abuse. On presentation to the emergency department, the patient appeared diaphoretic and pale with stable vitals. Troponin levels were 1.01 and EKG showed ST elevations with hyperacute T waves in leads V3 and V4. An Echocardiogram demonstrated preserved ejection fraction with hypokinesis of apical segments. Aspirin and nitroglycerin were administered along with a heparin drip and Ticagrelor. Angiography done showed a spontaneous dissection in D2 with minimal flow to the apex. No stent was placed. Later,
CT angiography of head and neck abdomen and pelvis ruled out fibromuscular disease. She was started on aspirin and metoprolol. She remained pain free and stable and was advised against heavy lifting. She is followed outpatient and is currently doing well.

**Discussion** SCAD is a rare cause of MI and should be considered in young females who do not have cardiovascular risk factors of MI. They must be screened for fibromuscular dysplasia as it has been implicated as a strong risk factor for the development of SCAD. Proposed mechanisms of SCAD suggest intraintimal tears or damage to the vasa vasorum leading to intra-medial hemorrhage.1 Predisposing conditions such as pregnancy, vasculopathies such as fibromuscular dysplasia increase the likelihood of SCAD occurrence. Chest pain is the most common presenting feature of SCAD. Coronary angiography divides SCAD into 3 categories. Type 1 is most pathognomonic and angiographically appears when contrast stains the arterial walls showing multiple radiolucent lumens. Type 2 is diagnosed when there is diffuse stenosis and can be long and extensive, almost reaching the distal tip of the involved coronary artery. Type 3 mimics an atherosclerotic lesion and is most difficult to diagnose. Long lesions with hazy and linear stenosis on angiograms can be helpful in differentiating true SCAD from atherosclerosis.2 Further confirmation with intracoronary angiogram techniques such as OCT and IVUS is helpful.3 There is a lack of guidelines when it comes to the management of SCAD. A conservative approach is ideal because it usually heals in 4–6 weeks. PCI is challenging and only considered in patients with strong clinical indications such as hemodynamic compromise or those with TIMI flow less than 3. Studies have discussed intracoronary imaging and biodegradable stents during PCI.4 Medical therapy includes aspirin, clopidogrel and statins. Hypertension is associated with recurrent SCAD and is controlled with beta blockers. Moreover, patients are advised against heavy lifting and a cardiac rehabilitation program for a favorable long-term prognosis.

**REFERENCES**


**Educational/Outcome Research**

**T4 TRANSLATION IN THE CLASSROOM: TEACHING GENETICS THROUGH PROJECT-BASED LEARNING IN UNDERSERVED SCHOOLS AND COMMUNITIES**

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4.1136/jim-2021-MW.21

**Introduction/Background** Understanding the steps from DNA transcription to phenotype (glucose response, thrill-seeking and addictive behavior) is no small task for middle school students. From Oct 2014 through May 2019, the Michigan State University CREATE for STEM Institute and University of Michigan School of Public Health, under an NIH Science Education Partnership Award (SEPA), engaged 1,271 6th through 8th grade students from Flint, MI (77% African American; 5% multiracial; 3% Latino), with pilot testing in Detroit and Flint, in the project-based ‘Health in Our Hands’ genetics educational program. The curriculum closely adhered to Next Generation Science Standards, with inquiry-based use of observational data and scientific reasoning. In-class projects included simulated glucose tolerance and insulin testing and population growth modeling, and Monkeyflower selective adaptation experiments. The effort involved T4 (translation to communities) educational research – family and community members took part in student type 2 diabetes (smoothie content, food buddies, exercise and screen time) and addiction (duration of social media use) ‘community action research projects’ and end-of-semester presentation events. The projects stressed genetic and environmental factors, gene-environment interaction, and the ability to make a change at the individual and community levels.

**Objective(s)** Describe the biological phenomena used to anchor the teaching of genetics to middle school students. Compare outcomes and level of participant involvement in three different didactic approaches: (1) formal curriculum; (2) in-class projects; and (3) community action research projects.

**Methods** Project impact was measured with student (Year 4: N=719 forms handed-in) and teacher (N=6) pre/post class-room surveys; presentation event student (Year 4: N=293 forms) and adult participant (N=26) event questionnaires; and adult participant (11 parent, 8 other adult) interviews. The SPSS V. 25.0 Generalized Linear Mixed Modeling program was used to generate ANOVA tables listing the significance level (Pre- to Post-) for Student Survey variables. Mixed qualitative/quantitative Methods were used to analyze event questionnaire and interview data.

**Results** Students in the fall 2017 6th grade diabetes enactment showed statistically significant Pre-/Post- gains in perceived learning about genetics and the environment (P<0.003), and health and disease (P<0.001), while those in the fall 2018 7th/8th grade addiction enactment showed significant gains for the health and disease question. Recruited judges at the end-of-semester presentation events registered the kids’ excitement explaining the in-class Monkeyflower experiments, though observing parents did not mention them during the interviews. Student displays at these presentations contained charts of sugar metabolism in the body, plant response to salty and non-salty environments, and neural pathways in the brain’s reward system. Spring 2017 diabetes presentation event questionnaires displayed a gradation of adult attendee responses: 64% strongly and 27% somewhat agreeing with a statement on curricular awareness; 9/11 parents/family members and 5/9 community members having talked with a student about diabetes; and 10/11 parents/family members affirming having subsequently discussed food changes within their family. 6/11 adults attending the spring 2018 event affirmed discussing the addiction community action research project with a student.

**Conclusion** Multiple tandem approaches – didactic lessons, modeling, and community research projects – can successfully be used to teach DNA translation to the phenotypic level in middle school science classes in underprivileged communities. In-class experiments correlate these lessons with natural selection. Further efforts are needed to engage parents and make

**Project Impact**

4/11 students at the summer 2017 diabetes research project event affirmed discussing the addiction community action research project with a student. Spring 2018 students (4/5) affirmed discussing the addiction community action research project with a student.
them aware of these projects and the role of evolution, these activities being evaluated at the T4 translational research stage. Chronic disease and behavioral conditions can serve as biological phenomena anchoring middle school genetics education.

**PREVENTING TIPPING POINTS IN HIGH COMORBIDITY PATIENTS: A LIFELINE FROM HEALTH COACHES**

1Mary E Charlson, 2Anisa Mian, 1James Hollenberg, 2Roxane Padilla, 2Rosio Ramos, 2Erica Phillips, 2Nivedita Mohanty, 2Andrea Cassells, 2Ti Lin, 2Jonathan N Tobin, 1Weill Cornell Medicine; 2Clinical Directors Network, Inc; 3AllianceChicago

**Introduction/Background** This pragmatic cluster randomized clinical trial (cRCT) enrolls patients with multiple chronic diseases (MCDs) who are at highest risk for destabilization (unplanned hospitalizations, increased disability). Patients with multiple chronic diseases are often excluded from clinical trials because of their multiple medical conditions and worse health outcomes, which significantly confound results. Few evidenced-based strategies exist to comprehensively address the needs of these patients.

**Objective(s)** Among 1920 adult patients with multiple chronic diseases defined as a Charlson Comorbidity Index (CCI) > 4, who are established primary care patients of 16 Federally Qualified Health Centers (FQHCs) in NYC (n=8) and Chicago (n=8), which serve predominantly low income, Black and Latino patients, this pragmatic cluster RCT evaluates the comparative effectiveness of two approaches to preventing significant destabilization (‘tipping points’) that leads to unplanned hospitalization and increased disability.

**Methods** Federally Qualified Health Centers (FQHCs, n=16) are cluster-randomized to: 1) Patient Centered Medical Home (PCMH) (Usual Care); or 2) PCMH plus a Health Coach (PCMH + HC) intervention that employs a positive affect/self-affirmation strategy to motivate patients to set life goals, improve self-management and handle psychosocial and other stressors (Experimental). Primary and secondary outcomes include: unplanned hospitalizations and emergency department (ED) visits aggregated by PCORnet Clinical Research Networks, Health Information Exchange (New York City), and hospital alerts (Chicago), at baseline, 6, 12, 24-months and changes in disability. With the COVID-19 pandemic, we shifted to remote recruitment, and added oral consenting, e-gift cards and mailed letters.

**Results** The PCMH + HC arm is designed to identify and prevent destabilization leading to hospitalization or ED visits that are more often triggered by psychosocial issues—family, community and environmental—than by medical issues. The study is powered to detect a 33% relative reduction in% hospitalization (a 5% absolute reduction) in PCMH + HC compared to PCMH only. Additionally, we expect that reducing hospitalization will result in reduced disability.

**Conclusion** This intervention is designed to help participants manage life events that lead to ‘tipping points’ or overwhelming situations that result in unplanned hospitalizations and increased disability. FQHCs with PCMH recognition focus on care coordination. Patients need assistance to deal with many social and health related challenges they face and need help in communicating with health care providers and navigating a complex health care system. The PCMH + HC intervention will determine if adding health coaches helps patients to better manage their sources of stress, improve self-care and reduce unplanned hospitalizations. The impact of COVID-19 on changes to study processes and patient outcomes will be examined.

**INVESTIGATING THE ‘FAUCI EFFECT’: THE IMPACT OF COVID-19 ON UNDERGRADUATE INTEREST IN THE MEDICAL FIELD**

Arjun Kumar, Rahul Sandella, John Wilson, Yannan Huang, Anil Menon. University of Cincinnati College of Medicine

**Introduction/Background** Data collected by the American Medical College Application Service (AMCAS) indicate an increase of over 7,500 applications to enter medical school in 2021 compared to 2020 - approximately an 18% increase. This phenomenon has been called the ‘Fauci Effect’ and is based on the hypothesis that Dr. Anthony Fauci has inspired a wave of young people to pursue a career in medicine. However, the exact reasons underlying the substantial increase in student desire to pursue a medical career remain unknown. Furthermore, it remains unclear how the pandemic has impacted pre-health college students (first and second years of baccalaureate degrees) in their attitudes towards careers in medicine.

**Objective(s)** The objective of this study is to determine whether the ‘Fauci effect’ was of the same magnitude in pre-health baccalaureate students at the University of Cincinnati compared to the population reported in the AMCAS data.

**Methods** This study was designed as a longitudinal trend study over the period of one year. A cohort of 145 students was polled three times with the identical survey at intervals of 4 months. Participants were 1st and 2nd year pre-health baccalaureate students at the University of Cincinnati College of Medicine enrolled in the 2023 and 2024 classes of the Medical Sciences Program. Students were polled once during each semester of their enrollment to assess their future career interests in medicine. In Fall 2020, a closed-response question was added to this survey to assess whether COVID-19 increased, decreased, or resulted in no change in the students’ motivation to pursue a career in medicine. An open response option was available for students to explain their choice.

**Results** An average of 53.8% of the students polled indicated that COVID-19 increased their interest to pursue a career in medicine (63.1% in the Class of 2023 and 46.3% in the Class of 2024). 43.4% of the students indicated that COVID-19 did not change their interest to pursue a career in medicine while 2.8% of students said it decreased their interest.

Further analysis of the open-ended responses showed the reasons for increased interest in medicine fell into six major themes across classes: a greater appreciation for medicine, inspiration from frontline workers, a desire to improve inequalities within healthcare, increased motivation to make a change, increased desire to serve others, and drive to address the shortage of healthcare workers.

**Conclusion** The Results of this survey suggest that the ‘Fauci Effect’ may also be applicable to students early on in their pursuit of a career in the medical field. Though the AAMC saw a drastic increase in the number of medical school
applications this year, it appears this increased interest is not limited to just medical school applicants. This study not only suggests that COVID-19 has led to an increased interest in the medical field as early as the first and second years of undergraduate, but also helps elucidate some of the previously unclear reasons for this increased interest.

Endocrinology/Metabolism

58  FASTING MEDIATES THE METABOLIC, MOLECULAR AND GEROPROTECTIVE EFFECTS IN A CALORIE RESTRICTED DIET
Heidi H Pak, Spencer Haws, Mikaela Koller, Cara L Green, Nicole Richardson, Shany Yang, Sabrina Dumas, Michelle Sonsalla, Lindsey Bray, John Denu, Dudley Lamming. University of Wisconsin-Madison
10.1136/jim-2021-MW.24

Introduction/Background For almost a century calorie restriction (CR) has been the gold standard for geroprotective interventions, not only extending lifespan and healthspan, but also preventing or delaying many age-associated diseases. While effective in rodents and other mammalian species, an abstinenceous CR diet is difficult for most people to maintain. Understanding the mechanisms by which CR promotes health span and developing effective CR-mimicking dietary regimens or pharmaceuticals is therefore essential to harnessing the benefits of CR.

Recently, it has become apparent that when we eat may be just as important as what and how much we eat. Research into feeding paradigms have found that time-restricted feeding and intermittent fasting has metabolic benefits, protecting mice and perhaps humans from the negative metabolic effects of a high-fat, high-sucrose ‘Western’ diet. Similarly, meal-fed mice, which are fed nearly an ad libitum portion of food but consume it over ~12–15 hours, live longer than truly ad libitum fed animals. These findings significantly complicate the interpretation of CR studies done in a laboratory setting, as CR-fed animals are typically fed only once per day, consuming their food in ~2 hours, and are subjected to fasting for the remaining 22 hours per day. A largely overlooked question is whether the metabolic health benefits of CR arise solely from the reduction in calories, or if this enforced period of daily fasting is also required.

Objective(s) Here, we distinguish fasting dependent and independent effects by utilizing multiple feeding paradigms to determine if the metabolic effects of CR are mediated by reduced caloric intake, or also require prolonged fasting.

Methods We randomized male and female C57BL/6J and DBA/2J mice to four groups: 1) ad libitum diet or to one of three CR regimens in which calories were restricted by 30%: 2) animals fed once per day during the light period; 3) animals fed three equal meals during the course of the 12-hour dark period; and 4) animals provided with ad libitum access to a low energy diet diluted with indigestible cellulose, which reduced caloric intake by ~30%. Additionally, to fully address the impact of fasting duration from energy intake we used a 5) fifth feeding paradigm where mice were entrained to rapidly consume an ad libitum portion of food and were fasted for the remaining ~22 hours per day.

Results We observed that all three CR regimens improved fasting blood glucose levels and glucose tolerance for all strains and sexes. Intriguingly, we found that only mice on a traditional CR regimen, fed once daily, had improved sensitivity to insulin, a phenotype of CR that has been suggested to mediate many of CR’s beneficial effects on longevity. We examined the effects of CR at the molecular level by measuring metabolites and performing epigenetic profiling of the liver and found a distinct metabolomic signature associated with once-a-day CR compared to the ad libitum control. However, the metabolomic signature of the diluted diet group resembled closely that of the ad libitum control. This was also true with the acetylation profiles of histones, which suggest fasting, not reduced calorie intake, mediates the metabolic and epigenetic profile typically shown in calorie restriction studies. Additionally, we identified that fasting alone without a reduction in calorie intake recapitulates the metabolic phenotypes and transcriptional effects of a CR diet. Finally, we show that fasting is required for the beneficial effects of CR in aging C57BL/6J male mice, including improvements in insulin sensitivity, reduction in frailty, and extension of lifespan.

Conclusion We conclude that while many of the metabolic benefits of a CR diet are mediated by reduced caloric intake, the prolonged fasting induced in CR mice fed once a day is required for systemic insulin sensitivity, as well as the transcriptomic, metabolomic and epigenetic profiles observed in calorie restriction studies.

59    GERIATRIC MICE ARE LEANER AND HAVE IMPROVED GLUCOSE TOLERANCE AFTER DIETARY ISOLEUCINE RESTRICTION
Yang Yeh, Mariah Calubag, Dudley Lamming. University of Wisconsin-Madison
10.1136/jim-2021-MW.25

Introduction/Background Caloric restriction can improve metabolic health and extend lifespan, understanding its mechanisms is one of the most promising avenues to improve the quality of life in the global greying population. Interestingly, a general dietary restriction of proteins has been shown to provide the many benefits of caloric restriction with a paradoxical increase in calories intake. Further investigations have found that dietary restriction of branch-chained amino acids (BCAAs) is sufficient to reproduce these effects. The Lamming Lab has identified isoleucine (ile) restriction as a potent
component of this treatment and is by itself sufficient to promote leanness and improve metabolic health. These studies have established the benefits of ile restriction in younger mice, however the effects of this treatment on late-life geriatric animals remain to be investigated and represents the critical experiment for the translational aspirations of these novel findings.

Objective(s) Using naturally aged NIA mice, this present study evaluates the potentials of isoleucine restriction as a beneficial late-life intervention to improve the animals’ metabolic, physical, and cognitive conditions.

Methods At 20 months of age, male C57BL/6J.NIA mice were fed ad libitum iso-caloric diets that was isoleucine-restricted (1/3 ile), protein-restricted (1/3 protein), or amino acids-defined (control). Food intake and MRI body composition were monitored throughout the experiment. Frailty score of each animal was assessed monthly. After 3 weeks of the dietary treatment, a glucose tolerance and an insulin tolerance test were performed. After 3 months, the respiratory rate of these animals was evaluated in a metabolic chamber. Finally, cognitive tests including novel object recognition and Barnes Maze was carried out.

Results Within the first week of the dietary intervention, we observed a significant decrease in the bodyweight of animals fed the 1/3 ile diet compared to those fed the control diet. This decrease in bodyweight is of a greater magnitude than that of animals fed a diet of general protein restriction (1/3 protein). MRI revealed the body composition of the 1/3 ile animals to be leaner than the control animals. These changes were accompanied by a paradoxical increase in food intake, which is consistent with the animals fed a protein restriction diet. Importantly, at three weeks after the dietary intervention, the ile restriction group performed significantly better in a motor function test of accelerating rotorod.

Conclusion These current Results suggest that dietary isoleucine restriction may be a potent intervention for inducing rapid weight loss and improving the metabolic health of geriatric patients.
SHORT-TERM LOW PROTEIN DIET AMELIORATES METABOLIC DYSFUNCTION IN DIABETIC LIPODYSTROPHIC MICE

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10.1136/jim-2021-MW.26

Introduction/Background Insulin is an important regulator of metabolism and has both direct and indirect effects on most tissues in the body. When insulin signaling is absent in adipose tissue (adipocre IR KO) mice develop profound systemic insulin resistance, hyperglycemia, organomegaly, lipodystrophy, impaired adipokine secretion and brown adipose tissue dysfunction. Long-term ad libitum dietary restriction such as low-protein diet (LPD) improves metabolic health and extends the life span of mice and possibly humans. However, most studies conducted thus far have focused on the preventive, but not therapeutic, potential of LP diets.

Objective(s) To determine whether dietary protein or caloric restriction could be used to treat preexisting metabolic symptoms in a diabetic lipodystrophic mice model.

Methods We subjected hyperglycemic lipodystrophic IRFKO (adipose-specific insulin receptor knockout) mice to LPD (5.1% kcal from protein) measuring Body weight and blood glucose every 3 days until sacrifice when we harvested plasma and tissues. Chow diet was used as control. From plasma we determined Insulin, TG, ketone bodies and cholesterol. We perform histological analysis from BAT, LIVER and pancreas using HE staining. We also assessed BAT browning markers by qPCR technique as well as other metabolic functions related genes.

Results Interestingly, postprandial blood glucose values of the IRFKO began to improve 10 days after the introduction of LPD. The IRFKO mice became normoglycemic 2 weeks after the onset of LPD treatment. Activation of adaptive thermogenesis in brown (BAT) and beige adipose tissues promotes energy expenditure and utilization of glucose and triglycerides. LPD has been previously shown to promote energy expenditure via the sympathetic nervous system. Consistent with previous studies, we observed that LPD acutely and sustainably upregulates energy expenditure in both the WT and IRFKO mice. This is likely due to dramatic improvements in BAT function following LPD consumption. Within one week of LPD treatment, the BAT of the IRFKO mice transformed from a whitened, unilocular appearance, to a browner tissue containing multilocular lipid droplets typical of healthy BAT. Thermogenic marker expression was significantly increased in the BAT after LPD. We also observed a time-dependent regulation of gene markers for fatty acid transport, oxidation, and glucose metabolism following LPD.

Conclusion Together with changes in blood chemistry in the IRFKO mice, we hypothesize that glucose and lipid-lowering effects of LPD is the consequence of continuously elevated energy expenditure leading to utilization and depletion of systemic thermogenic fuels. Taken together, our data suggest that short-term LPD could be a potential strategy for the treatment of metabolic syndrome.

HEPATIC DELETION OF FOXO1 SIGNALING RESCUES THE METABOLIC DEFICITS CAUSED BY MTORC2 INHIBITION

Reji Babgirinja, Michaela E Murphy, Shelly Shonsella, Sabrina Dumas, Victoria Flores, Cara L Green, Heidi H Pak, Dudley Lamming. University of Wisconsin-Madison

10.1136/jim-2021-MW.27

Introduction/Background Rapamycin, an inhibitor of mechanistic target of rapamycin complex 1 (mTORC1) is an immunosuppressant and anticancer drug which has previously been shown to extend life span of model organisms including mice. We have previously demonstrated that impaired glucose homeostasis, which is notably one of the most severe negative effects of chronic administration of rapamycin Results from the inhibition of mTOR complex 2 while its beneficial effects on aging is mediated via mTORC1 inhibition. Hepatic deletion of Rictor, which is one of the proteins in mTORC2 complex can reproduce the metabolic deficits caused by rapamycin. One major question that needs to be answered is how can we block the side effects of rapamycin? Can the inhibition of any of the downstream targets in PI3-AKT-FOXO rescue these metabolic defects? Forkhead boxO (FOXO) transcription factors, Foxo1 are important targets of insulin activity within cells, required to maintain glucose homeostasis especially during fasted state by promoting gluconeogenesis.

Objective(s) Foxo1 can be the primary effector of many of the metabolic phenotypes observed either in mice lacking hepatic Rictor or as a result of treatment with rapamycin and therefore we hypothesized that genetic deletion of Foxo1 can have a protective effect in rescuing the metabolic defects caused by mTORC2 inhibition.

Methods We compared the metabolic health of both male and female mice (10 weeks) in which we have deleted hepatic Rictor (Alb-Cre RictorLoxP/LoxP), hepatic Foxo1 (Alb-Cre Foxo1LoxP/LoxP) along with mice lacking both Foxo1 and Rictor, (Alb-Cre RictorLoxP/LoxP Foxo1LoxP/LoxP) as well as wild-type littermates (RictorLoxP/LoxP Foxo1LoxP/LoxP, RictorLoxP/LoxP and Foxo1LoxP/LoxP ).

Results Male Rictor knockout (KO) mice were glucose intolerant following GTT. However female mice didn’t show any significant differences in glucose levels compared to their wild type littermates. Hepatic deletion of Foxo1 resulted in a decrease in blood glucose levels in both male and female mice and male mice lacking both Foxo1 and Rictor exhibited a better glycemic control compared with their wild type littermates. Foxo1 has been shown to regulate hepatic gluconeogenesis, we examined this using pyruvate tolerance test in all the phenotypes. After the pyruvate injection, blood glucose was decreased in Foxo1 KO as well as the double knock out mice compared with their littermates.

Conclusion
- Hepatic deletion of Foxo1 resulted in a decrease in blood glucose levels in both male and female mice.
- Inhibiting Foxo1 signaling rescued the impaired glucose tolerance caused by deletion of rictor, with a stronger effect seen in males than females.
- These preliminary Results suggests that blocking Foxo1 signaling can rescue metabolic effects caused by mTORC2 inhibition
Overall, our Results could potentially open new treatment options for diabetes as well as other metabolic syndromes thereby promoting health aging and an increase in overall survival rate.

This is an ongoing study and future studies focus on further differentiating the metabolic phenotyping in these mice and perform a series of glucose, insulin, and pyruvate tolerance tests, and a glucose–stimulated insulin secretion assay in both sexes.

**Conclusion**

Histidine showed a strong correlation with BMI. The higher the percent of total protein coming from histidine, the higher the BMI. If histidine is increased by 1%, BMI increases by 5.38. The higher the shift in organismal metabolism. At the molecular level we have seen this loss of adiposity is may not be in result of adipose tissue being. We teamed up with a statewide survey of the health of Wisconsin (SHOW), to view the effects of dietary histidine transposition. To test this, we fed 67% reduced histidine to obese induced mice.

**Methods**

Histidine restricted mice show increased food consumption (normalized to body weight) and diminished activity (at night), with an increased respiratory exchange ratio indicating a major reduction of this epidemic. An intervention is needed to put an end to the rise of this epidemic.

**Objective(s)**

We hypothesized that reducing amino acids, the building blocks of protein, such as histidine in the diet obese induced mouse, would lead to an improvement on body composition. To test this, we fed 67% reduced histidine to obese induced mice and assessed their body composition, glucose metabolism, and metabolic parameters over 9 weeks.

**Results**

Our study shows that consumption of a low histidine diet rapidly reduces body weight and adiposity. In addition, histidine restricted mice show increased food consumption (normalized to body weight) and diminished activity (at night), with an increased respiratory exchange ratio indicating a major shift in organismal metabolism. At the molecular level we have seen this loss of adiposity is may not be in result of adipose tissue being. We teamed up with a statewide survey of the health of Wisconsin (SHOW), to view the effects of dietary histidine transposition. Histidine showed a strong correlation with BMI. The higher the percent of total protein coming from histidine, the higher the BMI. If histidine is increased by 1%, BMI increases by 5.38.

**Conclusion**

Overall, we have demonstrated that short-term dietary restriction of histidine Results in rapid and profound reductions in adiposity and improved glucose homeostasis in obese mice despite increased food consumption and diminished physical activity. In addition, a positive correlation in BMI and histidine consumption is seen when applied to human health status. Leading to the reduction of dietary histidine a possible intervention of obesity and diabetes.

**Introduction/Background**

Obesity and Diabetes are global health issues. An intervention is needed to put an end to the rise of this epidemic.

**Objective(s)**

Low protein diets are associated with a decreased risk of diabetes in humans, and we recently demonstrated that a low protein diet promotes leanness and glycemic control in lean and obese rodents as well as in obese humans. The focus of our present work is to identify effects of a low protein diet on glucose metabolism and body composition on obese induced mice.

**Methods**

The higher the percent of total protein coming from histidine, the higher the BMI. If histidine is increased by 1%, BMI increases by 5.38. The higher the shift in organismal metabolism. At the molecular level we have seen this loss of adiposity is may not be in result of adipose tissue being. We teamed up with a statewide survey of the health of Wisconsin (SHOW), to view the effects of dietary histidine transposition. Histidine showed a strong correlation with BMI. The higher the percent of total protein coming from histidine, the higher the BMI. If histidine is increased by 1%, BMI increases by 5.38.

**Conclusion**

Overall, we have demonstrated that short-term dietary restriction of histidine Results in rapid and profound reductions in adiposity and improved glucose homeostasis in obese mice despite increased food consumption and diminished physical activity. In addition, a positive correlation in BMI and histidine consumption is seen when applied to human health status. Leading to the reduction of dietary histidine a possible intervention of obesity and diabetes.
Abstracts

A CASE OF UNDETECTED PHEOCHROMOCYTOMA PRESENTING AS TAKOTSUBO’S CARDIOMYOPATHY

Moaz Abdelrehim, Adhiraj Bhattacharya. Tufts School of Medicine; St. Elizabeth’s Medical Center

Introduction/Background Pheochromocytomas are neuro-endocrine tumors arising from chromaffin cells in the adrenal medulla. The classic triad of symptoms include paroxysmal hypertension, headaches and diaphoresis. Rarely, cardiac complications related to catecholamine excess such as Takotsubo’s stress cardiomyopathy can be presenting manifestations in such patients. We present a case of pheochromocytoma manifesting as Takotsubo’s cardiomyopathy and uncontrolled hyperglycemia.

Case Presentation A 64-year-old female with a past medical history of type II diabetes who presented to the emergency department with sharp, substernal chest pain, associated with palpitations, dizziness, and diaphoresis. She was hemodynamically stable with normal heart rate and blood pressure on arrival. EKG showed normal sinus rhythm with no ST segment and T wave changes. Cardiac enzymes such as troponin I and CKMB were elevated. She was started on dual-antiplatelet therapy with aspirin and clopidogrel as well as a continuous unfractionated heparin infusion. She was taken for a coronary angiogram which revealed no obstructions in any of the coronary arteries. Transthoracic echocardiogram (TTE) demonstrated an ejection fraction (EF) of 31%, anterolateral wall motion abnormalities (WMAs) not related to vessel distribution and ballooning of the apical part of the heart suggesting stress induced cardiomyopathy/Takotsubo’s cardiomyopathy. The patient was started on an appropriate regimen with a statin, beta blocker and ACE-inhibitor. After a brief stay, she remained chest pain-free and was discharged.

After discharge, the patient continued to complain of persistent episodes of palpitations accompanied by severe headache and epigastric discomfort with forward bending. These episodes lasted several minutes before subsiding and had become more frequent. She measured her blood pressure during one of these episodes and found it to be 170/86, although her outpatient visit measurements were found to be within normal range. Suspicion for pheochromocytoma was raised. Plasma metanephrine and plasma normetanephrine were obtained and found to be significantly elevated. Plasma metanephrine level was found to be 542 pg/ml (normal ≤57 pg/ml) and plasma normetanephrine level was found to be 558 pg/ml (normal ≤148 pg/ml). Urine metanephrine and normetanephrine were also high. Magnetic resonance imaging (MRI) of the abdomen was obtained and showed an arterially enhancing mass involving the right adrenal gland measuring 3.6 x 2.5 x 3.1 cm causing mass effect on the IVC and the right hepatic lobe. The patient agreed to surgical resection. Prior to operative management, she was started on Phenoxybenzamine 5 mg daily and the dose was slowly up titrated to 10 mg BID for a month. She underwent successful resection of pheochromocytoma without post-operative complications. Pathology showed a 4.6 cm pheochromocytoma that was likely benign. Serum and urine metanephrine and normetanephrine levels were repeated and were found to be negative. 6 weeks after surgery. A repeat TTE done during an outpatient follow up showed resolution of regional wall motion abnormalities and an improvement in her EF to 66%. She remained symptom-free in subsequent follow ups.

With regards to her diabetes, at 3-month follow-up, hemoglobin A1c decreased from 6.6% to 5.7%. Her sugars have been under control with no further changes in medications or lifestyle.

Discussion Pheochromocytomas are rare catecholamine-secreting tumors that arise from chromaffin cells of the adrenal medulla and the sympathetic ganglia. The incidence of pheochromocytomas is approximately 0.8 per 100,000 persons per year. Due to catecholamine secretion, pheochromocytomas present with a classic triad of episodic headaches, tachycardia, and sweating. The catecholamine surge may also present with a classic triad of episodic headaches, tachycardia, and sweating. It is often related to tumor burden as well as extent of liver involvement. It is important to identify the cause of the hypoglycemia by ruling out the common causes first, including sepsis, medications, and cirrhosis as well as insulinoma. Without supportive treatment, outcomes can be fatal, hence prompt diagnosis and treatment is the key to the management.
catecholamines from a pheochromocytoma can result in Takotsubo’s cardiomyopathy, which although a rare occurrence, has been reported in several publications. The findings of regional wall motion abnormalities in a non-coronary distribution with a coronary angiogram devoid of any disease or stenosis, led us to her diagnosis of Takotsubo’s cardiomyopathy. Takotsubo cardiomyopathy is a self-limited cardiomyopathy that occurs in response to an intense emotional or physical stressor.1 However, there was no specific stressor that could be identified in the patient’s history. Therefore, physicians must be aware of patients diagnosed with symptoms of acute coronary syndrome without coronary artery stenosis or spasm and conduct a comprehensive evaluation to determine the cause of WMAs, keeping rare causes such as pheochromocytoma in mind.

Pheochromocytomas also cause hyperglycemia due to catecholamine release. The excess catecholamines directly suppresses pancreatic insulin secretion and induce glycolysis in the liver via α-adrenergic receptor stimulation, leading to hyperglycemia. In patients with a diagnosis of type II diabetes, who have persistently elevated blood glucose levels, despite diet and lifestyle modifications, a diagnosis of pheochromocytoma should be considered. Once the tumor is removed, blood glucose levels are better controlled without any additional interventions.3

Physicians should strongly suspect an undiagnosed pheochromocytoma when unexplained non-coronary distributive regional wall motion abnormalities representing Takotsubo’s cardiomyopathy, are identified on TTE, especially with a lack of physical stressors. Uncontrolled persistent hyperglycemia can also be explained by the catecholamine excess in pheochromocytomas.

Epidemiology/Health Outcomes/Quality Improvement/Bio-informatics

COVID-19 VACCINE HESITANCY IN THE GREATER CHICAGO AREA: A COMPARATIVE STUDY AND SOME FACTORS INFLUENCING NEGATIVE RESPONSES

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Introduction/Background Vaccinations offered for various illnesses have been received often with hesitancy from the public. We conducted a survey to assess perceptions of the COVID-19 vaccine in the population. The intent was to determine a broad range of factors which influence vaccination hesitancy. This we believe would facilitate the development of strategies to improve public confidence in vaccination.

Objective(s) Vaccination is one of the strategies to control spread of the virus. Recently, two vaccines have been approved for use in the US and vaccination has started for health care workers and elderly nursing home residents. Our goal was to determine questions and concerns that the public have regarding vaccination and in doing so, determine areas of education/awareness that would ameliorate these concerns.

Methods We conducted a survey which was sent out to a broad range of the population but concentrated on the Greater Chicago area. The survey was created using Google forms and distributed using various media platforms including text forms, email, Facebook and Whatsapp. The survey questions were deliberately kept simple with no complicated terminology and limited questions about personal details, namely specific information about age, address, income, education, and religion. Most questions were not mandatory. The age categories were created based on the minimum cutoff for vaccination (> 18 years) and the category to receive the vaccine first (> 65 years). The survey respondents were asked to categorize themselves as health care workers (HCW) or non-health care workers (nHCW) and to provide the zip code where they lived. This was followed by a series of questions addressing concerns that individuals might have about vaccinations including side effects, vaccine constituents (animal products), allergies, affordability, access to vaccination location and room to write in any other comments. The responses were collected between 1/11/2021–1/17/2021 in a timely manner, prior to launch of vaccinations for the general population in the US and India. The data was analyzed to determine the relationship of the region of residence, whether a healthcare worker and their decision to be vaccinated. We analyzed the relationship of the decision to be vaccinated with the region of residence and whether the respondent was a HCW or nHCW.

Results We conducted a survey centered around the greater Chicago area, but also reached out to communities around the world. Given that the authors belong to the healthcare system, a significant number of our associates were in healthcare, creating a bias in the distribution of the survey respondents. Several social and religious organization listservs were contacted mainly in the Greater Chicago area. We received 594 responses over a six-day period with the responses coming from fifteen countries, covering four continents (figure 1). We analyzed our data in 3 categories: the Greater Chicago area, the rest of the US and the rest of the world. We also analyzed responses separately for the HCW and the nHCW. For each of these categories we determined the number of people who were planning to take the vaccine, and those who were not. We then compared the level of concern expressed by each of these groups for vaccinations, including side effects, vaccine constituents (animal products), allergies, affordability, and access to vaccination. Statistical analysis was performed using Pearson’s chi-squared test.

Of a total of 594 respondents, 13 did not provide zip code information and so were removed from the analysis.

Of the remaining respondents 415 (71.4%) were from the US and 166 (28.6%) were from mainly Asian countries. Of the US respondents 78.8% stated that they were willing to take the vaccine vs. 51.2% non-US respondents (p< 0.001). Furthermore, 90% of the US HCW and 73.5% of nHCW stated that they would take the vaccine (p< 0.001).

Of the total US respondents, we analyzed the level of concern about animal products in the vaccine between those who were planning to take the vaccine, and those who were not. Of those who were willing to be vaccinated 28.8% were concerned about the vaccine containing animal products vs. 52.9% of those who were unwilling to be vaccinated (p< 0.001). Thus, the belief that the vaccine contains animal products was likely to be a principal factor in leading people to not take the vaccine (p< 0.001).

We further analyzed the subgroup of US respondents unwilling to take the vaccine. Of this group 42.8% HCWs and 54.8% nHCW, not planning to take the vaccine were
concerned about animal products (p=0.3) (figure 2). This indicated that hesitancy due to concern about animal products is a non-negotiable hinderance to vaccination.

Of the US respondents, 76.3% from the Greater Chicago area, Illinois said they would take the vaccine and 85.5% from the rest of US (non-Illinois) said yes to the vaccine (figure 3).

In the US, 89.2% HCW and 71.9% nHCW from the greater Chicago area said they would take the vaccine and 90.9% HCW and 79.3% nHCW from the rest of the US said yes to the vaccine (p=0.83). Once we correct for HCW status there is no difference in willingness to receive the vaccine.

**Conclusion** We prepared a simple survey where we did not ask for too much personal information so as to reduce hesitation in performing the survey. Also, the simplicity of the questions was intended to reach individuals with lower education levels and make the survey amenable to translation.

We found a significant difference in the compliance of respondents (to taking the vaccine) between US (78.8%) and non-US (51.2%).

Health care workers generally are more informed about medical interventions but at the same time have a separate set of concerns about any new therapy. Of the survey participants those with a healthcare background in the US were more likely to be agreeable to vaccination.

Also, we concluded that the belief that the vaccine contains animal products was likely to be a principal factor in leading people to not take the vaccine. Hesitancy due to concern about animal products appears to be a non-negotiable hinderance to vaccination. These findings provide a basis for vaccine-related education which would lead to improved vaccination compliance.

**Gastroenterology/Clinical Nutrition**

**Abstract 23 Figure 3** Comparison of Illinois with the remaining US for vaccine acceptance
Responses of survey respondents from the Greater Chicago area, Illinois and the rest of the US

**Gastroenterology/Clinical Nutrition**

**64** MULTI-DISCIPLINARY APPROACH TO DIAGNOSIS AND TREATMENT OF RECTAL CARCINOMA: THE ROAD TO NATIONAL ACCREDITATION PROGRAM FOR RECTAL CANCER INSTITUTIONAL ACCREDITATION

Saman S Karimi, Maria Gonzalez. University of Illinois at Chicago

10.1136/jim-2021-MW.32

**Introduction/Background** Colon cancer is the third cause of cancer-associated mortality in the United States. While the incidence of colon cancer has been declining over the past several decades, the incidence of rectal carcinomas in patients under the age of 40 has quadrupled over the last four decades.

**Objective(s)** The National Accreditation Program for Rectal Cancer (NAPRC) used a multidisciplinary approach to
optimize the diagnosis and treatment of rectal adenocarcinomas. There are only 17 institutions in the USA with NAPRC accreditation. Our institution is working towards the accreditation.

**Methods** All patients with a diagnosis of rectal adenocarcinoma treated surgically at our institution between 2016 and 2020 were included in our project. As part of the accreditation process, we assessed our rectal resection specimen as a quality indicator for NAPRC Accreditation. Completeness of the mesorectum and reporting of the College of American Pathology’s protocol parameters as nodal status, distal margin status, treatment response, and posttherapy pathological stage are not only important diagnostic and prognostic indicators but also quality parameters of the surgery and pathological assessment. We modified our grossing techniques to improve gross, microscopic, and magnetic resonance imaging correlation of the rectal specimens. The Quirk technique allows a better assessment of the depth of invasion and margin status by levelling. Four photographs of the specimen are taken to assess the integrity of the mesorectum and electronically stored with the patient identifier (figure 1 and figure 2). The slides are read, and the pathology report is completed by a pathologist who is an appointed member of the rectal cancer multidisciplinary team.

**Results** The findings are discussed at the rectal cancer multidisciplinary tumor board conference within four weeks of the surgery to provide an optimal approach to treatment. Sixty rectal resection specimens have been received, from 2016 to 2020. The quality of the evaluation of rectal specimens has increased significantly since these changes were implemented (table 1), and currently, our program is fulfilling the compliance criteria for accreditation.

**Conclusion** We share our approach in hopes of assisting and inspiring other centers that may benefit from NAPRC accreditation.

### Abstract 64 Table 1 Comparison of Pre- and Post-Implementation of NAPRC Multi-Disciplinary Quality Assurance Parameters

<table>
<thead>
<tr>
<th>PARAMETERS</th>
<th>PRE-IMPLEMENTATION DATA</th>
<th>POST-IMPLEMENTATION DATA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal cancer program director and coordinator</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>A defined Rectal cancer multidisciplinary team with a lead physician member from each specialty.</td>
<td>Established but no lead physician appointed.</td>
<td>Yes</td>
</tr>
<tr>
<td>Rectal cancer multidisciplinary team meetings with the attendance requirements</td>
<td>No strict requirements (At least one physician of each specialty was present) 100%</td>
<td>Yes 100%</td>
</tr>
<tr>
<td>Review of diagnostic pathology (95% of previously undiagnosed, previously untreated rectal cancer patients must undergo a biopsy at the Rectal cancer program for confirmation of rectal cancer diagnosis.)</td>
<td>60% 100%</td>
<td>100%</td>
</tr>
<tr>
<td>Internal medical record review</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Clinical staging before definitive treatment with CT or PET/CT scan of the chest, abdomen, and pelvis, and MRI of the pelvis</td>
<td>CT or PET: 96%</td>
<td>100%</td>
</tr>
<tr>
<td>Standardized reporting for MRI of the pelvis highlighting the depth of tumor penetration into the mesorectum, status of the circumferential resection margin, involvement of adjacent organs, lymph node involvement, extramural venous invasion, and relation to the anal sphincter complex.</td>
<td>Variable. Some MRI were interpreted by radiologists without special training on rectal specimens. Some MRIs were performed in outside institutions without a standardized format.</td>
<td>100% of all the MRI reports have a standardized format containing all required elements.</td>
</tr>
<tr>
<td>CEA levels</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Rectal cancer multidisciplinary team treatment planning discussion</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Treatment evaluation and recommendation summary</td>
<td>&gt;90%**</td>
<td>100%</td>
</tr>
<tr>
<td>Definitive treatment timing (within 60 days of patient’s initial clinical evaluation)</td>
<td>No prior standardization protocol</td>
<td>100% Rectal cancer surgeries are performed by a member of the Rectal cancer multidisciplinary team.</td>
</tr>
<tr>
<td>Surgical resection and standardized operative reporting.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adequate fixation time</td>
<td>15%</td>
<td>100% (48-72 hours in average)</td>
</tr>
<tr>
<td>Pathology reports (95% of the specimens are read by a pathologist who is an appointed member of the Rectal Cancer Multidisciplinary Team. Reports are completed within 2 weeks.</td>
<td>93% reports completed within 2 weeks</td>
<td>100%</td>
</tr>
<tr>
<td>Cancer summary with the pathological parameters required by the National Accreditation program</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Multidisciplinary team post-surgical treatment outcome discussion</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Post-surgical treatment outcome discussion summary</td>
<td>**</td>
<td>100%</td>
</tr>
<tr>
<td>Adjuvant therapy after surgical resection (within 8 weeks of definitive surgical resection)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectal cancer program education (CAP protocols and Supplemental education materials are provided by the NAPRC)</td>
<td>NAPRC’s supplemental education materials became available on October 2017</td>
<td>100%</td>
</tr>
</tbody>
</table>

** variable considering referral cases from outside institutions
tation and multidisciplinary approach to diagnosis and treatment of patients with rectal adenocarcinomas. High-quality data are critical to report quality improvement and measure the performance of programs.

**FALLS ARE COMMON, MORBID, AND PREDICTABLE FOR PATIENTS WITH CIRRHOSIS: A PROSPECTIVE STUDY**

Elliot Tapper, Lili Zhao. University of Michigan

10.1136/jim-2021-MW.33

**Introduction/Background** Falls are a devastating complication of cirrhosis. The risk of falls in contemporary patients without HE is unclear. Further, bedside tools for predicting falls are lacking.

**Objective(s)** To prospectively determine the incidence, risk factors, and impact of falls in patients with cirrhosis.

**Methods** We prospectively enrolled 299 subjects with currently compensated Child A-B (70% Child A) cirrhosis and portal hypertension without prior HE from 7/2016–8/2018. We followed patients for a median of 1003 days (IQR640-1102) for incident falls accounting for the competing risk of death or transplantation. Candidate baseline fall predictors included patient reported outcomes (e.g. SF-8), physical function (e.g. chair-stands), blood tests (e.g. MELD-Na and its components), and cognitive function (using Inhibitory Control Testing). We internally validated a predictive model for falls and evaluated the association between incident falls and mortality.

**Results** During follow-up, 141 (47%) patients experienced falls, 38 (13%) with injuries, 49 (16%) died, and 13 (4%) underwent transplants. Median time to a fall was 279 (98–595) days. The overall probability of falls was 28.8% and 50.2% at years 1 and 3; the probability of injurious falls was 9.1% and 16.3%. We derived a predictive model for falls. The FallSSS score (prior falls, chair-stands, sodium, and SF-8) had an AUROC for injurious falls at 6- and 12-months of 0.79 and 0.81 while MELD-Na’s AUROC was 0.57 for both. Adjusting for baseline Child class, MELD-Na, albumin level, disability status, and comorbidities, both incident falls – sHR 2.91 95%CI(1.55–5.44) – and HE – sHR 4.36 95%CI(2.33–8.53) – were strongly and independently associated with mortality.
Conclusion Our prospective study of patients with cirrhosis without a baseline history of HE demonstrates that falls are common, morbid, and predictable. These data highlight both the value of expanding screening to patients with cirrhosis and the potential for benefit in studies of interventions to address fall-risk in this vulnerable population.

Introduction/Background While calorie restriction (CR) is the gold standard for interventions that prolong mammalian lifespan and health span, 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 that lower consumption of dietary protein is associated with longevity and health in humans. Our lab has found that the branched-chain amino acids (BCAAs) are key mediators of metabolic health and longevity, with restriction of all three or specific BCAAs promoting metabolic health, fitness, and lifespan in mice. We and others have also determined that dietary BCAAs are negatively associated with metabolic health in humans.

While there are many factors and theories on what makes a healthy diet, including macronutrient distribution, fiber, micronutrient density, and more, our lab’s research suggests that low protein and/or low BCAA diets could promote metabolic health and slow the aging process, preventing or delaying age-related diseases.

Objective(s) To determine the average intake of BCAA and protein for Americans from a wide variety of diets.

Methods Here, we utilize Food Processor software to analyze 10 different diets for total protein and BCAA content. These diets include the DASH diet, Mediterranean, Atkins, Ketogenic, Japanese, Vegetarian, Vegan, MIND diet, and the Western/American diet. For each diet, an easily accessible meal plan was found online and entered into Food Processor using the USDA database. Each meal plan provided 7 days’ worth of meals, and each included at least a breakfast, lunch, and dinner. For the Western/American diet, food data was extracted from the What We Eat in America (NHANES) survey. Each diet was adjusted to provide 2000 calories per day. Using the average body weight of male and female Americans from CDC data, we calculated the RDA for protein and BCAA for both sexes, as the RDA for both are based on body weight. We then compared the protein and BCAA provided by each diet with the average RDA. We then developed a custom low BCAA diet using widely available foods.
Results Surprisingly, we find that many popular therapeutic and fad diets can provide between 200–435% of the Recommended Dietary Allowance (RDA) for individual (not shown) and total BCAAs, suggesting that these diets may not be optimal for metabolic health. These diets range from 14 to 26% of protein from BCAA.

Conclusion Many therapeutic and fad diets consumed in the United States emphasize protein and therefore BCAA. Except for vegan and vegetarian diets, the diets examined here generally exceed the RDA for BCAA and protein, which have been associated with increased BMI and decreased metabolic health.

There are a few limitations to this study. For example, only 7 days of meal information was collected, so there is a chance that actual BCAA and protein provided on these diets is different. Secondly, this study only examined protein and calories, leaving many other dietary components out of the analysis. It is also important to note that food composition is variable based on season and location of harvest but using the Food Processor software gives our best approximation of dietary composition.

Our Results suggest that it should be possible for many persons to reduce their BCAA content while remaining at or above the RDA (for both BCAA and total protein), and we hypothesize that such a diet would promote metabolic health and lifespan. This diet could be easier to adhere to than other CR diets. Finally, such diets could be potentially be deployed in the therapeutic context to treat obesity and diabetes, though more research is needed.

Introduction/Background Pleural effusion is a common cause of hospital admission. Iatrogenic and traumatic etiologies occasionally give rise to pleural effusion. We present a rare case of bilothorax as a result of iatrogenic hepatobiliary fistula formation due to microwave ablation of hepatocellular carcinoma.

Case Presentation 71-year-old male with history of hepatocellular carcinoma status post locoregional therapy presented with right upper quadrant abdominal pain worse with inspiration and radiating to the right axilla for 2 days. Associated symptoms included nausea and loss of appetite. He had received 3 treatments with trans-arterial chemotherapy 2 years ago, and microwave ablation of a 2 cm lesion in segment 8 of the liver 2 weeks prior to presentation. Physical exam included normal vital signs, decreased breath sounds in the right lower lung, and right upper quadrant tenderness without any rebound tenderness. Chest X ray and CT of the chest, abdomen and pelvis demonstrated right loculated pleural effusion, and a defect extending from the liver ablation site, across the diaphragm and into the effusion, without abdominal ascites. A chest tube was placed, and 2L of bile colored fluid was removed. Pleural fluid analysis was negative for malignant cells; however, it was consistent with exudative pleural effusion and was positive for presence of bilirubin with pleural to serum bilirubin ratio >1. Hepatobiliary iminodiacetic (HIDA) scan showed a hepatobiliary fistula originating at the percutaneous hepatic entrance site used for the microwave ablation. Subsequently, he underwent sphincterotomy and received a biliary stent placement via endoscopic retrograde pancreatobilio-angiography (ERCP) in order to decrease output through the fistula by decreasing the pressure gradient across the sphincter of oddi.

Discussion Bilothorax is an extremely rare cause of exudative pleural effusion, usually occurring from a connection between the biliary system and the pleural space through the diaphragm, or in some cases via spread through the muscular fibres in diaphragm with bilious peritonitis, or through disruption in the lymphatic system. When unilateral, the etiology points most likely to a traumatic or iatrogenic cause, such as...
in our case. While the first case was reported by Rowe in 1988 due to biliary pancreatitis, other rare etiologies include biliary obstruction, hydatid disease of the biliary tract, post ERCP and hepatic/subphrenic abscess. Less than 20 cases have been reported after the year 2000, and to our knowledge, our case represents the first case of bilothorax due to procedural complication of microwave ablation therapy of hepatocellular carcinoma. Thoracentesis with demonstration of bile in the pleural fluid, along with pleural fluid to serum bilirubin ratio of greater than 1 is highly suggestive of bilothorax. It is also imperative to establish the presence of a pathway leading the bile into the pleural space, which may be seen on CT, MRI, HIDA scan, cholecystography, or in some cases, laparotomy. Since bile is a good culture medium, patients can present with concurrent infection, leading to empyema with gastrointestinal pathogens including Escherichia coli and Enterobacter. The management of bilothorax consists of conservative and surgical measures. Non conservative measures shown to be useful are somatostatin analogs and low-fat diet, to decrease the production of bile. Surgical measures are focused on decompressing the biliary system with options including percutaneous drainage, biliary stenting, sphincterotomy and thoracostomy. Fistula closure is usually not attempted unless the above therapies fail to improve the patient’s condition and/or if there is formation of an abscess. In Conclusion, one should be aware of the possibility of bile causing pleural effusion, as the management of bilothorax differs from other more common causes of pleural effusion.

A RARE CASE OF ASYMPTOMATIC PANCREATITIS DUE TO ATEZOLIZUMAB, AN IMMUNE CHECKPOINT INHIBITOR
Natasha Chandler, Aapaar Dadlani, Sudeepthi Bandikatla, Endashaw Omer. University of Louisville

Introduction/Background Immune checkpoint inhibitors (ICPI) have changed the landscape of cancer treatment. They are used in the treatment of various types of cancers, including breast cancer, hepatocellular carcinoma, melanoma, metastatic non-small cell lung cancer, small cell lung cancer, and urothelial carcinoma. They are by far better tolerated than conventional chemotherapy. However, ICPI’s are notorious to cause autoimmune side-effects in any organ system due to their mechanism of increasing the activity of the immune system. The pancreas, however, is one of the rarely affected organs by ICPI. Atezolizumab is a PD-L1 inhibitor, part of the broad ICPI class. We present a case of asymptomatic pancreatitis diagnosed based on laboratory and radiological findings, resulting in discontinuation of atezolizumab.

Case Presentation We present a 54-year-old female with triple-negative grade 3 invasive ductal carcinoma of the breast, with metastasis to the lungs who underwent chemotherapy with paclitaxel/atezolizumab. She was due for cycle 3, day 8 of this therapy when she presented for a routine follow up evaluation without any symptoms. Physical exam significant for normal vitals (T 98.4°F, HR 96, RR 18, BP 118/81, SpO2 95%) and no epigastric tenderness. A routine CT abdomen was obtained for evaluation of metastasis. Interestingly, her pancreas showed minimal peripancreatic inflammatory changes consistent with acute pancreatitis (see images below). Lipase was 1109 units/L (normal 10–50), and amylase was 293 units/L (normal 28–100). A diagnosis was made based on positive biochemical and radiological findings. A complete pancreatitis workup including CBC, electrolytes, ALT (21 units/L), AST (22 units/L), bilirubin (0.4 mg/dL), TSH (3.28 uIU/mL) was negative. With the patient being on an ICPI, it was thought that this was drug-induced pancreatitis, and atezolizumab was discontinued to prevent progression to overt pancreatitis with its potentially serious complications. The patient was started on high dose steroid therapy with prednisone 1 mg/kg/day. The patient returned to clinic 2 weeks later when lipase decreased to 54 units/L and amylase decreased to 59 units/L. The patient was then
started on a prednisone taper and continued therapy off atezolizumab.

**Discussion** The introduction of ICPIs has been revolutionary with their utility in many malignancies. However, they come with multiple significant side effects, and gastrointestinal side effects of ICPI immunotherapy have become an increasingly studied topic. Our case highlights the occurrence of asymptomatic pancreatitis due to ICPI therapy. Asymptomatic lipase and amylase elevation with PD-1 inhibitors has been previously documented, with both being <5% for nivolumab (1). No such data is available for atezolizumab. Additionally, pancreatitis due to PD-1 inhibitors like nivolumab and pembrolizumab has been estimated to <2%, but <0.1% for atezolizumab (2). In patients on ICPI therapy presenting with pancreatitis, one should be vigilant of other causes as well, including alcoholism, gallstones, post-procedure, hypertriglyceridemia, etc. ICPI-induced pancreatitis may be acute or chronic, with the possibility of progression to secondary pancreatic insufficiency (3). Typically, a patient presenting with pancreatitis is managed with intravenous fluids and pain medications. The management of immune-related pancreatitis comprises of discontinuing the offending agent (atezolizumab in our case) and high dose steroid therapy (4). Steroid therapy should be extended to a slow taper to prevent relapse (3). Endocrine and exocrine pancreatic insufficiencies may occur after months of normalization of pancreatic enzymes (5). According to the Common Terminology Criteria for Adverse Events (CTCAE) guidelines, our case would classify as a grade 2 adverse event. According to the latest ASCO guidelines, ICPIs may be restarted once the toxicity recovers to grade 1 or less (4). In Conclusion, it is important for all physicians to keep ICPI-induced pancreatitis in the differential diagnosis of acute pancreatitis in patients on immunotherapy as this has a specific treatment.

**Genetic and Molecular Medicine**

3 **EXTRACELLULAR NICOTINAMIDE PHOSPHORIBOSYLTRANSFERASE (ENAMPT) NEUTRALIZATION PREVENTS AGGRESSIVE PROSTATE CANCER PROGRESSION**

Belinda L Sun, Lin Tang, Nancy Casanova, Alexander Garcia, Radu Oita, Amit Algotar, Xiaoguang Sun, Anne Cress, Joe Garcia. University of Arizona Health Sciences

**Introduction/Background** Prostate cancer (PCa) is the most common cancer in men with an urgent unmet need to prevent the aggressive progression of invasion and metastasis. We previously showed that secreted extracellular nicotinamide phosphoribosyltransferase (eNAMPT) is a multifunctional innate immunity regulator via TLR4 ligation which is highly implicated in PCa progression.

**Objective(s)** We investigate the role of eNAMPT in PCa progression and the therapeutic effects of anti-eNAMPT neutralizing antibodies in preventing aggressive PCa invasion and metastasis.

**Methods** PCa tumor NAMPT expression and plasma eNAMPT level were evaluated in human subjects with various PCa tumor stages and high risk subjects followed-up clinically for PCa. The genetic regulation of NAMPT expression in PCa cells and the role of eNAMPT in PCa invasion were investigated utilizing *in vitro* and *in vivo* models. The therapeutic effects of anti-eNAMPT neutralizing antibodies were evaluated in preclinical PCa orthotopic xenograft SCID mouse models.

**Results** Human extraprostastic-invasive PCa highly expressed NAMPT and released eNAMPT as significant elevation of plasma eNAMPT level detected in PCa subjects especially with extraprostastic-invasive PCa compared to subjects with organ-confined PCa. Plasma eNAMPT levels showed significant predictive value for diagnosing PCa and its invasion. NAMPT expression and eNAMPT secretion were highly upregulated in human PCa cells in response to hypoxia-inducible factors and EGFR.

**In vitro** cell culture and in vivo preclinical mouse model studies confirmed eNAMPT-mediated enhancement of PCa invasiveness into muscle tissues and dramatic attenuation of PCa invasion by weekly treatment with an eNAMPT-neutralizing polyclonal antibodies.

In preclinical PCa orthotopic xenograft models, peritoneal injection of eNAMPT-neutralizing monoclonal antibody cause significant tumor necrosis and markedly inhibit aggressive PCa cell local invasion in prostate, lymph node metastasis and distance organ metastasis.

**Conclusion** This study demonstrates that eNAMPT is a potential diagnostic and therapeutic biomarker for invasive PCa. Neutralization of eNAMPT by specific antibodies has high potential to be developed into effective therapeutics to prevent aggressive PCa invasion and metastasis.

**GENETIC APPROACHES TO TREAT VISION LOSS IN A MURINE MODEL OF ACADIAN USHER SYNDROME**

1Katelyn N Robillard, 1Bhagwat Alapure, 2Sanford Boye, 1Shannon Boye, 1Nicolas Bazan, 1Jennifer Lentz, 1Louisiana State University Health Sciences Center — New Orleans; 2University of Florida

**Introduction/Background** Usher syndrome Type 1C (USH1C) is an inherited deaf-blinding disease that affects Acadian populations in the United States and Canada. Specifically, the USH1C c.216G>A mutation encodes a truncated harmonin protein that disrupts photoreceptor and hair cell function. Antisense oligonucleotides targeting the 216A mutation transiently restore full-length harmonin in USH1C mice, which correlates with short-term improvements in hearing, vestibular, and visual function.

**Objective(s)** The goal of this study was to develop long-lasting therapies for vision loss in USH1C mice. We hypothesized that subretinal delivery of AAV vectors carrying the wild type Ush1c gene would increase full-length expression to improve retinal structure, function, and visual behavior in USH1C mice. Furthermore, we predicted that in vitro delivery of gene editing products would restore full-length Ush1c in mutant cells.

**Methods** An AAV vector co-expressing Ush1c-a1 and GFP was delivered via subretinal injection to USH1C mice at different postnatal (P) ages (P17, P22, P98). Transgene expression was determined by confocal scanning laser ophthalmoscopy (cSLO), immunohistochemistry (IHC), and polyacrylamide gel electrophoresis (PAGE). Changes in retinal structure, function, and visual behavior were assessed using optical coherence tomography (OCT), electroretinography (ERG), and a visual cliff assay, respectively. As an alternative approach, multiple
gene-editing systems targeting the 216A mutation were developed and introduced into 293T cells alongside an USH1C minigene or introduced into USH1C murine fibroblasts. Editing efficiency was determined by restriction fragment length polymorphism (RFLP) and sequencing analyses.

Results AAV-treated retinas showed increased full-length Ush1c mRNA and GFP fluorescence localized to the outer nuclear layer (ONL) and photoreceptor inner/outer segments (IS/OS) up to 6 months of age. Although cSLO showed GFP in approximately 20% of the fundus, these molecular changes did not correlate with improvements in retinal structure, function, or visual behavior. Multiple combinations of gene-editing plasmids yielded high rates of on-target editing (up to 46% in sorted 293T cells) with minimal off-target effects in the protospacer region.

Conclusion This study demonstrated successful AAV-mediated transgene expression in USH1C murine retina and successful gene editing of the human USH1C c.216G>A mutation, in vitro. Future studies will modify viral dose, Ush1c variant, gene promoter, and capsid structure to optimize long-term improvements in retinal structure, function, and visual behavior. We are currently optimizing the transfection protocol for murine fibroblasts to determine editing efficiency at the genomic 216A site.

Hematology and Oncology

8 MIR-1253 POTENTIATES CISPLATIN RESPONSE IN PEDIATRIC MEDULLOBLASTOMA BY REGULATING FERROPTOSIS

Sidharth Mahapatra, Ranjana Kanchan, Naveenkumar Perumal, Ishwor Thapa, Surinder K. Batra. University of Nebraska Medical Center; University of Omaha

Introduction/Background Among CNS tumors, medulloblastoma (MB) is the most common malignant pediatric brain tumor. Of the four subgroups, group 3 (G3MB) tumors fare the worst due to a high-risk phenotype characterized by c-Myc amplification and isochromosome 17q; frequent metastasis at presentation; and high recurrence. Haploinsufficiency of 17p13.3 is a hallmark of these high-risk tumors; included within this locus is miR-1253, which has tumor suppressive properties in medulloblastoma. Therapeutic strategies capitalizing on the anti-neoplastic properties of miRNAs can provide promising adjuncts that can improve efficacy while mitigating toxicity of current chemotherapeutic drugs.

Objective(s) In this study, we explored the chemosensitization properties of miR-1253 with respect to cisplatin cytotoxicity in group 3 MB.

Methods Using 2 classical group 3 MB cell lines, possessing c-Myc amplification and i17q, we first determined the IC_{50} of cisplatin in the presence of miR-1253 expression using MTT assay. Further delineating the potentiating effect of miR-1253 on cisplatin cytotoxicity, we studied colony formation, apoptosis and oxidative stress, as cisplatin is an inducer of both. To hone in on a mechanism for the effects noted in our functional studies, we used RNA Sequencing to isolate a putative target for miR-1253 that is upregulated in G3MB, has a poor prognostic profile, and is involved in iron balance. Confocal microscopy and FACs analyses were used to examine ROS generation and lipid peroxidation, as mediators of ferroptosis. Calein AM quenching, COX IV staining and multiple stains for iron were used to study mitochondrial vs. free cytosolic iron generation due to miR-1253 and cisplatin. Finally, ROS
and ferroptosis inhibitors were used to study effects on tumor cell rescue from miR-1253 and cisplatin therapy.

**Results** Overexpression of miR-1253 sensitized group 3 MB cell lines to cisplatin therapy, leading to a pronounced downregulation in cell viability, in colony formation and induction of apoptosis and oxidative stress. Cisplatin is reported as an inducer of both apoptosis and ferroptosis-mediated cancer cell death. *In silico* analysis revealed an upregulation of several ABC transporters in high-risk MB abstracts.

**Abstract 8 Figure 1** ABCB7, an iron transporter, is upregulated in group 3 medulloblastoma

(A) Heatmap depicting effect of miR-1253 on ABC transporter expression in vitro. (B) ABCB7 expression is high in G3MB tumor samples. (C) High ABCB7 expression is associated with poor overall survival. (D) Representative confocal images showing intense staining for ABCB7 in G3 tumor specimen. (E) In vitro expression of ABCB7 in classic medulloblastoma cell lines compared to normal human astrocytes (NHA). (F) Seed sequences on ABCB7 for miR-1253 binding

**Abstract 8 Figure 2** MiR-1253 inhibits ABCB7 and increases free iron within the cell

(A) MiR-1253 inhibits expression of ABCB7 and GPX4, key mediators of ferroptosis, in vitro in cancer cells. (B) Expression deregulation is demonstrable along the mitochondrial membrane (by COX IV staining) where ABCB7 is expressed. (C) Quenching of calcein AM, by free iron, is notable in miR-1253 treated tumor cells. (D) This effect is abrogated in the presence of an iron chelator, deferoxamine (DFO)

**Abstract 8 Figure 3** MiR-1253 induces ROS and lipid peroxidation in G3MB

(A) MiR-1253 induces oxidative stress, concurrently elevating superoxide and hydrogen peroxide species in vitro. (B) MiR-1253 also induces lipid peroxidation, a pre-requisite step for triggering ferroptosis

**Abstract 8 Figure 4** MiR-1253 potentiates cisplatin cytotoxicity in G3MB in vitro

(A) Determining the IC50 of cisplatin with miR-153 overexpression in classic G3MB cell lines. (B) Using the IC50 of ~5nM in HD2MB03 cells, colony formation experienced the highest reduction with concurrent treatment (miR+CIS). (C) Potentiation in apoptotic markers seen with concurrent treatment. (D) Highest induction in ROS-mediated and apoptotic cell death observed with concurrent treatment
Abstract 8 Figure 5 Effect of ROS and ferroptosis inhibitors on miR-1253 + cisplatin cytotoxicity

(A) The potentiated oxidative stress induced by concurrent treatment with cisplatin and miR-1253 is near-abrogated in the presence of a ferroptosis inhibitor, ferrostatin (Fer). (B) Effect of ferroptosis inhibition (Fer) or ROS inhibition (MeTAP) on tumor cell viability shows clear rescue of cells from the potentiated cytotoxic effects of cisplatin + miR-1253.

Conclusion

Tumors. When compared to cell lines overexpressing miR-1253, the ABC transporter ABCB7, which regulates both apoptosis and ferroptosis, was revealed as a putative target of miR-1253 with poor survival that may facilitate its chemosensitizing effects by modulating mitochondrial ROS and HIF1α-driven NFKB signaling. We observed high expression of ABCB7 and GPX4, ferroptosis regulators, in MB patients with poor overall survival. MiR-1253 inhibited expression of both ABCB7 and GPX4 in Group 3 MB cell lines and induced cytoplasmic ROS and mitochondrial O$_2^-$, suggesting ROS-mediated induction of ferroptosis through regulation of ABCB7 and GPX4. Treatment with ROS and ferroptosis inhibitors effectively rescued miR-1253 transfected cells treated with cisplatin.

Conclusion

Taken together, we conclude that miR-1253, by targeting ABCB7 and its partners, potentiates the cytotoxic effects of cisplatin by triggering iron imbalance, inducing ROS and augmenting ferroptosis.
reactions with their alpha, beta-unsaturated carbonyl. cyPGs regulate the inflammatory response by interfering with NF-kappaB, AP-1, MAPK, and JAK/STAT signaling pathways, via both a group of nuclear receptor proliferator-activated receptor gamma dependent and independent mechanisms. cyPGs are not impartial to cell type as they can exert anti-inflammatory effects in various ways depending on the type of cell. The concentration of cyPGs and time of exposure to cyclopentenone have effects.

Conclusion Cyclopentenones are lipids derived from arachidonic acid that can influence different types of cells in various ways. They exert anti-inflammatory effects in various ways depending on type of cell, concentration of cyPG, and time of exposure. Further research on outcomes based on specific concentrations should be done. This information could impact how inflammation is treated.

Abstract 10 Figure 1  PPAR-γ dependent Cyclopentenones anti-inflammatory modes of action
Once 15d-PGJ2 binds to PPAR-γ, the protein binds to RXR; the complex enters the nucleus. The complex blocks transcription factors AP-1 and NF-κB, thereby inhibiting transcription of genes involved in tumorigenic, proinflammatory, angiogenic/metastatic/fibrosis, and oxidative stress

Abstract 10 Figure 2  Biosynthesis of cyclopentenones and modes of action
When the cell is activated by stressful stimuli, such as mechanical trauma, interferon, interleukin, or growth factors, the enzyme phospholipase A2 is moved from the cytoplasm to intracellular membranes to liberate arachidonic acid from the nuclear envelope or endoplasmic reticulum. AA is converted by COX-1 or COX-2 to PGG2, followed by hydroperoxidation of PGG2 to PGH2. PGH2 is converted to other PGH2 metabolites such as PGD2, PGE2, PGF2, PGI2, and TXA2 by their respective synthases. Of the metabolites, PGD2 is dehydrated to form J2 PGs. PGJ2 may be located to exosomes, transport systems, or nuclear receptors to execute its function. PGE2 is dehydrated to form PGA2. PGA1 is a metabolite of linoleic acid, which is obtained through diet.

Abstracts

A RARE CASE OF ANORECTAL MUCOSAL MELANOMA
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Introduction/Background Anorectal melanoma (AM) is a rare aggressive type of mucosal melanoma. AM accounts for approximately 1% of all melanomas and 20% of mucosal melanomas. Mucosal melanomas in general have lower five-year survival compared to cutaneous or ocular melanoma. Standard of care for management is unclear but the usual approach is surgical resection during early stage. Systemic treatment options for metastatic disease include immuno-therapy, targeted therapy with KIT, BRAF and angiogenesis inhibitors. Here we report a rare case of anorectal melanoma.

Case Presentation The patient is a 46-year-old man with a history of Hepatitis C, opiate dependence and cigarette smoking. He presented to his primary care physician for worsening rectal pain, rectal bleeding and constipation for over 3 months. He had never had colonoscopy and had no history of anal intercourse. His HIV testing was negative.

A colonoscopy showed a large 6 x 7 cm pedunculated necrotic fungating mass arising from the anorectal area. Biopsy of the mass showed malignant infiltrating cells in an organoid pattern with abundant intra- and extracellular brown pigment, large nuclei with coarse chromatin and prominent nucleoli, abundant eosinophilic cytoplasm, and conspicuous atypical mitoses. Immunohistochemistry was positive for HMB-45 and Melan-A, and negative for CDX-2 and GATA3. Histopathological findings were consistent with anal mucosal melanoma. CT of the chest, abdomen, and pelvis showed a polypoid lesion in the right lateral bladder wall as well as enlarged right inguinal lymph nodes, the largest one measuring about 22 mm in size. Otherwise there was no evidence of distant metastasis.

Cystoscopy showed a papillary bladder tumor; biopsy of this mass was consistent with malignant melanoma with histopathologic findings similar to those of the anal mass. A PET scan found an area of increased uptake in the left lower pelvis adjacent to the sigmoid colon measuring about 1.2 cm, multiple enlarged lymph nodes in the right groin. The largest lymph node measured about 2.3 cm and with an adjacent node measuring 2.1 cm. Otherwise there was no evidence of distant metastasis.
He was treated with ipilimumab 3 mg/kg and nivolimumab 1 mg/kg 3 times weekly for 4 cycles. He developed Grade 3 immune hepatitis with elevation of AST, ALT, bilirubin and PT. He completed a six-week steroid taper after which his liver enzymes normalized. Throughout the course of immunotherapy, a significant regression of the anal melanotic anal mass was noted.

Post treatment PET scan done 6 months from the date of diagnosis showed increased activity in the pelvic mass area and new PET activity in right lobe of the liver and right lung consistent with progression of disease. Analysis of the melanoma was positive for C-KIT gene Exon 11 (C.1727T>C, p. Leu576Pro) and negative for NRAS and BRAF. Based on this he was initiated on imatinib 400 mg bid, which he has now been on for the past three months.

Discussion Anorectal melanoma is rare subtype of mucosal melanoma, and very little is understood about its pathogenesis. Some theories suggest AM originates from intestinal Schwann cells versus neural crest cells during embryogenesis. Clinical presentation of AM can be similar to rectal carcinoma and presenting symptoms can range from anal pain, mass lesion, bleeding and rectal fullness. Amelanotic AM lesions can masquerade as rectal adenocarcinoma. Biopsy with Immunohistochemistry positive for S-100, HMB-45 or Melanin A can confirm the diagnosis. KIT mutation reported in 35.5% of anorectal melanomas. BRAF gene mutation occurs less often in AM than in cutaneous melanomas.

AM is often diagnosed in advanced stages, which along with the aggressive nature of disease is a reason for the generally poor prognosis. PET/CT scan is the preferred modality for staging of AM. In the absence of randomized trials, there is no universally recommended treatment strategy to date. In early stages surgical resection techniques include abdominoperineal resection (APR), wide local excision (WLE) and endoscopic mucosal resection (EMR). Studies with small sample sizes demonstrated no survival differences between WLE and APR. The choice of the optimal surgery technique is focused on minimizing surgical morbidity and complications.

High dose interferon as adjuvant treatment of patients with node positive disease has been shown to have overall survival benefit. In metastatic disease, several treatments strategies have been explored. Interleukin-2 (IL-2) combination therapies have high response rates but no overall survival benefit. Traditional chemotherapeutic agents like temozolamide, dacarbazine and paclitaxel alone or in combination with high dose interferon or IL-2 have response rates of 10–20%. Several KIT inhibitors like imatinib, dasatinib, sunitinib and sorafenib have been
studied with good responses but mixed survival. BRAF mutations can occur in 50% of AM patients. In those patients BRAF inhibitors have shown increased progression free survival and overall survival. Immunological checkpoint blockage with CTLA-4 antibodies like ipilimumab and PD-L1 inhibitors like nivolumab or pembrolizumab have shown responses in smaller studies. Despite the many available treatment options, the prognosis of AM remains poor, with 5-year survival rates less than 20%.

In Conclusion AM is a subtype of mucosal melanoma which differs biologically from cutaneous melanoma and has a poorer prognosis. Management of AM is often translated from cutaneous melanoma despite those biological differences due to paucity of evidence. When feasible, AM should be managed in a high volume center with a multidisciplinary care team and access to clinical trials. Future research to understand the biology, genetics, and prognostic factors will help develop effective treatments.

17 Diffuse Alveolar Hemorrhage as a Rare Complication of Severe Atypical Hemolytic Uremic Syndrome

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Introduction/Background Atypical hemolytic uremic syndrome (aHUS) is a rare type of thrombotic microangiopathy (TMA) that presents as a triad of microangiopathic hemolytic anemia, thrombocytopenia, and renal impairment. Pathogenesis is found to be due to dysregulation of alternative complement pathway and in some cases, due to mutations in the diacylglycerol kinase ε gene. Extra-renal organ injury may be seen in a significant proportion of these patients but pulmonary involvement such as diffuse alveolar hemorrhage (DAH) is an extremely rare complication. DAH has a multitude of etiologies and early recognition and treatment of its underlying etiology will help prevent further lung injury and other life-threatening complications.

Case Presentation A 40-year-old male with chronic kidney disease and hypertension was admitted to the hospital with hypertensive emergency. Presenting symptoms were dyspnea, a small amount of hemoptysis, and abdominal pain. On admission, he was found to have thrombocytopenia of 92,000/mcL which declined the next day to 33,000/mcL, hemoglobin of 13.8 g/dL which decreased to 6.5 g/dL in 2 days, and WBC at 16,000/mcL which remained stable. LDH was 766 units/L (ref: 100–242 units/L), reticulocytes 4.3% and haptoglobin <15 mg/dL. Peripheral blood smear showed at least 5 schistocytes/hpf [Image A]. A clinical diagnosis of TMA was made. Additional lab work showed creatinine 5.0 mg/dL and ADAMTS13 activity 41% (ref: >10%). Fibrinogen, thrombin time, PTT were in the normal range, PT slightly prolonged to 11.6 seconds. Lupus anticoagulant and ANA were negative and complement C3 and C4 were in the normal range. HIV, hepatitis B, and C were nonreactive.

Patient was emergently started on therapeutic plasma exchange (PLEX) and high dose steroids for treatment of TMA. Platelets and LDH improved with 2 days of PLEX but the kidney function did not improve, and he had to be started on hemodialysis. Hospital course was complicated by clinical decompensation with frank hemoptysis with increasing oxygen requirements and down trending hemoglobin levels. CT chest showed features suggestive of diffuse alveolar hemorrhage (DAH) [Image B]. Bronchoscopy was deferred as the patient was already on high-dose steroids for TMA which would be the treatment for DAH. Anti-proteinase 3 Abs, C-ANCA, P-ANCA, Atypical pANCA, anti-glomerular BM antibodies were negative. Notably, pulmonary involvement has been described with aHUS but is not known to occur as a complication of TTP. By day 3 of PLEX, therefore, the leading diagnosis was aHUS. TTP was thought to be unlikely given sub-optimal response to PLEX, degree of renal injury, involvement of the lungs, ADAMTS13>10% and platelet count >30,000/mcL. As a result, the patient’s treatment was changed to eculizumab. He was conservatively managed in ICU for one day and remained stable with no more episodes of frank hemoptysis. Over the next 6 months of outpatient treatment with eculizumab, hemodialysis, and antihypertensive medications, his platelet levels increased to normal range. He did not report subsequent episodes of hemoptysis. Atypical HUS gene panel was tested and did not identify disease-associated mutations but reported few possible ‘benign’ mutations or ‘variants of unknown significance’.

Abstract 17 Figure 1 Peripheral smear
Peripheral smear showing schistocytes
Abstract 17 Figure 2  CT chest
Diffuse confluent ground-glass airspace opacities involving upper and lower lungs bilaterally suggestive of diffuse alveolar hemorrhage

Discussion aHUS is a form of TMA which, in the absence of rapid institution of appropriate therapy, is associated with poor clinical outcomes. It predominantly affects the kidneys but has the potential to cause multi-organ dysfunction. Pulmonary hemorrhage is a rare but life-threatening complication of aHUS. It is not known to occur in TTP. Mechanism of DAH in such patients is unclear; however, thrombocytopenia and thrombi formation in pulmonary vasculature are thought to be contributing factors.

aHUS is suspected based on presence of thrombocytopenia, abnormal hemolytic markers, schistocytes on peripheral blood smear, and one or more of the following: neurological, gastrointestinal or renal impairment. Once TMA is suspected, empiric therapy with PLEX should be started immediately to prevent end-organ damage. However, distinction should be made early between different types of TMA due to different pathophysiology and therapy. Reports show that empiric PLEX in patients with aHUS is unsatisfactory and poses risk for ESRD and premature death. Eculizumab, a humanized monoclonal antibody targeted against complement C5; terminal complement inhibitor, is the current recommended and FDA-approved treatment for primary aHUS which has shown to drastically improve the prognosis of this disease. Studies have additionally demonstrated that immediate rather than delayed treatment with eculizumab in aHUS patients leads to better outcomes. In Conclusion, aHUS with DAH is rare but it is important to include aHUS as a differential in pulmonary-renal syndromes as timely diagnosis of aHUS and treatment with eculizumab is imperative to prevent morbidity and mortality.

Introduction/Background Small cell carcinoma (SmCC) is an aggressive neoplasm typically found in the lung, the majority of which is associated with a longstanding history of smoking. Extrapulmonary SmCC is very rare, comprising only 2.5 to 5% of all cases. These are found in the larynx, nasal cavity, sinuses, oral cavity, esophagus, and parotid gland.4–5 Salivary gland SmCC is particularly rare, comprising no more than 10% of all extrapulmonary SmCC, with only a few case reports published to date. These salivary gland SmCCs are particularly aggressive and often present in the advanced stage. Here we describe a case of an elderly male with an extrapulmonary small cell carcinoma of the parotid gland.

Case Presentation The patient is an 89 year-old male who presented to his primary care provider with a left neck mass that was non-tender. He denied any weight loss or fever. He had a history of chewing tobacco but not of smoking. On physical exam, it was a 2 cm firm mass that was fixed. He had an ultrasound which showed a hypoechoic macrolobulated solid nodule with some vascular flow. CT of the neck with contrast showed an enhancing septate mass as seen in figure 3. He underwent ultrasound guided biopsy with histology which showed SmCC as seen in figures 1–2.

Immunochemistry stain was positive for synaptophysin, chromogranin, and CD 56. It was focally positive as perinuclear dot like for CK20 and CAM 5.2 but negative for TTF-1. Preoperative PET scan showed no metastatic disease. He then had a left parotidectomy, but the inked margin was positive for carcinoma; 3 lymph nodes were negative for carcinoma. He declined chemotherapy at that time but opted for radiation.

Prognostic factors for salivary gland SmCC involve the size (< 3 cm) and type and number of neuroendocrine markers (> 4).5 Our patient’s tumor was only 2 cm and had only three neuroendocrine markers present, both of which are suggestive of a more favorable outcome.

5 months after radiation, his PET scan showed that the hypermetabolic spots of the left neck were surgically absent; however, he had metastases noted of the left thoracic inlet, both hilum, and right axilla. At that time, options of palliative chemotherapy with carboplatin+etoposide versus supportive care were discussed. Patient and his family choose to go with best supportive care. He eventually succumbed in the next month.

Discussion Salivary gland SmCC is classified under extrapulmonary SmCC originating from head and neck and are rare, aggressive neoplasm. In a recently published SEER review, the average age of presentation was 72.6 ± 12.4 and the male to female ratio was 3.4:1. To be considered neuroendocrine, an immunohistochemistry stain has to be positive for at least one of the following markers: synaptophysin, chromogranin, CD56 neutral cell adhesion molecule, CD57, and neuron specific enolase.4–6 Our patient’s tumor was only 2 cm and had only three neuroendocrine markers present, both of which are suggestive of a more favorable outcome.

Current treatments vary between surgery, radiation, chemotherapy, or a combination of any of the above. Surgery may include surgical removal of the lesion, an expanded resection, or a modified neck dissection on the same side of the lesion, but surgery is associated with a 75% chance of recurrence.5
Our patient underwent surgery followed by radiation, which has a local recurrence rate of just 20%. It has also been shown that surgery followed by radiation improves survival.8 Patients who received chemotherapy had significantly longer overall survival time than those without chemotherapy (28.0 months vs 20 months; P=0.04). Chemotherapy is often offered for poorly differentiated types, generally as a platinum-based type like cisplatin in combination with etoposide.4

The survival analysis demonstrated that old age (>72 years), lymph node (N3) and distant metastases were independent factors for poor survival, whereas radiotherapy was an independent factor for favorable survival. With limited data available, local tumors are generally treated with surgery followed by adjuvant chemotherapy. Though no studies have been done, a chemotherapy combination of cisplatin or carboplatin with etoposide appears to be commonly used. To date, there is no evidence for using immunotherapy in salivary gland SmCC.

With its aggressive nature, SmCC of the parotid gland often leads to metastases due to the abundance of lymph nodes located near the parotid gland.9 Our patient was negative for TTF-1 which excluded the lung as a primary site. The first PET scan only showed hypermetabolic activity within

Abstract 18 Figure 1  H & E stain
H&E stain: Small cell carcinoma. Medium sized hyperchromatic cells with scant cytoplasm and molding

Abstract 18 Figure 2  Immunohistochemistry stain
Positive synaptophysin IHC

Abstract 18 Figure 3  Head CT scan
CT soft tissue neck showing left parotid gland is prominent, and there are 2 enhancing septate mass is seen in the left parotid gland. One measures about 18 mm size, and the second measures about 26 x 19 x 20 mm size

Abstract 18 Figure 4  PET scan
PET scan: Hypermetabolic activity of left parotid gland
the left side of the neck. However, repeat PET scan after surgery and radiation showed metastases.

Since small cell carcinoma of the parotid is rare, accurate diagnosis needs to be made by immunochemistry stain in order to determine its etiology for treatment options before metastases occur.

Introduction/Background Lymphomas are classified into Hodgkin and non-Hodgkin subtypes. A common region for lymphomas is the head and neck region; however, the nasopharynx is a rare location for a primary Hodgkin and non-Hodgkin Lymphoma. The majority of non-Hodgkin lymphomas (NHL) reported in the nasopharynx were diffuse large B cell lymphoma (DLBCL). However, we present a rare case of nasopharyngeal mantle cell lymphoma (MCL) presenting at an early stage. Nasopharyngeal mantle cell lymphoma (MCL) is rare, and only a few cases are reported in the literature.

Case Presentation A 77-year-old man presented with right-sided ear fullness and pressure with difficulty hearing. He denied fatigue, fever, and weight loss. On otoscopic examination, the right tympanic membrane was dull with effusion. There was no cervical lymphadenopathy, lymphadenopathy of other chains, or other significant exam findings. Oral examination showed no tonsillar enlargement. Throughout the period of his complaints, he was treated with fluticasone for one month and later with a myringotomy tube to manage a diagnosis of Eustachian tube dysfunction. However, the symptoms of hearing loss, ear fullness, and pressure were not relieved.

The patient underwent nasopharyngoscopy, which revealed a smooth mass extending from the superior choanal cavity into the posterior nasal cavity, with no ulceration. A transnasal endoscopic biopsy from the nasopharyngeal mass was done. Histopathological exam and immunochemical staining revealed CD5 positive B cell lymphoma. A consequent Cyclin D1 stain was positive, confirming a diagnosis of Mantle cell lymphoma (MCL). A standard treatment protocol does not exist as MCL is a rare entity.

Discussion MCL, an aggressive mature B-cell non-Hodgkin lymphoma (NHL), is one of the rare subtypes of NHL. Patients with MCL have multiple variable clinical presentations but they usually present with lymphadenopathy, splenomegaly, and bone marrow infiltration, as well as gastrointestinal involvement. The stage of MCL at presentation is usually 3 or 4. When MCL presents itself as an in-situ tumor, it is considered an indolent lymphoma.

The cytogenetics behind MCL is a t (11;14) chromosomal translocation, which Results in overexpression of Cyclin D1 early during the course MCL. There are other less frequent subtypes of MCL that encode cyclin D2 and D3 and lead to their overexpression; however, these subtypes lack the t(11;14) translocation. A biopsy from the affected lymph node, tissue, or bone marrow is used to diagnose MCL. Relapse is extremely common in MCL, and patients who relapse have a low response to therapy and a poor prognosis.

Our case reports a patient presenting with an early stage MCL, an uncommon occurrence. A Standard approach to manage early MCL presentations is not available, but radiation therapy is considered appropriate management for localized disease. A combined modality therapy is also appropriate.

As MCL is a disease with variable presentations, varying stages at presentations, and varying locations, the treatment strategies vary as well. MCL is still an incurable disease despite the recent progress that led to advancement in patients’ clinical outcomes. Early-stage MCL has no standardized therapeutic approach.

Therapies of MCL depend on the patient's age, fitness at presentations, and symptoms at diagnosis. Therapy is usually aggressive, with most patients receiving a combination of rituximab along with chemotherapy, such as R-CHOP. However, it’s acceptable to defer therapy in a fraction of patients with indolent MCL and manage them temporarily with careful observation without compromising their long-term prognosis. However, all patients with MCL require therapy.

A standard treatment protocol does not exist as MCL is a rare entity. Previously it was believed that early diagnosis and treatment are important to improve survival, but an individualized approach tailored to a patient’s age, fitness, and symptoms is more appropriate. Deferring treatment in a subset of patients is appropriate. More future advances are warranted to continue to study targeted therapies and individualized approaches to this heterogeneous disease.

REFERENCES
AN UNCOMMON CAUSE OF HEMORRHAGIC SHOCK AND LIVER MASS IN CIRRHOSIS

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Introduction/Background

Primary hepatic angiosarcoma (PHA) is rare, representing less than 1 percent of primary liver malignancies. In contrast, hepatocellular carcinoma accounts for 85 percent of all primary liver malignancies and develops in up to one-third of patients with cirrhosis. Here, we report a case of PHA, which is an uncommon cause of hemorrhagic shock and liver mass in cirrhosis.

Case Presentation

A 70 year-old man with severe heart failure, prior ventricular arrhythmia resulting in internal cardiac defibrillator, atrial fibrillation on anti-coagulation, and cirrhosis was admitted for undifferentiated shock. He reported fevers, abdominal pain, nausea, and lightheadedness. Upon presentation, the patient was hypotensive. Laboratory Results demonstrated leukocytosis, new anemia (hemoglobin 7 mg/dL), elevated lactate, and elevated brain natriuretic peptide. Initial chest and abdominal radiography were unrevealing. The patient was resuscitated with intravenous fluids and packed red blood cells, was started empirically on broad-spectrum anti-microbial agents, and briefly required norepinephrine for refractory hypotension. Workup for a cardiogenic cause of the patient's shock state was unrevealing. Computed tomography (CT) of the chest demonstrated a pulmonary infiltrate, which was concerning for community acquired pneumonia, resulting in septic shock. The patient continued to report abdominal pain, so CT of the abdomen was obtained. This demonstrated extensive infiltrative, hypervascular, and necrotic hepatic lesions (figure 1) with hepatic capsule rupture and hemoperitoneum. Diagnostic paracentesis confirmed hemoperitoneum. Due to ongoing blood loss, hepatic artery embolization was completed (figure 2). The patient's hemoglobin subsequently stabilized. Pathology was obtained and demonstrated PHA (figures 3 and 4). Due to poor functional status and advanced...
malignancy, the patient was not a candidate for systemic chemotherapy. Thus, he elected to enroll in hospice and died two weeks after discharge.

Discussion PHA is a highly vascular malignancy, which arises from endothelial cells and fibroblasts. Exposure to carcinogenic substances, specifically vinyl chloride and arsenic, is one of the few established risk factors for PHA development. Clinical presentation is highly variable, ranging from absence of symptoms to fulminant hepatic failure or, as in this case, hemorrhagic shock. Diagnosis remains challenging due to the rare nature of the disease, non-specific clinical presentation, lack of serum tumor markers, and non-specific radiographic findings. PHA is associated with a poor prognosis, with an overall survival of approximately 5 months after diagnosis. Though surgical resection is considered curative, less than 20 percent of PHA's are amenable to resection due to advanced disease at time of diagnosis. Palliative treatments include systemic chemotherapy and trans-arterial chemoembolization. Liver transplantation is contraindicated in all PHA cases due to high risk of tumor reoccurrence and rapid progression of recurrent disease. Due to the hypervascular nature of PHA, tumor rupture is a common complication, leading to hemorrhagic shock and death in approximately 25 percent of patients.

Infectious disease

24 DYNAMIC STRATIFICATION OF DISEASE SEVERITY AND PROGNOSIS OF HOSPITALIZED COVID-19 PATIENTS USING HIDDEN MARKOV MODEL

Introduction/Background Risk factors such as obesity or age >80 is highly correlated with adverse outcomes in COVID-19 patients. The effects of individual patient characteristics (e.g., demographics and comorbidities) on disease progression, and how the relative risk of an adverse outcome changes over the course of a patient’s hospitalization, are not well characterized. A better understanding of how individual characteristics influence not just the final outcome, but the full patient trajectory, could lead to better care and improved patient outcomes.

Objective(s) To investigate the impact of demographics and comorbidities on the disease progression of hospitalized SARS-CoV-2 positive patients and to demonstrate the utility of probabilistic machine learning in providing dynamic stratification of disease severity and prognosis.

Methods A retrospective study was performed using electronic health records (EHRs) from patients in the largest health care system in northwest Ohio and southeastern Michigan (ProMedica health system). The patient data in this study corresponds to patients who had 1) a positive nasopharyngeal PCR test for SARS-CoV-2 between 03/20/2020 and 12/29/2020, and 2) were admitted to the hospital shortly before or after the positive result. A total of 1362 patients met these criteria. Demographic information of these patients (e.g., age, race, social determinants of health), as well as the history of 5 vital signs and 10 laboratory test Results collected throughout the hospitalization were used to train a covariate-dependent, continuous-time hidden Markov model (ct-HMM) with 4 states: discharge, moderate-illness, severe-illness, death. The ability of the ct-HMM to predict patient risk was examined by plotting calibration curves and calculating the Brier score. The relevance of the different patient features for risk prediction was analyzed by performing an ablation study.

Results Given a patient’s unique demographics and comorbidities, the covariate-dependent ct-HMM is capable of computing the probability of being in a moderate or severe disease state at any future time. This allows patient-specific risk forecasting. Figure 1 and figure 2 show examples of these predictive probabilities for various demographic groups when it is assumed the underlying disease state is known. Of note in Figure 1 are the significant differences in disease burden forecasts between male and female patients. For example, when starting from a moderate disease state, male patients are more likely to end up in the death state, regardless of insurance status. However, when starting from a severe illness state this discrepancy vanishes. In fact, uninsured females in the severe illness state are more likely to end up in the death state than their male counterparts. Also note that there is a much more pronounced difference in forecasted outcomes between the moderate and severe illness states for uninsured patients compared to the insured patients. Figure 2 shows the impact on race (Black versus White) on patient risk forecasts. As has been widely reported in numerous other studies, Figure 2 shows that Black patients have slightly higher risk of death compared to White patients. However, it is interesting to observe that the difference of risk for insured versus uninsured patients is more pronounced when a patient (irrespective of race) is in the moderate disease state. The difference in risk for insured versus uninsured patients reduces significantly when a patient is in the severe disease state.

Because the disease burden states are latent variables in our model, they are never known with complete certainty. However, given observed data (vital measurements and lab Results), maximum a posteriori (MAP) estimates of the latent disease burden state can easily be computed. To validate the inferred
disease states, the posterior predictive probability (PPP) of ending up in the death state was taken as a forecast of the final state of the patient. The calibration of the model was estimated by comparing the PPPs over all patients at all observation times. The PPP forecasts were run on 10 random 60%/40% train/test splits of the entire data. The range of PPPs was between 0.01 and 0.61. For PPPs between 0.3 and 0.5, which accounted for the majority of PPPs in each test set, the mean forecast was consistent with observed frequency of deaths for patients with PPPs in that range. The model tended to slightly overestimate the risk of death outside this range. The mean (variance) of the Brier scores over the ten train/test splits was 0.1454 (1.282 × 10⁻⁵).

Conclusion This study provides evidence that a simple ct-HMM is able to capture the main temporal dynamics of hospitalized COVID-19 patients, while at the same time providing simple metrics that can be used as indicators of patient risk. Compared to many reported studies which ignore the temporal progression of disease in their analyses, the current study provides a unique modeling-based approach on the progression of COVID-19. The proposed approach performs risk forecasting and stratification based on the full patient trajectory and serves as an exploratory tool for generating novel clinical hypothesis.

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Introduction/Background As the number of COVID-19 cases surges in the United States, health care facility resources are strained to capacity. Hence it is critical at the first encounter with a COVID-19 patient as evidenced by a positive nasopharyngeal PCR test for SARS-CoV-2, to determine whether hospitalization is required, or outpatient treatment can be utilized without risk of deterioration or increased morbidity and mortality using readily available demographic information, co-morbidities and available biomarkers (vitals and laboratory Results). With the increasing availability of Electronic Health records (EHR) of hospitalized COVID-19 patients, machine learning (ML) based decision support systems for patients with COVID19 triaged at the point of contact with the health care system is a promising solution which has been explored extensively in the recent literature. However, for wide-spread adaptability of such ML based systems, two fundamental challenges remain. First, to gain the confidence of health care providers, clinical interpretability of the ML algorithms is crucial. Second, the cost as well as accessibility of various laboratory tests vary substantially across different facilities as well as across geographic locations. Hence accounting for general test availability and costs in the ML based decision tool is also critical.

Objective(s) On this background we sought to 1) develop a machine learning (ML) based approach for predicting adverse outcomes, such as the need for mechanical ventilation or death based on demographic information, co-morbidities and biomarkers collected close to the date of a positive PCR test; 2) gain insight into the decision-making process of the ML algorithm based on interpretable ML tools such as SHAPley values; and 3) identify and account for unequal costs of clinical features in the ML based decision support system by finding the optimal set of biomarkers that Results in the highest utility under a given cost structure.
Methods A retrospective study was performed using electronic health records (EHRs) from patients in the largest health care system in northwest Ohio and southeastern Michigan (ProMedica Health System). The patient data used in this study corresponds to patients who 1) had a positive nasopharyngeal PCR test for SARS-CoV-2 between 03/20/2020 and 12/29/2020, and 2) were admitted to the hospital shortly before or after the positive result. A total of 1312 patients met these criteria. Demographics (e.g., age, race, co-morbidities, insurance status), vitals and a wide range of lab tests available within 3 days of a first positive PCR test were used to train machine learning models to predict a patient’s risk of adverse outcomes, namely, composite ventilation and death. Extensive hyperparameter search was carried out with cross-validation to find best model parameters and avoid overfitting. Model performance was evaluated with Average Precision and AUC ROC. Moreover, game theoretic SHAPley values were used to gain clinical insight and validation of the feature attributions of the ML models. The best set of features under a budget constraint was optimized via exhaustive search across all combinations of features. Naively iterating through the possible permutations of features would result in intractable

Abstract 25 Figure 1  Top 30 most important features for predicting composite ventilation. The higher the SHAPley value, the higher the influence of that feature on the prediction task. The top 5 attributing features are Procalcitonin, Pulse Oximetry, Age, CRP and Calcium. Mean feature importance is calculated by averaging individual feature importance across 5 test data splits

Abstract 25 Table 1  Adverse outcome prediction performance at the point of entry for the various ML models in terms of Average Precision (AP) and AUC ROC. Missing values are imputed using the best strategies out of Mean, Median, MICE, as supported by cross-validation Results for each model/target

<table>
<thead>
<tr>
<th>Model</th>
<th>Target</th>
<th>AP mean [std]</th>
<th>AUC ROC mean [std]</th>
</tr>
</thead>
<tbody>
<tr>
<td>XGBoost</td>
<td>Composite Ventilation</td>
<td>0.377 [0.070]</td>
<td>0.724 [0.049]</td>
</tr>
<tr>
<td>Random Forest</td>
<td>Composite Ventilation</td>
<td>0.326 [0.039]</td>
<td>0.670 [0.041]</td>
</tr>
<tr>
<td>Gaussian Process</td>
<td>Composite Ventilation</td>
<td>0.376 [0.027]</td>
<td>0.719 [0.0168]</td>
</tr>
<tr>
<td>Logistic Classifier</td>
<td>Composite Ventilation</td>
<td>0.369 [0.030]</td>
<td>0.723 [0.011]</td>
</tr>
<tr>
<td>XGBoost</td>
<td>Death</td>
<td>0.348 [0.047]</td>
<td>0.816 [0.031]</td>
</tr>
<tr>
<td>Random Forest</td>
<td>Death</td>
<td>0.282 [0.0248]</td>
<td>0.751 [0.031]</td>
</tr>
<tr>
<td>Gaussian Process</td>
<td>Death</td>
<td>0.311 [0.058]</td>
<td>0.809 [0.0279]</td>
</tr>
<tr>
<td>Logistic Classifier</td>
<td>Death</td>
<td>0.321 [0.063]</td>
<td>0.795 [0.039]</td>
</tr>
</tbody>
</table>

Abstract 25 Table 2  Pre-defined cost structure for each group of features (may be modified based on the healthcare facility) based on a relative cost score where 0 indicates clinical features that are least expensive and 3 indicates clinical features that are most expensive.

<table>
<thead>
<tr>
<th>Group</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCM (Demographic and comorbidities: Age, Sex, Gender, Race, Respiratory Rate, BMI, Temperature, Systolic/Diastolic Blood Pressure, Pulse Oximetry, FICO, O2 Sat, SpO2, Asthma, Chronic Kidney Disease, Diabetes, Hypertension)</td>
<td>0</td>
</tr>
<tr>
<td>BMP (Basic Metabolic Profile: Sodium, Chloride, Glucose, GFR, MORD Non Al Amy, Creatinine, BUN, Calcium, Potassium, Bili)</td>
<td>1</td>
</tr>
<tr>
<td>CBC (Complete Blood Count: Hemoglobin, Lymphocyte, MCH, Hematocrit, White Blood Cells, Platelets, MCHC, MCV, MPV)</td>
<td>1</td>
</tr>
<tr>
<td>D-Dimer</td>
<td>2</td>
</tr>
<tr>
<td>LDH</td>
<td>2</td>
</tr>
<tr>
<td>Sed rate</td>
<td>2</td>
</tr>
<tr>
<td>CRP</td>
<td>2</td>
</tr>
<tr>
<td>BMP</td>
<td>3</td>
</tr>
<tr>
<td>Troponin</td>
<td>3</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>3</td>
</tr>
<tr>
<td>Ferritin</td>
<td>3</td>
</tr>
</tbody>
</table>

Abstract 25 Table 3  For a pre-defined budget and cost structure for groups of features, we optimize for the set of features that provides the highest utility, in terms of AP. For instance, with a budget of 14, [DCM, BMP, CBC, D-Dimer, Sedrate, CRP, BNP, Procalcitonin] is the set that offers the best performance
exponential runtime. Instead, features were grouped into clinically meaningful subsets (e.g., Complete Blood Count, Basic Metabolic Profile, Blood Gases, etc.), thus significantly reducing the possible search space.

**Results** Based on readily available demographic information, co-morbidities and available biomarkers, the performance of various Machine Learning (ML) approaches (e.g., XGBoost, Random Forest, Gaussian Process, etc) for predicting ventilation status or death were tested. Compared to a baseline Linear Logistic Classifier model, more advanced nonlinear or tree-based classifiers provide improved performance both in terms of Average Precision (AP) and AUC ROC (table 1). The importance of individual features is captured via game theoretic SHAPley values and is provided in Figure 1.

While recent studies have investigated ML approaches as well as feature attribution in the context of prediction of adverse outcomes for COVID positive patients, our study is unique in terms of incorporating the cost of collecting a clinical feature for feature selection. For a pre-defined cost structure as provided in table 2, the optimal feature sets for a given cost constraint is provided in table 3. It is interesting to note that despite Procalcitonin being a highly relevant feature (as seen in figure 1), the addition of Procalcitonin to the models, in some cases, yielded only marginal increases in utility as measured by AP. For example, adding Procalcitonin to the set of features [DCM, BMP, LDH, Sedrate, BNP, Ferritin] increases AP by 4% (from 0.344 to 0.357) while increasing cost by 27%. Thus, relatively expensive features such as Procalcitonin may not provide meaningful benefit to patient care in a setting of cost-constraints or limited test availability. Of even greater interest is the observation that a feature set consisting of the following clinical variables [BMP, CBC, D-Dimer, LDH, CRP] provides an AP which is within 6% of the AP provided by the best set of variables. Thus, an increase of the budget/cost constraint of 75% (i.e., from ‘8’ to ‘14’) only provides a 6% increase in the AP of the model (table 2).

**Conclusion** This study presents a fast and accurate method to evaluate risk of clinical deterioration for patients with SARS-CoV-2 infection at the time of medical evaluation and to determine appropriate medical management for newly admitted patients. By identifying the top leading risk factors, health care providers can now determine a patient’s outcome in a cost-effective manner. The current method provides a point-of-care model that allows improved resource allocation and evidence-based management that can be applied to improve patient care not only in the setting of COVID-19 but also other clinically challenging diseases.

**Acknowledgements** This work was performed under the auspices of the U.S. Department of Energy by Lawrence Livermore National Laboratory under Contract DE-AC52-07NA27344 and was supported by the LLNL LDRD Program under Project No.19-ERD-009. LLNL-ABS-818777.
Conclusion Exposure of human monocytes to certain commensal species of Prevotella leads to differential activation of inflammatory pathways in response to SARS-CoV-2 glycoproteins. Contrary to what is observed in tissue, P. bisticola increases the inflammatory response of blood immune cells, such as monocytes to SARS-CoV-2 S glycoproteins. The simultaneous decrease in IRF activation may translate into a reduction of Type I IFNs, which appear important in controlling viral infections.

Methods We compiled a variety of previous studies related to PLD and its role in various signaling pathways and developed a clear consensus on the ability of PLD to be used as a therapeutic agent for both certain viral infection and neoplasms, as well as a need for more extensive research on PLD inhibition to treat these conditions.

Results Receptor tyrosine kinases (RTKs) like epidermal growth factor receptor (EGFR) play roles in the transition of cells into a tumorigenic state and are known to be involved in the catalytic activation of PLD activity. Elevation of PLD enzymatic activity is associated with the activation of cellular pathways that promote tumor formation and growth as well as the stimulation of modified cellular metabolism that is vital for cancer cell propagation. PLD1 and PLD2 have been found to assist with endocytic and phagocytic pathways that assist with normal cellular function as well as viral entry and exit in infected host cells. There are several other smaller roles in individual viruses where PLD1 and PLD2 can be found to play a role in such as the Epstein Barr Virus (EBV), human immune deficiency virus (HIV), etc.

Objective(s) Phospholipase D (PLD) is a naturally occurring ubiquitously expressed enzyme found in almost all mammalian tissues and is involved in various cell signaling pathways regulating cellular metabolism, inflammation, resisting apoptosis, promoting cell differentiation and proliferation, and response to tissue injury. There are six isoforms of PLD, the most widely studied being PLD1 and PLD2. There is ample evidence pointing to the effectiveness of PLD1 and other isoforms in treatment for viral infections and cancers of lung, breast, stomach, liver, and brain. There are several downstream signaling pathways of PLD that are important for cell survival and proliferation such as the mammalian target of Rapamycin (mTOR), Wnt/β-catenin, and pathway, both proven essential for cell proliferation and survival. Looking beyond its normal physiological role in cellular function, PLD also plays an important part in tumorigenesis as well as metastasis of cancer cells. PLD signaling when inhibited shuts down tumorigenesis and Ras-related oncogenesis. Looking further into cancer, PLD serves as an important mediator in cancer cell migration, invasion, and angiogenesis. Lastly, PLD is also found to be a key modulator in multiple viral infections including the influenza, herpesvirus, hepatitis C virus and HIV. Due to its array of roles and importance in both cancer and viral infections, it is an excellent therapeutic target for multiple different pathologies and disease processes.

Introduction/Background Phospholipase D is an enzyme that commonly exists across a wide variety of viruses, yeast, bacteria, animals, and plants, and works on the substrate phosphatidylcholine (PC), a ubiquitous component of the plasma membrane’s phospholipid bilayer, to hydrolyze PC to phosphatic acid (PA) and soluble choline. PA is a negatively charged phospholipid, and this structure can help facilitate interactions such as vesicle fusion and fission, and vesicular trafficking, exocytosis, autophagy, regulation of cellular metabolism, and tumorigenesis. This function, alongside PAs ability to recruit and activate enzymes as well as convert into signaling lipids, allows PA to serve as a messenger molecule in a variety of subcellular signaling pathways.

Abstract 27 Figure 1 Representation of the phosphatidylcholine downstream pathway
Phosphatidylcholine, which is a common phospholipid found on cellular lipid membranes. Phosphatidylcholine can be broken down into several byproducts including Phosphatidic Acid + Choline and Arachidonic Acid. The Arachidonic acid molecule can yield many byproducts such as prostaglandins, leukotrienes and EETs which are all involved in the body’s immune response. Phosphatidic acid can be further broken down into IP3 and DAG which are involved in several other downstream signaling pathways including ca2+ regulation.
Additional investigation is needed to better understand the precise role of each isoform and the coordination of its enzymes concerning pathology. With an increased understanding of PLD, there holds great potential for effective therapeutics in the targeted treatment of many forms of cancer and viral infection.

28 THE ENIGMA OF KAPOSI SARCOMA MANAGEMENT
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10.1136/jim-2021-MW.52

Introduction/Background Kaposi Sarcoma (KS) is a vascular lesion with low-grade malignant potential that is associated with Human Herpesvirus-8 (HHV8)/KSHV infection. KS is a soft tissue tumor that manifests as cutaneous lesions most frequently on the skin of the lower extremities, face, mouth, and genitalia. However, KS can progress to a disseminated disease with multi-organ involvement.

Risk factors include a compromised immune system most commonly from an HIV diagnosis, organ transplantation or the patient is on a long-standing immunosuppressive therapy, such as those diagnosed with Inflammatory Bowel Disease. Disseminated KS most often involves the lymphatic system and visceral organs such as the respiratory and gastrointestinal tracts. However, in rare cases, KS can occur in the liver, adrenal glands, kidneys, mammary and cardiac tissue, bone, and the nervous system. KS was first described in 1872 by Moritz Kaposi, a Hungarian dermatologist, as a mucosal or cutaneous neoplasm with brownish or red-to-bluish lesions in the larynx, trachea, stomach, liver, and colon. Until the HIV epidemic in the 1980s, KS was viewed as a slow-growing low-grade cancer.

In 1981, Kaposi sarcoma was one of the first conditions to define AIDS. Our current understanding is that KS arises from mesenchymal cells, which are influenced by HIV, various cytokines or growth factors, and potentially other viruses or environmental factors that suppress the immune system. AIDS-KS arises in a unique environment characterized by profound immunosuppression in conjunction with sustained immunostimulation. Persistent inflammation and the accompanying increased production of reactive species can promote carcinogenesis by numerous routes including sustained cell proliferation, initiation of nuclear and mitochondrial DNA mutations, and induction of a proangiogenic environment. During conditions of continuous inflammation, protein nitration can result in irreversible inactivation of enzymes including the cytoprotective and reactive species degrading enzymes such as mitochondrial superoxide dismutase (MnSOD).

A breakthrough in 1994 identified KSHV/HHV8 and linked it with all four epidemiologic-clinical forms of KS: classic (traditional, often benign), endemic (African), epidemic (AIDS-related), and iatrogenic. The tumor itself has various clinical presentations, ranging from indolent cutaneous tumors to the aggressive tumors that invade the lungs and other viscera. KS presents with characteristic skin lesions that appear as brown, red, blue, or purple plaques, and nodules. The KS lesions then develop from early macules into plaques and then grow into larger nodules (tumor stage). In this literature review, we will explore the epidemiology of Kaposi Sarcoma, current and novel drug treatments, as well as rare clinical presentations of KS.

Objective(s) The goal of this research was to review the literature on Kaposi Sarcoma to evaluate the most recent and effective drug therapies based on the sub-type of Kaposi Sarcoma and how to effectively recognize and diagnose the rare clinical presentations of KS based on case studies.

Methods To find relevant articles, PubMed was the primary search engine, and searches were made for the following: Kaposi Sarcoma, AIDS, HIV, Castleman’s Disease, Psoarisis, LANA-1, CD31, CD34, KSHV DNA, HIV-1 Tat, MinSOD, Molluscum Contagiosum, HAART, Radiotherapy, Electrochemotherapy, Paclitaxel, Liposomal Anthracyclines, Interferon, Chemotherapy, Rutamarin, Heat Shock protein Inhibitors, Gal-1, Anti c-kit, Tumor Associated Fibroblasts, Rapamycin, Calcineurin Inhibitors, SRL, Nef Upregulated cellular miRNA, Imatinib Mesylate, NFkB, Kaposin, Sulfated polymannuro guluronate (SPMG), Immune checkpoint inhibitors, Vinorelbine, Acroangiomeratitsis, Lymphangiomata-like KS, Immune reconstitution inflammatory syndrome-related KS, Oral Kaposi Sarcoma, Mucosal Kaposi Sarcoma, Gastrointestinal Kaposi Sarcoma, Liver Kaposi Sarcoma, Adrenal Kaposi Sarcoma, Mammary Glands, Kaposi of the heart, Kaposi of cardiac tissue. A total of 109 papers were used in the literature review.

Results Although the four clinical subtypes of Kaposi Sarcoma share many similarities, our review revealed important distinctions between the subtypes that may require different therapeutic interventions.

Classic KS is predominantly diagnosed in men 50–80 years old of Mediterranean or Eastern European origin. The lesions are often confined to the lower legs and visceral involvement is uncommon. Classic KS is usually indolent and has a survival rate of 10–15 years. For therapy options, radiotherapy and Vinorelbine are well-tolerated and were effective for the treatment of skin and mucosal lesions. Electrochemotherapy is ‘the new first-line’ for cutaneous and subcutaneous lesions. Tumor-Associated Fibroblasts are a promising new therapy for Oral KS. Volumetric-modulated arc therapy showed promising Results for the treatment of cutaneous lesions of the lower extremities.

Endemic (African) KS is common in adult males and children in Africa. It is locally aggressive and commonly presents with lower extremity edema and remains only locally invasive in adults. The cutaneous disease is usually absent and visceral involvement is the most common presentation in children. Liposomal Anthracyclines work well for advanced KS with visceral or oral disease.

Iatrogenic KS is most often diagnosed in organ transplant recipients, steroid users, and patients on immunosuppressive therapy over the age of 50. The distal lower extremities and viscera are usually involved. Some studies show that lesions may regress with lowering the dose of immunosuppression therapy, but this is not always effective. This can progress to a very aggressive form of Kaposi Sarcoma that is difficult to treat. Rapamycin and Calcineurin Inhibitors are novel options for organ transplant recipients with KS. SRL Therapy can be used to reduce the dose of immunosuppression therapy and lower the risk of graft rejection which may prove to be a promising preventative measure.

Epidemic (AIDS-related) KS is most prevalent in homosexual men in developed countries and females in Africa that show genetic susceptibility. It varies from locally invasive to disseminated and visceral involvement is common in poorly managed HIV patients. AIDS-KS with systemic invasion can involve multiple KS lesions in the lungs, duodenum, small intestine, colon, liver, and kidneys and often leads to
INFLAMMATION ASSOCIATED WITH SARS-COV-2 INFECTION

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Introduction/Background A novel coronavirus stain SARS-CoV-2 was detected in Wuhan, China in December 2019, and now is spreading worldwide at an exponential rate. In the U.S alone, there have been over 12.9 million cases over the year. One of the reasons why COVID-19 is so feared is because the virus has never been seen in humans. Therefore, no one is immune to it. The virus also spreads so easily through respiratory droplets so just by coughing, sneezing, or talking can spread the virus (2). Once the virus has infected a host cell, it takes days before symptoms appear which Results in people unknowingly spreading the virus. Once the virus has entered the body, it can trigger an inflammatory response which releases pro-inflammatory cytokines and leukotrienes and induces systemic damage. In Dr. Walia’s laboratory, antiviral therapies for herpesvirus infection are tested and there is an interest to study COVID-19 infection. Theoretically, since SARS-CoV-2 utilizes its spike proteins to bind to ACE2 (angiotensin-converting enzyme 2) on the host cell, then blocking the ACE2 receptor should inhibit viral entry into target cells and thus act as a potential antiviral treatment. In addition, our lab is investigating how the pro-inflammatory cytokines and eicosanoids play a role in COVID-19. Therapies that can target this cytokine storm will reduce inflammatory damage to the lungs, cardiovascular system, and renal system and thus minimize systemic effects caused by the virus.

Objective(s) Investigate potential antiviral therapies for SARS-CoV-2 infection.

Explore the pro-inflammatory and eicosanoid storm-related to SARS-CoV-2 infection.

Methods We utilized peer-reviewed articles to gather information pertaining to the SARS-CoV-2 infection.
Abstracts

Results The coronavirus strain SARS-CoV-2 utilizes the ACE2, a protein attached to the cell membranes, for entering into cells. ACE2 is a subtype from the ACE family but has a slightly different physiologic role. The traditional RAAS pathway uses ACE1, an enzyme residing in the pulmonary capillary endothelial, converts angiotensin I to angiotensin II. Angiotensin II then is able to bind to angiotensin II receptor type 1 and induce vasoconstriction and pro-inflammatory effects. On the other hand, ACE2 is responsible for degrading angiotensin II into angiotensin 1–7, which in turn binds to the Mas receptor and evokes a vasodilatory and anti-inflammatory effect (Busse et al., 2020). The SARS-CoV-2 virus utilizes its spike proteins on its viral coat to bind to ACE2 in order to gain entry into target cells (Busse et al., 2020). Research has shown that the degree of ACE2 expression directly correlates to the degree of infectivity. Further research is needed to fully grasp the extent of SARS-CoV-2 and its relationship with RAAS (Busse et al., 2020).

Hydroxychloroquine is an immunosuppressive drug derived from the quinoline molecule. It is widely used as an antimalaria and antirheumatic drug; however, recent studies have shed light on the potential use for COVID-19 patients. It is proposed that hydroxychloroquine can increase the pH endosomes and disrupt the glycosylation of cellular receptors found on the SARS-CoV-2 strain, which in turn will prevent viral entry into the host cell (Wang et al., 2020). Recent studies have shown that the lack of glycosylated receptors on the viral cell surface impairs viral attachment to angiotensin-converting enzyme 2 (ACE2) receptors located on the heart, lung, intestines, and kidney (Colson et al., 2020). Since SARS-CoV-2 expresses a similar surface receptor to ACE2, it can be hypothesized that hydroxychloroquine can disrupt ACE2 receptor glycosylation and ultimately prevent SARS-CoV-2 entry into target cells (Colson et al., 2020). Hydroxychloroquine can also change the pH of viral lysosomes which will disrupt the function of proteases such as cathepsins (Wang et al., 2020). This will induce the formation of autophausomes which will cleave SARS-CoV-2 spike proteins (Wang et al., 2020). In addition, hydroxychloroquine can inhibit quinone reductase-2, an enzyme involved in the synthesis of sialic acid (Singh et al., 2020). Sialic acids are found on cell surfaces and act as receptors for entry via viral glycoprotein hemagglutinin (Singh et al., 2020). Thus, by interfering with sialic acid biosynthesis, viral strains such as SARS-CoV-2 cannot induce ligand recognition and are unable to enter the host cell.

Remdesivir is a nucleotide analog that inhibits RNA synthesis. It has been commonly used to treat a broad range of viral infections such as paramyxovirus, pneumovirus, filovirus, and nipah virus (Singh et al., 2020). Recently, Remdesivir has been shown to have in vitro activity against the newest strain of coronavirus SARS-CoV-2. Remdesivir has been developed to deliver the monophosphate nucleoside analog GS-441524 into cells (Singh et al., 2020). Once inside the target cell, the GS-441524 monophosphate becomes phosphorylated into its active nucleoside triphosphate form GS-443902 (Singh et al., 2020). GS-443902 behaves in a similar manner as adenosine triphosphate (ATP) and tries to outcompete ATP in order to selectively inhibit viral RNA-dependent RNA polymerase (RdRp) (Singh et al., 2020). This is done by incorporating the nucleoside triphosphate GS-443902 into the nascent RNA chains via viral RdRp, resulting in delayed chain termination during viral replication (Singh et al., 2020). Using Remdesivir’s antiviral activity, this drug can potentially be used to target SARS-CoV-2 viral replication and serve as a treatment for COVID-19 infected patients. Recent studies have shown that Remdesivir interferes with viral replication in cell-based assays with IC₅₀ values of 100 nM, while human RNA Polymerase (RNP) II and mitochondrial RNP are not affected by the drug (Wang et al., 2020). This 500-fold selectivity ensures that viral cells are being targeted without interfering with human metabolism.

Corticosteroids are derived from a class of steroid hormones produced by the adrenal cortex (Brattsand et al., 2020). These hormones are used to reduce inflammation within the body and provide relief from a multitude of conditions such as rheumatoid arthritis, asthma, and lupus. Corticosteroids can be administered through local injection, inhalation, oral, and parenteral depending on the site of action of the drug (Brattsand et al., 2020). Recently, researchers have attempted to use corticosteroids as a potential therapy to reduce inflammation-induced lung injury in patients with COVID-19. Once the corticosteroid binds to its receptor, the corticoid-receptor complex becomes activated. This complex can then bind and inactive proinflammatory transcription factors such as NFKbeta and AP-1 (Russell et al., 2020). Without the activation of these transcription factors, cytokine production is prevented and in turn, the downstream cascade of inflammatory events will be inhibited. In SARS-CoV-2, the virus will enter host cells and induce systemic overactivation of the immune response leading to a drastic increase in cytokines such as IL-2, IL-7, IL-10, and TNF-alpha. (Russell et al., 2020). This cytokine storm can overwhelm the immune system resulting in metabolic dysfunction. Clinically, this will be exhibited by symptoms of fever, headaches, nausea, shortness of breath, and muscle aches. Glucocorticoids ability to suppress cytokine release and inflammatory response in SARS-CoV-2 can alleviate early pro-inflammatory damage and inhibit the formation of the cytokine storm (Russell et al., 2020). However, it is important to note that there have been concerns raised regarding the adverse effects of corticosteroids and their ability to exacerbate further respiratory distress. While the early use of corticosteroids may alleviate pro-inflammatory response, prolonged administration of corticosteroids has shown to enhance viral replication (Song et al., 2020). A randomized controlled study has found that COVID-19 patients treated with corticosteroids were found to have higher concentrations of viral RNA when compared to the placebo group (Song et al., 2020). In addition, corticosteroids can promote lymphocytopenia, which will promote further pro-inflammatory responses and worsen the pathological disease (Song et al., 2020). While the current data does not
support or refute the use of corticosteroids in the treatment of COVID-19 patients, more research should be conducted to better understand this hormone.

Conclusion The challenges in the treatment of SARS CoV-2 continue to dawn the scientists and the medical fraternity. Drugs like Remdesivir and hydroxychloroquine, though they have some effects on the inflammatory responses, are not very effective in reducing ARDS associated with CoV-2.

The use of corticosteroids in COVID-19 has conflicting views as they can help reduce the cytokine storm and lead to severe disease. The significance of dexamethasone in dexamethasone in COVID-19 could be attributed to its ability to induce pro-resolving lipid mediators in addition to anti-inflammatory and non-immunosuppressive properties. Thus, dexamethasone can be a promising therapy in COVID-19 patients.

Removins are chemical molecules derived from omega 3 fatty acids and are naturally very effective in controlling inflammation in the body. Removins can help in the endogenous resolution pathways, reduce inflammation, and maintain tissue homeostasis. Therefore, these endogenous resolution pathways could be a novel approach to treating COVID-19.

In search of a drug to mitigate the novel virus’s effects, traditional herbs and treatment practices are also explored to find solutions. These approaches seem promising to help reduce the severe impact of infection.

REFERENCES

A WOMAN WITH ABDOMINAL PAIN WHILE BEING TREATED WITH STEROID
Suha Abu Khalaf, Taylor Nelson. University of Missouri, Columbia

Introduction/Background Saccharomyces cerevisiae is a yeast of the phylum Ascomycota which can be used in food production. It has been rarely mentioned in the literature as a cause of human disease. Various types of infections have been reported, primarily bloodstream infections. Whether Saccharomyces is a cause of true infection in other sites as compared to a culture contaminant is controversial, as it is considered a normal part of the gastrointestinal (GI), vaginal, and respiratory mucosal flora. The main risk factors for infection with Saccharomyces are immunodeficiency including chemotherapy, history of a central venous catheter, gastroenterological surgery, and use of antibiotics or probiotics. We present the case of an 80-year-old woman who, after five days of dexamethasone treatment for COVID-19 pneumonia, presented with worsening abdominal pain. The patient was diagnosed with perforated diverticulitis, complicated by Saccharomyces cerevisiae fungemia. We will discuss the management of Saccharomyces cerevisiae fungemia and other infections to highlight the difficulty in management and high mortality risk associated with similar infections.

Case Presentation An 80-year-old woman with no known medical history was admitted for COVID-19 pneumonia and hypoxia, for which she required four liters of oxygen. She was initially treated with dexamethasone, remdesivir, cefepime, and azithromycin. On the fifth day of hospitalization, she developed acute generalized abdominal pain. Computed tomography of the abdomen and pelvis (figure 2) showed pneumoperitoneum, sigmoid versus terminal ileum perforation, and two abscesses (measuring 5.5 cm and 8 cm in the largest diameters) in the pelvis. Surgical team recommended non-operative management.

On days eight and ten of illness, blood cultures were obtained and grew Saccharomyces cerevisiae. Piperacillin-tazobactam was started for empiric GI coverage. Micafungin was started when yeast was identified in blood cultures and was subsequently switched to oral voriconazole once the yeast was identified as Saccharomyces. Blood cultures cleared four days after first positive.

Due to persistently worsening leukocytosis, an exploratory laparotomy with sigmoidectomy and end colostomy was performed on day twelve of hospitalization. Intraoperative diagnosis of Hinchey stage IV diverticulitis (diverticulitis with generalized fecal peritonitis) was made. A drain was placed, and cultures from the abscess fluid grew Saccharomyces cerevisiae. In addition to the Saccharomyces isolate, a Mucor species grew in the abscess culture after four days, and the

Abstract 33 Figure 1 Laboratory blood work up on day 1 and 12 of hospitalization.
Abstract 33 Figure 2  CT scan of the abdomen revealed a small volume of pneumoperitoneum secondary to sigmoid versus terminal ileum perforation. Deep within the pelvis, adjacent to the sigmoid and uterus are two air and fluid collections with partial rim enhancement consistent with developing abscesses.

Better susceptibility Results were observed with voriconazole and posaconazole. The mortality rate of Saccharomyces cerevisiae fungemia remains high and was reported in one study as 29.5%. Saccharomyces cerevisiae fungemia is a rare, life-threatening disease with no clearly defined treatment guidelines. Further studies are needed to better understand the therapeutic antifungals options.

Abstract 34  AN IMMUNOCOMPROMISED WOMAN WITH LEFT EYE VISUAL LOSS

Suha Abu Khalaf, Andres Bran. University of Missouri, Columbia

10.1136/jim-2021-MW.55

Introduction/Background Nocardia is one of the Aerobic Actinomycetes which are characterized by being gram-positive branching, filamentous rods, typically taking prolonged duration to grow, so it needs to be isolated on special types of cultures. Also, due to their cell wall component with mycolic acid, they stain positive with modified acid-fast stain. Nocardia can cause a variety of infections, especially in immunocompromised transplant hosts; including lung, brain, and skin infections. Ocular infections were reported but very rarely in the literature. We present a case of an 86-year-old female who is immunocompromised who presented with left eye visual loss. Clinical thinking, detailed treatment, management and follow-up are discussed to highlight the importance of keeping Nocardia under our radar in such cases, reducing the time to diagnosis and facilitating immediate treatment as we have more immune-compromised hosts through various new definitions simultaneously as improving our laboratory techniques in detecting different types of infection.

Case Presentation An 86-year-old woman with a history significant for Sjogren’s disease, ILD on immunosuppression with hydroxychloroquine and prednisone, chronic hypoxic respiratory failure requiring 3L of oxygen, diabetes mellitus who came from an ophthalmology clinic to be evaluated for vision problems in her left eye for four days. Symptoms began four days ago with central spot, dull pain and progressive vision deterioration on the left side. She has a dry cough, started the previous month with recurrent oral thrush, no fever, abdominal pain, headache, dizziness, weakness, sensory deficit or rash. She was diagnosed with bilateral chorioretinitis and left-sided panuveitis. Vital signs and physical exam were unremarkable.

The patient was further evaluated in the emergency room, including CT scans of her chest, abdomen and pelvis. The CT scan shows a ring-shaped hypodense lesion in the left gluteus medius and right paraspinal muscle. The CT scan showed chronic interstitial changes, a new consolidation of the left lower lobe, and the MRI scan of the head also showed a bicerebral, many rim-enhancing masses with surrounding vascogenic edema concerning for metastatic deposits. The working diagnosis at this time was broad and was managed by the infectious disease team in a way that included widespread nocardiosis, fungal infections, HIV, tuberculosis and others.

Further tests included Aspergillus and histoplasma antigen, Mycobacterium tuberculosis, HIV screening, toxoplasma test, beta-D-glucan test. Biopsy of the gluteus medius muscle was performed, the gram stain showed gram-positive rods, partial acid-fast bacilli and cytology stain consistent with Nocardia spp further identified as Nocardia farcinica.
Since admission, the patient was started on meropenem. Upon obtaining the gluteus muscle biopsy result, intravenous sulfamethoxazole-trimethoprim (SMX-TMP) was added to her regimen. Within five days, the patient developed an intolerance to SMX-TMP (nausea, vomiting and kidney damage). The second-line drug doxycycline was used alternatively. The patient also reported a deterioration of her vision in her left eye, and the patient underwent an ophthalmological examination, which was notable for a deterioration of chorioretinitis and abscess formation in her left eye. The antibiotic was switched to amikacin 10 mg/kg every 24 hours and imipenem-cilastatin 500 mg IV every 8 hours. Concerns about superimposed Candida ophthalmitis were raised, and oral fluconazole 400 mg once daily was added. The patient was discharged home after 18 days of hospitalization on amikacin, imipenem-cilastatin and fluconazole with significant improvement in her vision on follow-up one month after.

**Discussion**

The presentation of the patient carries a very high suspicion of disseminated nocardiosis. It is an opportunistic infection associated with various causes of having suppressed immune system. Nocardia can cause local or widespread infections. Since Nocardia can be inhaled from the environment, pulmonary manifestations are considered the most common. Ophthalmic nocardiosis is extremely rare. Diagnosis and treatment are challenging, as a consequence, the mortality rate is high. Nocardia farcinica which was the final isolate in this case was found to be isolated in from the right paraspinal muscle biopsy.

**Abstract 34 Figure 1** MRI of the brain showing abnormal rim-enhancing intracranial lesions with surrounding vasogenic edema as evidenced.

**Abstract 34 Figure 2** (A on the left): Rim-enhancing hypodense lesion in the left gluteus medius muscle; (B on the left): Rim-enhancing hypodense lesion in the right paraspinal muscle.

**Abstract 34 Figure 3** Laboratory work up of the patient:

<table>
<thead>
<tr>
<th>Lab test (unit)</th>
<th>Result</th>
<th>Reference value</th>
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<tr>
<td>Hemoglobin (g/dl)</td>
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<tr>
<td>Hematocrit (%)</td>
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<td>34-44.5</td>
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<tr>
<td>MCV (fL)</td>
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<tr>
<td>WBC (x 10^9/L)</td>
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<td>3.5-10.5</td>
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<tr>
<td>ANC (x 10^9/L)</td>
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<td>1.7-7.7</td>
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<tr>
<td>Platelets count (x10^9)</td>
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<td>150-450</td>
</tr>
</tbody>
</table>

**Miscellaneous infectious work up**

- Aspergillus antigen: ≤500 Index ≤5
- Toxoplasma IgG and IgM: Negative
- Urine histoplasma Antigen: Negative
- HIV Ag Ab: Negative
- Serum crypts Ag: Negative
- Fungitell Ag: ≤31 pg/mL, ≤60 pg/mL
- Blasimycin quantitative antigen: Negative

**Abstract 34 Figure 4** (A on the left): Nocardia with Fite stain; (B on the right): Modified acid-fast stain of nocardia.
Abstracts

Aerobic Actinomycetes
SOURCE: BUTTOCK, gluteal fluid
SUSC, AEROBIC ACTINOMYCETES
NOCARDIA FARCINICA

<table>
<thead>
<tr>
<th>Organism</th>
<th>NOCARDIA FARCINICA</th>
<th>Antibiotic</th>
<th>MIC (mcg/mL)</th>
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<td></td>
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<tr>
<td>Ceftriaxone</td>
<td>64</td>
<td>R</td>
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<td>Imipenem</td>
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<td>Linezolid</td>
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<td>S</td>
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<td></td>
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</tbody>
</table>

Abstract 34 Figure 5 Nocardia farcinica susp results

Case Report-A Case of Rothia Dentocariosa Endocarditis with Severe Complications

Esther Bak, Nicole Giddens, Tyler D Sharpe. University of Louisville School of Medicine; University of Louisville Hospital

Introduction/Background Infective endocarditis (IE) is a relatively rare but life-threatening disease with multisystem effects resulting from, most commonly, bacterial infection of the heart’s endocardial surface. It disproportionately affects those with structural valvular heart disease or prosthetic valves as well as intravenous drug users. Diagnosis involves a multifaceted clinical, microbiological, and image-guided approach, which are factored into the modified Duke Criteria- the current gold standard for diagnosis of IE.1 While IE with negative cultures may be seen in fungal infections like Candida, Histoplasma, and Aspergillus, and bacterial infections like Legionella, Coxiella, and the HACEK group (Haemophilus species, Aggregatibacter actinomycetemcomitans, Cardio bacteria hominis, Eikenella corrodens and Kingella kingae), streptococci and staphylococci have collectively accounted for approximately 80% of positive culture IE cases, with enterococci being the third leading cause of IE and linked to healthcare contact.3 However, only a few cases of Rothia dentocariosa (R. dentocariosa) endocarditis have been reported to date.

Cardiac manifestations of valvular vegetations usually involve the line of closure of a valve leaflet on the atrial surface of atrioventricular valves (the mitral and tricuspid valves) or on the ventricular surface of semilunar valves (the aortic and pulmonary valves).3 Large vegetations reaching up to several centimeters in diameter pose increased risk for valve perforation or rupture and vegetations greater than 1 cm should warrant urgent cardiovascular surgical evaluation for operative therapy. Manifestations of IE outside the heart can involve multiple organs and warrant multidisciplinary evaluation as well. Extra-cardiac manifestations include petechiae, cutaneous infarcts, Osler’s nodes and Janeway lesions, cerebral septic emboli, neurovascular mycotic or cerebral aneurysms, splenic abscesses or infarcts, pulmonary septic emboli appearing as peripheral wedge-shaped densities or rounded ‘cannonball’ lesions mimicking tumors on chest radiographs4, and ophthalmic complications which all involve invasion of septic emboli to various organ systems. With the exception of pulmonary septic emboli, all above mentioned manifestations were seen in the following case.

Case Presentation A 61-year-old male patient with hepatitis C and IV drug use presented to the hospital with 3 days of weakness, chills, and headache. The patient was homeless for the past year and endorsed a 45+ year history of methamphetamine and cocaine use with 3 months of active IV drug use. Bedside ultrasound on arrival revealed the presence of vegetations. Patient was admitted with a diagnosis of infective endocarditis and started on vancomycin and piperacillin-tazobactam for broad spectrum coverage. Transthoracic echocardiography the next day showed no signs of vegetation; however, subsequent transesophageal echocardiography revealed a large, irregular, mobile 1.75 × 1.37 cm vegetation on the P1 scallop of posterior mitral leaflet, involving the lateral commissure with perforation of P1 and severe eccentric mitral regurgitation. Blood cultures on day 4 of admission resulted in growth of Rothia dentocariosa (R. dentocariosa) and patient was continued on vancomycin while awaiting sensitivity. Cardiothoracic surgery plans were placed tentatively for the following week. However, upon additional imaging, a CT of the abdomen/pelvis showed an acute splenic infarct, and CT/MRI of the head showed scattered multiple restricted diffusion lesions, all suggestive of acute and subacute infarcts read as likely to be septic emboli given the patient’s history. Additionally, on day 5 of admission, patient was observed to have blurry vision, pain, and restricted extraocular movement of the left eye unexplainable by the findings on brain imaging. He was found to have acute angle-closure glaucoma, requiring quadruple topical ophthalmic therapy while awaiting iridotomy outpatient. Dental recommendations included multiple extractions one week prior to valve surgery as the infection likely stemmed from the patient’s dental caries. New findings of acute possible hemorrhagic cerebral bleed in conjunction with ophthalmic and dental management were taken into consideration and valvular surgery was planned for 6 weeks later upon completion of a 6-week course of antibiotics. The patient completed 19 days of vancomycin before a 3-day interruption due to patient departure against medical advice and subsequent readmission to the hospital. Patient was involved in a motor-vehicle incident as a pedestrian during his period of
Abstracts

DAPTOMYCIN INDUCED RHABDOMYOLYSIS. WHEN DRUG-DRUG INTERACTIONS PLAY A CRUCIAL ROLE

Suha Abu Khalaf. University of Missouri, Columbia

Abstract 36 Figure 1  CK elevation pattern

Introduction/Background Rhabdomyolysis is a clinical disease resulting from muscle injury and usually leads to clinical symptoms including myalgia, muscle weakness and the release of high levels of muscle enzymes, which lead to pigment nephropathy, myoglobinuria and dark brown urine. The most sensitive marker of muscle injury is an increase in creatine kinase (CK), typically more than 11 times higher than the upper normal limit. Rhabdomyolysis can occur with any trigger of muscle injury. One of the known side effects of daptomycin is rhabdomyolysis, reported to occur in about 3% of cases in Phase III clinical trials. We present a case of a 54-year-old female who presented with muscular soreness seven days after starting daptomycin for polymicrobial (MRSA and VRE) skin and soft tissue infection (SSTI). Emphasis on potential risk factors, management and follow-up will be discussed to highlight the importance of maintaining this not unusual side effect of daptomycin.

Case Presentation a 54-year-old woman with a history significant for type II diabetes mellitus, coronary heart disease and psoriatic arthritis on immunosuppressive drugs with leflunomide. The patient was admitted one month before the current presentation for acute osteomyelitis of the left foot and underwent left partial foot amputation, pathological margin was negative for osteomyelitis, and she was discharged on oral sulfamethoxazole-trimethoprim for soft tissue infection. After three weeks she returned for wound dehiscence and underwent a revision and a debridement down to the bone. Tissue culture grew methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus faecium (VRE). She was started with daptomycin 10 mg/kg of ideal body weight (750 mg daily). A tunneled catheter was placed, and the patient was discharged on daptomycin to complete the therapy for 4 weeks for the management of left foot polymicrobial SSTI and possibly underlying osteomyelitis. Within three days of taking daptomycin, the patient developed a feeling of exhaustion, general weakness and worsening muscle soreness around her back, neck, shoulders and calves. She went to the emergency room on the seventh day after the daptomycin. She denies having a fever, chills, nausea, vomiting or rash. Physical exam was tachycardia of 105. Also, she had generalized muscles tenderness.

departure and on CT head was found to have hypodensities within the occipital and parietal lobes bilaterally consistent with acute to subacute infarcts in evolution with increased number and distribution when compared to previous studies. With continuously negative blood cultures, vancomycin Conclusion date was adjusted to reflect doses missed. Upon receiving neurologic and cardiovascular clearance for valvular surgery and successful dental extraction, the patient underwent total mitral valve replacement without complications. Postoperative echocardiogram showed mild left ventricular dysfunction with ejection fraction of 60%. Patient made a full recovery to discharge on post-operative day five.

This unique case confirms that although a rare organism and cause of infective endocarditis, R. dentocariosa infective endocarditis may present with various, severe complications, and an efficient multidisciplinary approach to evaluation, antibiotic treatment, and ultimately surgical intervention is critical to minimizing risk of patient morbidity.

Discussion Rothia dentocariosa is a rare gram-positive bacterial organism, one of the group of microbes that usually resides in the mouth and respiratory tract. R. dentocariosa rarely causes disease. Documented cases occur chiefly in patients with valvular or dental disease, or both. It is noted that only a few cases of R. dentocariosa endocarditis have been reported to date, almost exclusively in patients with an underlying heart condition as the predisposing risk factor. This current case introduces a unique setting in which a predisposing cardiac structural abnormality is absent in the mechanism of infection spread. History of intravenous drug use in conjunction with dental caries-facilitated bacterial seeding poses a more opportunistic narrative of the rare organism further substantiated by embolic sequelae that provide further evidence of the organism’s invasive potential. This serves as evidence to support that R. dentocariosa can cause endocarditis in patients lacking structural heart conditions, which were previously known to be the primary and exclusive source of infective endocarditis caused by this organism. Because of the rarity of pathogenic R. dentocariosa, risk factors for invasive infection are not well defined. Similar uncertainty surrounds the subject of treatment regimens. No definite guidelines are available, but distinct antibiotic agents have been recognized. A variety of agents have been described: of these, penicillin is the treatment of choice, and ceftriaxone has had similar success. Most patients are treated for at least 4 to 6 weeks.

Despite that more than 80% of bacterial infective endocarditis cases are caused by streptococci and staphylococci, clinicians should be aware of the remaining 20% of rarer IE causing organisms such as R. dentocariosa. It can cause severe, widespread extra-cardiac sequelae and as such, management should warrant an interdisciplinary approach with treatment care plan facilitated among cardiac, neurological, dental, ophthalmic, infectious and surgical disciplines, as needed.
The patient didn’t produce any urine output initially, the first sample was obtained 7 hours after presentation to ER. Urine analysis at that point showed colorless urine with moderate blood and negative RBC.

The patient didn’t miss any of her daptomycin doses. She continued taking her atorvastatin of 80 mg daily. She also was continued on leflunomide for psoriatic arthritis.

The patient was diagnosed with rhabdomyolysis secondary to daptomycin. Daptomycin was stopped, as were atorvastatin and leflunomide, and began aggressive IV hydration. CK peaked at 9846 (see figure 1) within 48 hours of daptomycin being discontinued and then started to trend downwards. Due to limited options covering MRSA and VRE and in the presence of daptomycin induced rhabdomyolysis, oritavancin 1200 mg IV one dose without any further IV antibiotics during admission or after discharge with close follow up.

Discussion The presentation of the patient is most likely associated with daptomycin-induced rhabdomyolysis. The patient was at high risk of developing muscle injury as she was taking a high dose of daptomycin (> 8 mg/kg) and several other medications that are also known to be prone to muscle injuries, including atorvastatin and leflunomide. The discontinuation of daptomycin and other medications with continuous supportive rehydration therapy were also sufficient to alleviate symptoms and decrease the CK level. Drug-drug interactions are very common problems that can be a potentially overlooked adverse effect and a challenge for any medical case.

Finding an adequate therapy for this case in place of daptomycin was a challenge given suspicion for osteomyelitis. Oritavancin was approved for skin infections in 2014 and is said to be clinically effective against gram-positive osteomyelitis, although further studies are needed. Doctors should be vigilant when prescribing daptomycin, especially when patients are taking other medications by holding some medications and carrying out more frequent CK checks.
1/Src signaling can attenuate the progression of renal injury and dysfunction.

**Methods** Experiments were performed on Dahl salt-sensitive rats (SS rats) and Pon-3 knock-out rats on the Dahl salt-sensitive background (SS-Pon3 KO). To investigate the renoprotective role of Pon-3, ten-week-old, age-matched male control SS and SS-Pon3 KO rats were maintained on 8% high salt diets for eight weeks to initiate salt-sensitive hypertensive renal disease characteristic of this model. We found that SS-Pon3 KO rats demonstrated significantly increased mortality and renal injury, as well as decreased renal function compared to SS rats despite similar degrees of hypertension. Next, to determine the role of NKA α-1/Src signaling participation in renal disease progression SS-Pon3 KO rats on 8% high salt diet were treated with pNaKtide (25 mg/kg i.p.), a specific NKA α-1/Src kinase complex inhibitor weekly for a total of 7 injections. Control SS-Pon3 KO rats on 8% high salt were given non-functional pNaKtide scramble peptide (25 mg/kg i.p.) weekly for 7 weeks.

**Results** We found that SS-Pon3 KO rats on high salt experienced significantly attenuated renal disease progression following inhibition of the NKA α-1/Src signaling pathway via pNaKtide treatment. Upon renal histopathological analysis, SS-Pon3 KO rats demonstrated significant decrease in renal injury as noted by reduced interstitial immune cell infiltration, hyaline cast formation and tubular atrophy (all p<0.05) following pNaKtide treatment. Kidneys from SS-Pon3 KO post pNaKtide treatment also demonstrated significantly decreased vascular hypertrophy and glomerular sclerosis (both p<0.05) compared to SS-Pon3 KO on high salt without pNaKtide treatment, despite similar degrees of hypertension. Finally, renal function was assessed by 24-hour urinary protein excretion (UPE), and glomerular filtration rate (GFR). While SS-Pon3 KO rats on high salt diet demonstrated significant decrease in renal function, we found that following inhibition of the NKA α-1/Src signaling pathway, UPE and GFR were both significantly (p<0.05) improved.

**Conclusion** These findings indicate that the impairment of renal function and renal injury seen in a model of hypertensive renal disease with reduced Pon-3 is regulated by the NKA α-1/Src signaling cascade and suggest a mechanism that can be therapeutically targeted to reduce hypertensive renal disease progression.

**CIRCULATING HEMOPEXIN ACCUMULATES IN KIDNEYS AND WORSENS RENAL INJURY IN CISPLATIN-INDUCED ACUTE KIDNEY INJURY**

Xiaoming Fan, Xiaolu Zhang, Shungang Zhang, Lijun Liu, Rajesh Gupta. The University of Toledo

10.1136/jim-2021-MW.60

**Introduction/Background** Hemopexin is a critical heme scavenging protein and has been shown to be protective in heme overload diseases. However, its role in acute kidney injury is controversial.

**Objective(s)** We sought to determine the role of hemopexin in cisplatin-induced acute kidney injury (AKI).

**Methods** Hemopexin wild type (WT) and knockout (KO) mice at the age of 12 weeks were used to study the role of hemopexin in AKI. AKI was induced using cisplatin injection at a dose of 30 mg/kg, a well-established AKI model. Mice were sacrificed and plasma and organs were collected on day 3 after cisplatin injection. Renal injury and kidney function were determined with kidney tissue H&E staining and plasma creatinine, respectively. Fluorescence immunostaining was utilized to determine the localization of hemopexin within the injured kidney. Cellular reactive oxygen species (ROS) were measured to determine the effect of hemoglobin and hemopexin in vitro using renal proximal tubular cells (HK-2 cells).

**Results** Cisplatin injection significantly induced renal hemoglobin deposition (3.35-fold increase, cisplatin vs control, p<0.05) and hemopexin accumulation (2.5-fold increase, cisplatin vs control, p<0.05). Co-localization immunofluorescence staining. (C) Plasma creatine levels on day-3 post cisplatin treatment in WT and KO mice. n=6–8 in each group.

**Abstract 42 Figure 1** Renal hemopexin protein levels increase following cisplatin treatment

Hemopexin WT and KO mice were treated with cisplatin (cis) or saline (sham) and organs were collected on day-3 following treatment. (A) Kidney homogenates were processed for Immunoblot analysis for the expression of hemopexin (Hpx) and β-actin (loading control). Representative blots are shown. (B) Immunoblots were subjected to densitometric analysis of the relative abundance of Hpx normalized to β-actin. *P<0.05 versus relative protein expression in WT sham group. n=6–8 in each group.

**Abstract 42 Figure 2** Worse renal injury and kidney function is observed in wild type mice following cisplatin injection

Animals were treated as elaborated in figure 1. (A) Kidney tissues on day-3 post cisplatin treatment were subjected to hematoxylin-eosin staining staining. Representative microscopic images are shown. Scale bar=50 μm. (B) Renal injury score assessed based on evaluation of HE staining. (C) Plasma creatine levels on day-3 post cisplatin treatment in each group. *P<0.05 versus renal injury in WT sham group. # P<0.05 versus renal injury in WT cis group. n=6–8 in each group.
staining identified that hemopexin accumulated within the proximal tubules and glomeruli. When compared with hemopexin KO mice, hemopexin WT mice had worse renal injury (renal injury score: 3.17 vs 2.0, WT vs KO, p<0.05) and worse kidney function (plasma creatinine (mg/dL): 1.43 vs 0.88, WT vs KO, p<0.05) on day 3 after cisplatin treatment. Furthermore, biomarker assessment demonstrated increased renal expression of Kidney Injury Molecule-1 (KIM-1) and HO-1 (C) normalized to β-actin. *P<0.05 versus renal injury in WT sham group. # P<0.05 versus renal injury in WT cis group. n=6–8 in each group.

Neurology/Neurodegeneration

WAXING AND WANING SENSORY AND MOTOR LOSS: A DIAGNOSTIC AND THERAPEUTIC DILEMMA

Sabaah Ahmed, Sheraz Hussain, Mohammad Sarhan, Michael Doerrler. Advocate Christ Medical Center

Introduction/Background Crescendo Transient Ischemic Attacks (TIAs) are disabling symptoms that occur in patients with high-grade carotid artery stenosis often within 3 months of the initial presentation of ischemic cerebrovascular disease. They are recurrent episodes of transient cerebral or retinal ischemia characterized by an increased frequency, duration, or severity of events. It is of particular interest to examine the role of carotid endarterectomy versus medical management alone in patients of varying degrees of internal carotid artery stenosis. In this report, we present a case of Crescendo TIAs manifesting as unilateral upper extremity numbness, weakness, and heaviness secondary to internal carotid artery stenosis.

Case Presentation The patient is a 68-year-old male with a history of hypertension (HTN), hyperlipidemia (HLD), type two diabetes and one documented TIA who presented with complaints of right upper extremity numbness, weakness, and heaviness as well as occasional tingling. His symptoms began that same morning when he awoke from his sleep. Onset of symptoms was abrupt and there was no progression of his symptoms. Of note, is his relevant smoking history of 60 pack years. Additionally, he had not been taking any of his medications for HTN, HLD, or daily Aspirin for the last two months due to insurance issues. During this admission, patient developed waxing and waning dysarthria, followed by facial droop on the lower right side of his face. He had prominent numbness in the fingers of his right hand. Magnetic Resonance Imaging (MRI) of the brain was performed and revealed multifocal areas of restricted diffusion in the high left frontal and parietal regions predominantly around the motor and sensory strip. Neurology and vascular surgery were placed on consult. Further stroke workup was done revealing 50–60% stenosis of the left internal carotid artery.

The patient was started on Aspirin and statin as per stroke protocol. Vascular surgery planned for carotid endarterectomy to be done 6 days status post onset of symptoms. The patient underwent this procedure without any complications. His presenting symptoms of right upper extremity weakness, numbness and heaviness resolved within 1 day of the procedure and medical management as monotherapy with daily Aspirin was employed upon discharge. Patient was discharged home in a stable condition with appropriate prescriptions for medications as approved by his insurance.

Discussion With ischemic strokes being one of the leading causes of death and disability in the United States, there is compelling reason to further investigate crescendo transient ischemic attacks, as a third of all patients diagnosed with TIA in the U.S. go on to develop a stroke. Interestingly, a systematic review of PubMed and Google Scholar between the years of 1985 and 2019 ascertained that patients with crescendo transient ischemic attack were found to have a higher risk of stroke or death after carotid endarterectomy compared with patients with a single transient ischemic attack or stable stroke. It was also found that, with medical management alone, these patients are at a higher risk of completing a stroke within months and carry a poor prognosis in the absence of intervention. Therefore, it is imperative to appropriately categorize, and risk stratify these patients. Numerous randomized trials compared outcomes in patients who underwent carotid endarterectomy versus medical management, in the setting of TIAs. Carotid endarterectomy was found to be beneficial for those who possessed moderate to high grade carotid stenosis, which is defined as luminal stenosis of at least 70% or higher. In patients with low grade stenosis (up to 49%), carotid endarterectomy actually fared worse than medical management alone. Although the patient in our case would be classified as ‘moderate grade stenosis’, between the range of 50 to 69%, we must keep in mind that his symptoms upon presentation are consistent with crescendo TIAs. In such cases, it is important to closely examine the indications for intervention and associated dependent factors including overall surgical candidacy, percentage compromise of the internal carotid artery lumen, frequency and severity of TIA.
ICTAL APHASIA VERSUS EPILEPTIC APHASIA

Olubosola H Amiola, Vanillyk Losada, Nicholas Helmstetter, Michael Soliman, Edward C Mader. Louisiana State University

Introduction/Background
Aphasia occurs when language function is impaired by a structural lesion. As an epileptic phenomenon, aphasia can manifest as ictal aphasia, epileptic aphasia, or both. Ictal aphasia is also known as aphasiform seizure. Epileptic aphasia is characterized by language impairment, whether or not seizures are present on the EEG. Although epileptic aphasia is often described in children as Landau-Kleffner syndrome, it is not a well-recognized diagnostic entity in adults.

Case Presentation
Patient-1 is a 44-year-old right-handed female with a 2-year history of seizures characterized by expressive aphasia, right gaze deviation, and occasional generalization. Seizures were controlled with levetiracetam until she presented with aphasia. EEG monitoring showed left temporal periodic delta activity with superimposed spikes and recurrent aphasic seizures. Seizures stopped and aphasia resolved after optimal antiepileptic therapy. Patient-2 is a 24-year-old right-handed female with no past history of seizures. She presented with a 2-day history of aphasia and right arm clonic seizures. Verbal output was limited to a few words. Brain MRI was initially normal, but a repeat study showed T2 FLAIR hyperintensity in the left temporal lobe. EEG showed frequent left temporal seizures. CSF studies showed lymphocytic pleocytosis and high anti-NMDAR antibody titer. She started uttering words and short phrases with antiepileptic therapy. Language function improved further with immunotherapy and was almost normal on the day of discharge.

Discussion
Ictal aphasia and epileptic aphasia are distinct phenomena. A wide range of pathologies can manifest with ictal aphasia, but the differential diagnosis for epileptic aphasia appears much narrower. Autoimmune encephalitis resulted in epileptic aphasia in Patient-2. This is interesting since Landau-Kleffner syndrome, a well-known epileptic aphasia syndrome in childhood, appears to be a form of autoimmune encephalitis.

Pediatrics

30 CLINICAL CHARACTERISTICS DISTINGUISHING BRONCHIOLITIS PATIENTS REQUIRING MECHANICAL VENTILATION

Rachel K Marlow, Sydney Bruquelle, Vannessa Ramos, Ariann Lenihan, Nichole Nemec, Joseph Lukowski, Sidharth Mahapatra. University of Nebraska; Children’s Hospital and Medical Center Omaha; Boy’s Town National Research Hospital; University of Nebraska Medical Center

Introduction/Background
The AAP recommends standardization of care for uncomplicated bronchiolitis admissions, largely focused on supportive care. Patients suffering acute respiratory failure secondary to bronchiolitis admitted to the intensive care unit (ICU) represent a distinct population whose pathophysiology is poorly understood. The need for mechanical ventilation in this population may be attributable to secondary bacterial infections, but hesitation in empiric antibiotic use stems from heightened antibiotic stewardship.

Objective(s)
In this study, we sought to identify key clinical features distinguishing bronchiolitis patients requiring mechanical ventilation. We hypothesized a higher incidence of multi-microbial, specifically secondary bacterial infections, and longer lengths of stay in these patients.

Methods
We interrogated our electronic medical record (EMR) for pediatric patients with a diagnosis of acute bronchiolitis admitted to the pediatric intensive care unit (PICU) from January 2015 to December 2019. Our exclusion criteria were 1) GA < 37 weeks or age > 2 years at admission, 2) chronic respiratory support, 3) congenital heart disease, 4) no escalation to NIPPV, and 5) directly post-operative status. Qualifying patients were divided into 2 groups based on whether or not they required intubations. Intubated patients were further subdivided into early (within 24 hours of admission) and late (after 24 hours of admission) intubation groups.

Results
Over the study period, 792 patients with acute bronchiolitis were admitted to the PICU. Of the 394 eligible patients, 134 required intubation (22%). Intubated patients were more likely to be premature (p<0.001) and have underlying neurologic and genetic abnormalities (p<0.001). Moreover, they were more likely to have multiple pathogens present, including bacterial co-infections, and had longer ICU stays (p<0.001). Within the intubated group, approximately 2/3 were intubated within the first 24 hours of PICU admission. Compared to this group, the late intubation group had a higher average number of pathogens (p=0.0043), was more likely to receive antibiotics for a longer duration (p<0.001) and have longer lengths of stay in the PICU (p=0.028).
Conclusion

Nearly 1/4 of critically ill pediatric patients admitted with severe respiratory failure secondary to acute bronchiolitis require intubation. Those that require mechanical ventilation are more likely to be younger, premature, and have genetic and/or neurologic abnormalities. This cohort also suffers from multi-microbial infections requiring longer duration of antibiotics, resulting in longer PICU stays. Those that are intubated later in their admission are noted to have a higher pathogen load, are more likely to require vasoactive medications, and ultimately require antibiotics for longer than their earlier-intubated cohorts.

PATIENT/PARENT ADMINISTERED EPINEPHRINE IN ACUTE ANAPHYLAXIS

Michelle Murata, Loren Yamamoto. Hawaii Pacific Health

Introduction/Background

Among patients with a known peanut allergy, previous studies suggest low carrying rates of epinephrine auto-injectors (EAIs) and hesitancy to self-administer epinephrine upon anaphylaxis onset.

Objective(s)

Given the high prescription rates of epinephrine and prevalence of peanut allergies, our aim was to identify rates of on-scene EAI use and affecting factors.

Methods

The electronic medical records of 217 patients—either with an ED diagnosis of peanut anaphylaxis or diagnosis of anaphylaxis with a known epinephrine prescription from 2010 through May 2020—were reviewed for physician notes and demographic factors.

Results

Epinephrine was administered on-scene by 25.3% of anaphylaxis patients. Of the 6 health care professionals identified, 100% administered epinephrine on-scene. Females (32.2%) were administered epinephrine on-scene more frequently than males (19.8%; p = 0.04). Rate of epinephrine administration increased from 2010 through 2019 (p = 0.005).

Conclusion

This study selected for individuals diagnosed with anaphylaxis, meaning EAI use should have been observed nearly 100% of the time. An administration rate of 22.6% observed among individuals not identified as health care professionals suggests that the majority of patients prescribed epinephrine have not used their EAsIs, even when presented.
an opportunity for application. The administration rate of 100% observed among health care professionals indicates that comfort with EAIs facilitates willingness to administer on-scene. EAIs can range up to $900 in expense, thus physicians should employ EAI training devices and other training strategies.

Pulmonary/Critical Care

1 HUMAN LUNG ENDOTHELIAL CELL BARRIER FUNCTION IS AUGMENTED BY KINDLIN-2

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Introduction/Background We previously reported that lung endothelial cell (EC) inflammatory responses in acute lung injury (ALI) models are mediated by integrin β4 (ITGB4). Kindlin-2 is a leading candidate adapter/activator in this context since ITGB4 contains a known distal consensus sequence (NxxY) for kindlin-2 binding. Moreover, kindlin-2 is known to interact with adherens junctions and focal adhesions to promote EC barrier integrity. Kindlin-2 expression levels are mediated by SMURF1 (Smad ubiquitination regulatory factor-1), an E3 ubiquitin ligase that promotes kindlin-2 ubiquitination and degradation.

Objective(s) We hypothesized that strategies aimed at augmenting kindlin-2 via SMURF-1 inhibition would be barrier protective and may represent a novel therapeutic strategy for ALI.

Methods Initially, to confirm kindlin-2 is involved in EC barrier regulation, we silenced kindlin-2 expression using siRNA (Dharmacon). Human pulmonary artery EC (HPAEC) cells were treated for 3 days with 100 nM of either siRNA specific (Dharmacon). Human pulmonary artery EC (HPAEC) cells were treated for 3 days with 100 nM of either siRNA specific for kindlin-2 (siFERMT2) or scramble siRNA prior to assessment with TER measured over time and, in separate experiments, transwell monolayer flux of FITC-dextran. Next, HPAEC were treated with the A01 (25 mM, 3 d, Millipore Sigma), a high affinity selective inhibitor of SMURF1, prior to thrombin (1 U/ml) mediated by SMURF1 (Smad ubiquitination regulatory factor-1), an E3 ubiquitin ligase that promotes kindlin-2 ubiquitination and degradation.

Conclusion Our data confirm kindlin-2 is an important mediator of EC barrier regulation. Moreover, we found kindlin-2 expression levels are increased in response to SMURF1 inhibition with A01 and treatment of human lung EC with A01 was associated with a significant attenuation of agonist-induced barrier disruption. These data implicate kindlin-2 augmentation as a potential therapeutic strategy for ALI and support further investigation of A01 as a novel treatment for patients with or at risk for inflammatory lung diseases including ALI.

11 PROPHYLACTIC BUT NOT THERAPEUTIC IFN-β DECREASES MORTALITY DURING INFLUENZA INFECTION IN CIGARETTE SMOKE EXPOSED MICE

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Introduction/Background Cigarette smoke (CS) exposure increases the frequency and severity of respiratory tract infections including those due to influenza A virus (IAV) in humans and increases morbidity and mortality in mouse models. During IAV infection, it is still unclear whether type I interferons (IFNs) have protective antiviral effects or contribute to immunopathology, especially in smokers.

Objective(s) To determine whether IFN induction reduces mortality and reduces lung injury in CS exposed mice.

Methods We treated mice exposed to CS for 6 weeks (or not) intranasally with early (prophylactic) or late (therapeutic) IFN-β (2,000 units intranasal). Lung injury was assessed by wet lung/body weight ratio, BAL total cell number, and histopathology. In the early group, mice were given IFN-β at 1 day before and 1 day after IAV infection. In the late IFN group, mice were given IFN-β at day 3 and 4 after IAV infection. We compared the mortality (at 1000 PFU IAV/mouse) and host immune responses (500 PFU IAV/mouse IAV) of early and late IFN treated mice following challenge with IAV.

Results In nonsmoking mice, both early and late IFN-β administration decreased the survival rate in mice infected with IAV. The late IFN-β administration group had the worst survival rate. However, in CS-exposed mice, early IFN-β administration remarkably increased the survival rate by 40% during IAV infection while late IFN-β administration did not alter mortality. In nonsmoking mice, IFN-β administration, especially late administration, significantly increased IAV-induced inflammation and lung injury. As we have shown in earlier publications, CS-exposed IAV-infected mice had a suppressed innate response profile in the lung compared to sham-exposed IAV-infected mice. Here, we found that early IFN-β administration restored the innate immune response in CS-exposed mice to that seen in nonsmoking mice during IAV infection. Additionally, early IFN-β administration to CS-exposed mice did not increase IAV-induced inflammation and lung injury as shown in nonsmoking mice.

Conclusion Our Results demonstrate, although IFN-β administration worsens the susceptibility of nonsmoking mice to influenza infection, early IFN-β administration in mice is protective for CS enhanced susceptibility of smokers during influenza infection. IFN-β administration to nonsmoking mice led to an excessive inflammatory response to virus and contributed to immunopathology. However, IFN-β administration to CS-exposed mice, that have suppression of the IFN response, improved outcomes during influenza infection. Thus, optimizing the IFN response may be an important treatment strategy for CS-enhanced lung infections, particularly those due to viral infection.

12 A ROLE FOR CARMIL 1 IN PULMONARY ENDOTHELIAL CYTOSKELETAL DYNAMICS AND BARRIER FUNCTION

Regain Demeritte, Steven M Dudek, Patrick Belvitch. University of Illinois at Chicago

Abstracts
Introduction/Background Acute Respiratory Distress Syndrome (ARDS) is a severe lung disease with high mortality in the general population. It is characterized by endothelial cell (EC) barrier disruption and vascular leak. Cell membrane associated cytoskeletal dynamics are an important determinant of EC barrier function. Capping Protein Arp 2/3 Myosin 1 Linker (CARMIL1), is implicated in peripheral cytoskeletal regulation in other cell types. Variations in the CARMIL1 gene (LRRC16a) have been associated with clinical ARDS outcomes through preservation of blood platelet count.

Objective(s) In this study, we explore CARMIL1 expression in the endothelium and its association with other known protein regulators of the EC cytoskeleton.

Methods Cultured human pulmonary artery ECs were treated with CARMIL1 siRNA (Santa Cruz) or scramble siRNA x 48 hrs. EC membrane fractions were obtained by differential centrifugation. Protein expression level and phosphorylation status was measured by western blot. Endothelial barrier resistance was determined by electric cell impedance sensing (ECIS). Protein association was determined by immunoprecipitation.

Results CARMIL1 is expressed and associated with the membrane in pulmonary ECs. Immunoprecipitation studies confirmed an association of CARMIL1 and other protein regulators of the cytoskeleton including cortactin. Decreased CARMIL1 expression causes a reduction in the p-mysin light chain (MLC)/total MLC ratio in siCARMIL1 cell lysate vs control (0.524 ± 0.04 vs 0.866 ± 0.06; p < 0.02) and exacerbates reductions in barrier function after thrombin by 15%. Conclusion CARMIL1 is expressed in the pulmonary endothelium. CARMIL1 is associated with other proteins implicated in EC barrier regulation and reduced expression exacerbates decreased barrier resistance secondary to an inflammatory stimulus. Further studies are necessary to investigate CARMIL1 in lung injury.

MLCK activation has distinct effects on proliferation between pulmonary artery smooth muscle and endothelial cells under normoxic and hypoxic conditions

Dustin R Fraidenburg, Noman Baig, Rachel Halstrom, Mariam Anis. University of Illinois at Chicago

Introduction/Background Pulmonary arterial hypertension (PAH) is a debilitating disease which is both progressive and fatal. Myosin light chain kinase (MLCK) phosphorylates myosin light chain and plays an important role in pulmonary artery smooth muscle cell (PASM) contraction and pulmonary artery vasoconstriction. Non-muscle MLCK (nmMLCK) in pulmonary artery endothelial cells (PAEC) causes cellular retraction and is linked to vascular permeability during lung injury. Our prior work has also linked nmMLCK activation to vascular permeability during lung EC retraction and is linked to vascular permeability during lung injury. We hypothesize that the proliferative effects of MLCK is mediated, in part, through extracellular signal-regulated kinase (ERK) activation and influenced by hypoxia.

Objective(s) We hypothesize that the proliferative effects of MLCK activation differ between PAEC and PASM. The pro-proliferative effect of MLCK is mediated, in part, through extracellular signal-regulated kinase (ERK) activation and influenced by hypoxia.

Methods Human PASMcs and PAEC were used in passages 5–7 and whole cell lysates were collected for Western blot experiments. MLCK activity was inhibited with the selective pharmacologic inhibitor ML-7; ERK phosphorylation was inhibited with U0126, a pharmacologic inhibitor of mitogen-activated protein kinase kinase. PASMC and PAEC proliferation was measured with proliferating cell nuclear antigen protein expression and WST proliferation assay. Hypoxia treatment was for 72 hours in 3% O₂ for PASMC and 1% O₂ for PAEC based on previously published Methods.

Results PAEC proliferation is highly correlated with MLCK phosphorylation (p-MLC), and inhibition of MLCK blocks the proliferative effects of vascular endothelial growth factor stimulation or bone morphogenetic protein type 2 knockdown. Inhibition of MLCK in PASMC had minimal effects on proliferation. Inhibiting ERK phosphorylation with U0126 decreased both MLC phosphorylation and proliferation of PAEC yet has no effect on p-MLC in PASMC. PAEC under hypoxic conditions show increased p-MLC that is not clearly associated with changes in proliferation. Similarly, PASMC under hypoxic conditions were associated with strong increases in p-MLC. Inhibiting ERK phosphorylation in hypoxic PASMC was associated with further increases in p-MLC, identifying a potential dissociation of cellular contraction and proliferation under hypoxia.

Conclusion Our data suggests that MLCK activation, at least in part through ERK activity, plays an important role in PAEC proliferation, yet had no apparent effect on PASMC proliferation. In both PAEC and PASMC, there was dissociation between MLCK activation and proliferation under hypoxic conditions. The balance between the contractile and proliferative effects of MLCK activation appear to favor contraction in PASMC under both normal and hypoxic conditions, while MLCK activation contributes to PAEC proliferation under normal conditions but not in hypoxic conditions, potentially favoring contraction.

MRSA modulates histone acetylation in lung endothelium

Elefteria Letsiou, Lucille Meliton, Lichun Wang, Steven M Dudek. University of Illinois at Chicago

Introduction/Background Lung endothelial barrier dysfunction is a hallmark of acute respiratory distress syndrome (ARDS), which is primarily caused by severe bacterial or viral infections. Recently, it has emerged that altered epigenetic processes contribute to the pathophysiology of ARDS. Major epigenetic modifications include lysine acetylation of the H3 histone protein (e.g., H3K9ac), which is a major regulator of transcription. Whether lung endothelial cells (EC) undergo histone acetylation alterations in ARDS is largely unknown.

Objective(s) To investigate the histone acetylation status of lung EC after stimulation with methicillin-resistant staphylococcus aureus (MRSA) and its effects on EC barrier function.

Methods Human pulmonary artery endothelial cells (EC) were treated with heat-killed MRSA (2 × 10⁸/ml) or vehicle for 30 minutes. A ChIP-seq grade antibody against H3K9ac was used to immunoprecipitate DNA bound to H3K9ac. After the DNA was isolated and sequenced, data analysis was performed by the UIC Research Informatics Core. Significant changes in H3K9ac (FDR< 0.05) after MRSA treatment were determined in comparison to control and then processed for further
Introduction/Background Controlled studies show engaging in physical activity (PA) at least 2 times per week, 20 minutes per day, for at least four weeks can improve cardiopulmonary fitness and asthma-related quality of life[1]. Few existing studies focus on lifestyle PA with only two studies assessing the maintenance of effects on PA and asthma outcomes post-intervention. None have focused on minority populations, such as African American (AA) women with asthma, who have poorer asthma outcomes and lowest rates of physical inactivity.

Objective(s) Using stakeholder feedback, we modified and tested a 24-week lifestyle PA intervention to address the unique asthma-related and cultural-specific barriers to PA in African American (AA) women with asthma[2]. Twelve weeks post the intervention (36-weeks), we assessed the maintenance of intervention effects on asthma and daily PA outcomes.

Methods AA women with asthma were recruited from an urban academic health center that cares for underserved populations. Eligibility was based on age (18–70 years old) and sub-optimally controlled persistent asthma based on Asthma Control Test (ACT<20). Data collection included: spirometry, incremental shuttle walk test (ISWT), questionnaires (asthma control, quality of life), daily PA levels measured by accelerometry at baseline, 24- and 36-weeks. Participants were randomized to enhanced usual care or lifestyle PA intervention (ACTION). All participants were given a Fitbit Charge HR™, and attended an asthma education session related to PA. Intervention participants were given an individualized step goal, sent motivational one-way text messages three times a week and asked to attend 5 group meetings over 24 weeks. After 24 weeks, all participants retained their Fitbit but intervention participants stopped receiving text messages and step goals.

One booster group meeting was held around 30 weeks for intervention participants.

Results Fifty-three AA women with asthma were enrolled. Participants were obese (36.44 ± 9.87), low income (60.4% household income <$30,000), had a mean age of 43.38 ± 12.21 and mean ACQ score of 1.76 ± 0.91. There were no differences in baseline characteristics between groups. Clinically significant (MCID=0.5) between group differences at 24-weeks was noted in quality of life (mini-AQLQ: 0.51, 95% CI: -0.11 to 1.14 and asthma control (ACQ: -0.55, 95% CI: -1.17 to 0.06). At 36-weeks, the between-group differences in asthma control or asthma quality of life were not clinically/ statistically significant. PA levels were comparable across groups at 24 weeks; however, significant between-group differences in light (103.33 minutes/day, 95% CI: 25.91 to 180.75, p=0.009) and moderate PA (23.10 minutes/day, 95% CI: 2.87 to 43.31, p=0.03) were found at 36-weeks.

Conclusion The maintenance effects of a lifestyle PA intervention for AA women with asthma impacted health and PA outcomes differently. Modifications in both the adaptive and maintenance phases of the intervention and a longer maintenance period must be considered. Further studies are needed to comprehensively assess the long-term impact of a tailored lifestyle PA intervention for AA women with asthma on health and PA outcomes.
0.05), thus suggesting a general inflammatory response. Importantly, this response was observed in the C57BL/6J but not the BALB/c mice, suggesting a specificity for Th1 and Th17 driven Type 1 inflammation. Specifically, male C57BL/6J mouse lungs exposed to MC-LR produced significant (p<0.05) fold increases in cytokines by protein abundance compared to vehicle control of multiple Th1 and Th17 related cytokines [IL-17a (6.0 ± 0.71), IL-12 (2.3 ± 0.09), CCL3 (8.6 ± 0.58), and CXCL1 (5.4 ± 0.39)], while male BALB/c mice produced no significant increase in these cytokines.

**Conclusion** The results of this study suggest aerosolized MC-LR induces Th1/Th17 pulmonary inflammation and warrants further investigation into the potential impact of MC-LR aerosol exposure in at-risk human populations with pre-existing Type 1 inflammatory pulmonary conditions.

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**Abstract 84 A RETROSPECTIVE ANALYSIS OF FEEDING PRACTICES AND OUTCOMES IN BRONCHIOLITIS PATIENTS ON NIPPV**

Sidharth Mahapatra, Ariann Lenihan, Vanessa Ramos, Nichole Nemec, Joseph Lukowski. University of Nebraska Medical Center, Children’s Hospital and Medical Center Omaha, Boy’s Town National Research Hospital

**Introduction/Background** Noninvasive positive pressure ventilation (NIPPV) refers to the delivery of mechanical ventilation through modalities, such as CPAP, BiPAP, and RAM cannula, that do not require an endotracheal airway. In bronchiolitis, in particular, NIPPV has become the preferred mode of treating acute hypoxemic and hypercarbic respiratory failure and has been shown to lead to lower intubation rates. However, patients with acute respiratory failure present with a profound catabolic response elicited by their critical illness superimposed upon their immobility and an inability to take oral nutrition. Delays in nutrition initiation have been associated with elevated morbidity and mortality in the ICU. That said, aspiration of gastric contents can lead to multiple and severe pulmonary complications, including cough, bronchospasm, pneumonia, and death. Currently, limited data exist regarding the safety of feeding pediatric patients on NIPPV.

**Objective(s)** With this single institution retrospective chart review, we aimed to study the feeding practices and outcomes of feeding pediatric patients with complicated bronchiolitis.

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**Abstract 84 Figure 1** Patient eligibility criteria

A total of 342 patients with acute bronchiolitis were screened for the study. After exclusion criteria, a total of 178 patients were eligible for further analysis. These patients divided into the EN group (114) vs. the NPO group (64).
and acute respiratory failure on non-invasive positive pressure ventilation.

Methods We first interrogated our electronic medical record (EMR) for all pediatric patients with a diagnosis of acute bronchiolitis admitted to the pediatric intensive care unit (PICU) and managed on NIPPV from January 2015 to December 2017. We excluded patients with 1) a corrected gestations age of < 37 weeks at admission, 2) chronic ventilator dependence, 3) post-operative cardiac status, 4) single ventricle physiology, 6) acute GI bleeds, 7) short-gut syndrome, and 8) chronic TPN dependence. We also excluded all patients intubated within the first 24 hours of admission to the PICU. Qualifying patients were divided into 2 groups based on feeding status, i.e., NPO vs. EN (enteral nutrition). We compared groups along the following variables: age, weight, gender, prematurity, pathogen type and burden, duration of PICU stay, days on NIPPV, intubation status. For the PO group, we additional assessed nutrition route, mode, time to full feeds, and feeding complications.

Results Over the 36-month period, 342 pediatric patients were admitted to our PICU with a diagnosis of acute bronchiolitis. After removing patients who met exclusion criteria, we had 178 eligible patients, with 64 in the NPO group and 114 in the EN group. Though well-matched with respect to baseline demographic data, a higher proportion of younger patients were noted in the EN group (p< 0.001). Despite low intubation rates, the NPO group experienced a 3.5-fold higher incidence of endotracheal intubations (p=0.003); multi-microbial infections led to higher rates on intubation in both groups. Although short, duration of PICU stay was shorter in the NPO group; intubation eliminated this difference. For the EN group, the route/mode of highest use for nutrition initiation was NG/continuous. A majority of these patients reached full feeds within 7 days, without complications. When complications were reported, none resulted in escalation of respiratory support. Finally, biomeric data analysis demonstrated a clear improvement in heart rate and respiratory rate after feeding initiation.

Conclusion Our retrospective study reveals important aspects of feeding pediatric patients with bronchiolitis and acute respiratory failure on NIPPV. Despite their younger age, we conclude that initiating feeds in complicated bronchiolitis patients managed on NIPPV is safe, well-tolerated and beneficial. Given that patients in the EN group were younger and had a lower rate of intubation, the benefits of nutrition initiation in this group likely outweighs the complication rate noted in our study. We conclude that nutrition initiation on NIPPV in bronchiolitis patients is both safe and beneficial to their overall disease trajectory.

Abstract 84 Table 3  EN group nutrition data
For the EN group alone, we describe route and mode of feeds, time to initiation and to full enteral nutrition, and any complications including aspiration experienced during their course.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route</td>
<td>PO</td>
<td>11 (10%)</td>
</tr>
<tr>
<td></td>
<td>NG</td>
<td>69 (63%)</td>
</tr>
<tr>
<td></td>
<td>NJ</td>
<td>14 (13%)</td>
</tr>
<tr>
<td></td>
<td>GT/JT</td>
<td>15 (14%)</td>
</tr>
<tr>
<td>Mode</td>
<td>Continuous</td>
<td>85 (78%)</td>
</tr>
<tr>
<td></td>
<td>Bolus</td>
<td>21 (19%)</td>
</tr>
<tr>
<td>Time to EN initiation</td>
<td>≤48h</td>
<td>97 (89%)</td>
</tr>
<tr>
<td></td>
<td>&gt;48h</td>
<td>12 (11%)</td>
</tr>
<tr>
<td>Reached full EN (&lt;7d)</td>
<td>Yes</td>
<td>91 (83%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>18 (17%)</td>
</tr>
<tr>
<td>Complications</td>
<td>Yes</td>
<td>9 (8%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>100 (92%)</td>
</tr>
<tr>
<td>Evidence of Aspiration</td>
<td>Yes</td>
<td>1 (1%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>108 (99%)</td>
</tr>
</tbody>
</table>

Introduction/Background Acute lung injury and the acute respiratory distress syndrome (ARDS) are characterized by pulmonary inflammation and alveolar flooding with protein rich edema fluid following decreased endothelial barrier integrity. Animal models are critical to uncovering the pathologic mechanisms of this devastating syndrome. Intravital imaging of the intact lung via two photon microscopy has proven a valuable method to investigate lung injury in small rodent models through characterization of inflammatory cells and vascular changes in real time. Respiratory motion complicates the analysis of these time series images and requires selective data extraction to stabilize the image. Intravital techniques have also been used to characterize individual alveolar dynamics following injury. However, analysis of individual alveoli may not provide a complete picture of the integrated mechanical, vascular and inflammatory processes occurring simultaneously in the intact lung.

Objective(s) To develop a web-based visualization application named Alveolus Analysis to process, analyze and graphically display intravital lung microscopy data.

Methods The application was created using HTML, JavaScript, and D3. It is supported by a preprocessing backbone built using Python and OpenCV to ingest raw microscopy data. Multiple channels containing data from immunofluorescent labeled leukocytes as well as vascular and interstitial structures are analyzed and quantified. Image playback is displayed next to temporally organized descriptive summary statistics using violin plots, Kiviat diagrams and slope charts.

Results The application presents the user with three views: the processed image at the current timestep overlaid with alveolar contours and simultaneous visualization of leukocytes; a plot of overlaid respiratory cycles across the experiment; and feature focused charts which highlight alveolar and interstitial areas as well as leukocyte counts in the current respiratory cycle and changes in these parameters over the experiment. This graphic display allows characterization of alveolar dynamics, lung edema and inflammatory cells at specific time points as well as summarized over the entire experiment. Two independent time series can be visualized simultaneously in a vertical layout to facilitate direct comparison between experiments.
Conclusion Application of a web-based visualization application, Alveolus Analysis, to intravital lung microscopy data has the potential to enhance the information gained from these experiments and provide new insights into the pathologic mechanisms of inflammatory lung injury.

Rheumatology/Immunology/Allergy

Abstract 13 Figure 1 Image processing and analysis of intravital data
Representative 2-photon microscopy images obtained from mice 16 hours after exposure to heat killed MRSA followed by (A) vehicle or (B) tycipionate were processed and analyzed using a novel web-based application (Alveolus Analysis). The interstitial space was stained with fluorescent dextran (blue). Individual alveoli contours are outlined in white. Neutrophils stained with a fluorescent Ly-6 antibody appear red. (B and D) Individual respiratory cycles are displayed graphically as a function of the percentage of alveolar area through a given time series. The viewed cycle is highlighted in orange and the dot indicates the location of the displayed image within the respiratory cycle. (E) Violin plot showing the distribution of interstitial area over the entire time series

Abstract 85 Figure 1 Image processing and analysis of intravital lung microscopy data

Introduction/Background Prostaglandins (PGs) are physiologically active lipid mediators that are derived from fatty acid arachidonic acid. Two types of prostaglandins have been described: 1) conventional or classic prostaglandins, such as PGD2, PGE2, PGI2 (prostacyclin), PGF2α, and thromboxane A2 (TXA2), and 2) cyclopentenone prostaglandins (cyPGs), which include PGA1, PGA2, PGJ2, and PGJ2 metabolites Δ12-PGI2, and 15-deoxyΔ12,14-PGJ2 (15d-PGJ2). Structurally, cyPGs contain a cyclopentenone ring with a reactive α, β-unsaturated carbonyl group that has the ability to act on proteins and alter their functional properties. CyPGs are potent regulators of many biological processes such as inflammation, cell proliferation, apoptosis, angiogenesis, cell migration, and stem cell activity. In addition, studies have shown that cyPGs have anti-viral activities that allow them to interfere with infection of many viruses, making cyPGs attractive as a potential antiviral therapeutic agent. It is important to understand the mechanisms of how cyPGs interfere with viral infections to fully explore its therapeutic potentials.

Objective(s) The objective of this literature review is to understand the anti-viral properties of cyclopentenone prostaglandins.

Methods This literature review was conducted by performing a comprehensive search of peer-reviewed journals using the PubMed database.

Results Mechanism of anti-viral activities of cyPGs differ between various virus and host cell systems. One-way cyPGs interfere with viral infection is by potently inhibiting viral replication (Figure 1). In the infection of Influenza A, Vesicular Stomatitis Virus (VSV), Herpes Simplex Virus Type 1 and 2 (HSV-1 and 2), and Human Immunodeficiency virus-1 (HIV-1), cyPGs suppress viral replication by altering the viral gene expression and protein synthesis (figure 1). In the infection of Vesicular Stomatitis Virus and Sendai virus, cyPGs inhibit the glycosylation of viral glycoproteins (figure 1). The altered viral glycoprotein lacks the ability to insert into the cell membrane, leading to an inhibition of virus maturation and production.

A second way CyPGs affect virus infection is by inhibiting cell-to-cell viral transmission (figure 1). This action is a result of cyPGs’ anti-proliferative effect on the host cells. In human T-cell leukemia virus type-I (HTLV-I) infected cells, cyPGs inhibit the proliferation of host cells by causing cell cycle arrest. For retrovirus like HTLV-1, integration of proviral genome into the host cellular genome is inhibited by these agents.

Abstract 13 Figure 1 Actions of Cyclopentenone Prostaglandins on various viral infections
Cyclopentenone prostaglandins inhibit the replication of many different viruses by altering viral genes and proteins expression and by inhibiting the viral glycoprotein glycosylation. They also interfere with virus cell-to-cell transmission in human T-cell leukemia virus type I (HTLV-I). In Influenza, human immunodeficiency virus-1 (HIV-1), and respiratory syncytial virus (RSV) infections, cyclopentenone prostaglandins downregulate the virus-induced inflammation.
DNA occurs after initiation of cellular DNA synthesis in dividing cells. Thus, a halt in cell proliferation and cell cycle can negatively impact the permissiveness of recipient cells to HTLV-1. Studies have further shown that cyclopentenone prostaglandins (cyPGs) have a more significant antiproliferative effect and subsequently, a more significant anti-viral effect in more differentiated host cells.

Another anti-viral action of cyPGs is suppressing viral infection induced inflammation (figure 1). Viral infections of Influenza virus, HIV-1, and Respiratory Syncytial virus (RSV) are marked by upregulation of proinflammatory cytokines and chemokines that result in excessive inflammation. Studies have shown that the concentration of proinflammatory molecules correlates with the severity of illness, indicating the importance of inflammation in viral pathogenesis. Treatment of cyPGs substantially decreases the influenza virus induced expression of proinflammatory cytokines IL-6 and TNF-α, as well as chemokines CCL2, CCL3, CCL4, and CXCL10 in mouse model. In RSV infection, cyPGs suppress the release of cytokines TNF-α, GMCSF, IL-1α, IL-6, and chemokines CXCL8 (IL-8) and CCL5. Moreover, in RSV-infected cells and HIV-infected cells, cyPGs are shown to reduce the activity of NF-κB, a transcription factor essential for inflammatory response.

Conclusion This literature review explores the various anti-viral properties of cyclopentenone prostaglandins. CyPGs can inhibit viral replication by reducing viral protein synthesis and by repressing the glycosylation of viral glycoproteins. They can also inhibit cell-to-cell viral transmission by inhibiting the host cell proliferation. Lastly, they can reduce the exaggerated inflammation induced by viral infection. Overall, cyPGs are able to interfere with viral infections and thus, have the therapeutic potential to serve as broad-spectrum antiviral agents.

MALONDIALDEHYDE-ACETALDEHYDE (MAA) AND/OR CITRULLINE (CIT) MODIFIED PROTEINS INDUCE UNIQUE PRO-INFLAMMATORY AND PRO-FIBROTIC RESPONSES BY HUMAN MACROPHAGES

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Introduction/Background Malondialdehyde and acetaldehyde are byproducts of oxidative stress that combine to form a highly stable adduct on proteins we have termed MAA. MAA and anti-MAA antibodies induce pro-inflammatory and profibrotic responses that have been implicated in rheumatoid arthritis (RA) and other inflammatory disease processes. Recently, MAA has been shown to co-localize in RA synovium and RA-affected lung tissues with a unique protein modification (citrullination or CIT) that is highly disease specific for RA.

Objective(s) Macrophages are a critical cell implicated in RA pathogenesis. When stimulated with foreign antigens, immature macrophages (M0) can differentiate into M1/pro-inflammatory-like or M2/pro-fibrotic-like macrophages. Whether proteins modified with MAA and/or CIT, characteristic of RA-impacted tissues, influence macrophage differentiation in RA remains unknown.

Our research question was What are the pro-inflammatory and pro-fibrotic responses that are observed following the stimulation of the THP-1 human macrophage cell line with human serum albumin (HSA) or fibrinogen (Fib) modified with MAA, CIT, and the combination of MAA-CIT?

Methods THP-1 cells were stimulated for 24 and 48 hours with the following antigens: Media, Fib, Fib-MAA, Fib-CIT, Fib-MAACIT, Fib-CIT-MAA, and Fib-CIT-MAACIT. THP-1 cells were also stimulated with HSA modified antigens: HSA, HSA-MAA, HSA-CIT, HSA-MAACIT, and HSA-CIT-MAA. Protein expression was measured by flow cytometry using antibodies for markers of pro-inflammatory (CD14, CXCR1/Fractalkine Receptor) and pro-fibrotic (CD163, CD169, CD206) phenotypes. TNF-α release was measured by ELISA.}

Abstract 32 Figure 1 Summary of THP-1 macrophages cellular responses upon stimulation with modified antigens. A) THP-1 cells macrophage differentiation upon stimulation with HSA modified antigens. B) THP-1 cells macrophage differentiation upon stimulation with HSA modified antigens. C) ELISA analysis for TNF-α release

Abstract 32 Figure 2 Summary of THP-1 macrophages cellular responses upon stimulation with modified antigens. *"NA" = not applicable experiment not done, not expressed, low expression †+medium expression, ‡+high expression

Abstract 32 Figure 3 MFI = median fluorescent intensity. Flow cytometry and ELISA data in 24h HSA antigens treated THP-1 cells. A) Flow cytometry analysis for expression of CD14 and CD169 B) Flow cytometry analysis for expression of CXCR1/Fractalkine Receptor C) ELISA analysis for TNF-α release

A) and B) n=3, *p<0.01, the experiment was repeated twice. C) n=9, *p<0.01
Fib-MAA-CIT, HSA, HSA-MAA, HSA-CIT, or HSA-MAA-CIT. THP-1 cell differentiation to a macrophage type I or II (M1, M2) phenotype was measured using flow cytometry for the expression of selected; M1 markers (CD14, CX3CR1, CD192), or M2 markers (CD163, and CD206). The following cytokines were measured in supernatants from THP-1 cells using ELISA: IL-10 (pro-fibrotic), TNF-α (pro-inflammatory), and IL-1β (pro-inflammatory).

Results THP-1 cells stimulated with HSA-MAA-CIT demonstrated the greatest increase in expression of CD14 and CX3CR1/Fractalkine Receptor and increased TNF-α release following incubation for 24 hours; this corresponded with a M1-like phenotype. An increase in TNF-α (pro-inflammatory) cytokine release occurred at a lesser extent following HSA-MAA-CIT stimulation compared to HSA-MAA. HSA-MAA stimulated THP-1 cells expressed high levels of CD206/Mannose Receptor and released the highest levels of both TNF-α and IL-10, which corresponded to a M2-like phenotype. HSA-CIT stimulated THP-1 cells decreased the expression of CD14 and CX3CR1 and released lower levels of TNF-α compared to HSA-MAA. Cellular responses to modified HSA are summarized in Figure 1A. In contrast to HSA antigens, Fib modified antigens expressed CD163 or CD192/CCR2. Also, unlike HSA-CIT stimulation, Fib-CIT stimulated THP-1 cells expressed higher levels of CD192 and released the greatest amount of both TNF-α and IL-10; and corresponded to a M1-like phenotype. Fib-MAA-CIT stimulated THP-1 cells demonstrated the greatest increase in expression of CD14, CX3CR1, and CD192. However, dually modified (Fib-MAA-
CIT) antigen released significantly lower levels of both TNF-α and IL-10 (pro-fibrotic) compared to Fib-CIT. In contrast, Fib-MAA had the greatest expression of CD163 and CD206 expression and increased IL-1β release, which corresponded to a M2-like phenotype. Cellular response to modified Fib is summarized in Figure 1B.

Conclusion These studies demonstrate that MAA and CIT, in isolation or in combination, yield different biologic effects on THP-1 cells and these effects differ based on the antigen modified. Antigen modification with dually modified MAA-CIT drives predominant M1-like phenotype with some M2-like features. In contrast, modifications with MAA alone drive an M2-like phenotype. The greatest difference was between CIT modified HSA and Fib, where the latter induced stronger M1-like/pro-inflammatory response. These unique MAA/CIT antigen combinations may influence the type and level of cellular responses in the joint and extraarticular tissues that could play a role in the pathogenesis of RA.

**Methods Note Positive controls preparation:**
- M1 phenotype/pro-inflammatory:
  - Stimulation with: 20ng/mL IFN-γ + 10pg/mL LPS
  - Flow: CD192/CCR2, CD14, CX3CR1/Fractalkine receptor positive
  - ELISA: TNF-α release
- M2 phenotype pro-fibrotic:
  - Stimulation with: 20ng/mL IL-4 and 20ng/mL IL-13
  - Flow: CD163 and CD206/Mannose receptor positive
  - ELISA: IL-10 release

**Abstract 32 Supplementary Figure 1** ELISA for TNF-α release after 48h incubation in THP-1 cells with A) HSA antigen B) Fb antigens, n=9, *p<0.01, *p<0.05

**Abstract 32 Supplementary Figure 2** ELISA for TL-90 release after Fb antigens treatment in THP-1 cells with A) 8h incubation and B) 48h incubation, n=9 *p<0.01, *p<0.05

**Abstract 32 Supplementary Figure 3** PCR for CD marker expression in Fb antigen treated THP-1 cells. A) C0192/CCR2 expression after 8h antigen incubation B) C0192/CCR2 expression after 48h antigen incubation C) CD206/Mannose Receptor expression after 48h antigen incubation. n=9, *p<0.01

THE HARMFUL ALGAL BLOOM TOXIN MICROCYSTIN-LR INDUCES AN ANTIBODY RESPONSE: IMPLICATIONS FOR MONITORING EXPOSURE

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Introduction/Background Climate change and eutrophication of water systems has dramatically increased the occurrence of cyanobacterial blooms worldwide. Some of the species of these cyanobacteria produce cyanotoxins, including microcystins (MCs) such as microcystin leucine-arginine (MC-LR) which is
one of the most common and toxic MC congeners. The incidence of human and animal exposure to these toxins mirrors the growing incidence of cyanobacterial blooms and can result in significant morbidity and mortality. The symptoms of MC exposure, like nausea, rash, headache, abdominal pain, fever, etc., overlap with those of many common pathogens, the clinical determination of exposure to this toxin is primarily a diagnosis of exclusion. Diagnosis can become even more challenging when the patients present to the clinic weeks or months after either acute or chronic exposure events. Furthermore, we have found experimental evidence that exposure to MC-LR in common pre-existing disease states such as non-alcoholic fatty liver disease (NAFLD) and inflammatory bowel disease (IBD) increases susceptibility to the negative health effects of MCs. On this background, we sought to determine if MCs such as MC-LR have the ability to induce an antibody response in order to monitor exposure, especially in at-risk populations.

**Objective(s)** The objective of this study was to investigate if oral exposure to MC-LR induced an immunological response and the production of anti-MC antibodies.

**Methods** Three different study designs were used. **Design 1:** Chronic exposure in healthy C57BL/6J mice (Control Study): Ten-week-old male mice were gavaged with vehicle or 100 μg/kg of MC-LR every 48 hours for 4 weeks (15 doses total). **Design 2:** High Fat Diet (HFD) Study: Six-week-old male C57BL/6J mice were fed a choline-deficient 0.1% methionine-containing high-fat diet (CDHFD) to induce NAFLD over a period of 6 weeks. During the 5th and 6th week, the mice continued to be fed on CDHFD and were gavaged with 15 total doses of vehicle or 100 μg/kg of MC-LR every 24 hours. **Design 3:** Inflammatory Bowel Disease (IBD) Study: Eight-week-old C57BL/6J male mice were either given normal water or water with 3% Dextran Sulphate Sodium (DSS) to induce IBD during days 1–7. During days 8–14, the vehicle group was gavaged with water whereas the IBD mice were gavaged with 1000 μg/kg of MC-LR daily. At the end of each study, blood was collected via cardiac puncture into EDTA KE/1.3 collection tubes. Plasma was used for detection of an immune response. An in-house ELISA method was developed to detect the anti-MC-LR antibodies in the plasma samples from the above-mentioned studies.

**Results** To determine if the toxin produces an immune response in the form of antibodies, we measured plasma antibody titers specific to MC-LR using a universal mouse Ig as secondary antibody in the study samples. The exposed samples from the Control study showed a significant 1.8-fold increase as compared to the control, indicating a specific antibody response that is distinguishable from the unexposed control plasma at titers 1:500 and 1:2000. To further characterize the immune response, we utilized an anti-mouse IgG secondary antibody, which revealed a significant 1.7-fold higher response at 1:200 dilution in the exposed vs control, indicating that anti-MC-LR antibodies include the IgG isotype. Similar analysis of plasma samples from the HFD Study and IBD Study revealed significant 1.6-fold higher response to universal Ig at 1:2000 titer in the exposed samples of both studies, and 1.5-fold and 1.9-fold, respectively, to IgG at titers up to 1:200 (p < 0.05 for all).

**Conclusion** These Results indicate that anti-MC-LR antibodies, including IgG antibodies, are detectable in the plasma samples from orally exposed mice in both healthy and pre-existing disease cohorts. Thus, measurement of anti-MC antibodies may be a clinically useful tool in studying the prevalence and in the differential diagnosis of MC-LR exposure.

**Abstract 54 Figure 1** Purpuric papules and patches on bilateral lower extremities
Colonoscopy demonstrated mucosal changes consistent with vasculitis (figures 4 and 5). High-dose intravenous methylprednisolone was administered, with resolution of symptoms. The patient was subsequently discharged on a prednisone taper. He recovered fully, without symptom recurrence or development of chronic kidney disease.

Discussion IgA vasculitis is less common in adults as compared to children but is associated with a worse prognosis. Renal disease is a feared complication of IgA vasculitis that is more frequent and severe in older patients. Though the pathogenesis of IgA vasculitis is not entirely certain, environmental triggers are presumed to inappropriately activate the immune system. This leads to deposition of IgA and Complement immune complexes in small blood vessel walls, which manifests clinically as the characteristic tetrad. Though typically a clinical diagnosis, biopsy with pathology and immunofluorescence may be necessary in patients with atypical clinical presentation or severe renal disease. Antecedent upper respiratory tract infection with Group A Streptococcus species is a common environmental trigger in children but infrequent in adults. Less common triggers include antibiotics, malignancy, and osteomyelitis, all of which were considered in this case. The

Abstract 54 Figure 2 Skin biopsy, Hematoxylin and Eosin, 400X. Polymorphonuclear cell infiltrate (rectangle) with lysis (curved arrow); small vessel injury with endothelial edema and fibrin deposition (double arrows); and red blood cell extravasation (oval)

Abstract 54 Figure 3 Skin biopsy, Immunofluorescence. Immunoglobulin A deposition in dermal papilla arteriole (arrows)

Abstract 54 Figure 4 Colonoscopy: Severe inflammation in terminal ileum, characterized by edema, erythema, and deep ulcerations

Abstract 54 Figure 5 Terminal ileum biopsy, Hematoxylin and Eosin, 40X. Epithelial sloughing (rectangle) and abundant polymorphonuclear cell infiltrate in papillae (oval)
mainstay of therapy for IgA vasculitis is supportive care. Gluco-corticoids are commonly administered and often provide symptomatic benefit. However, there remains a question as to whether these alter the course of disease and/or prevent or treat renal involvement. Further, much of the data regarding treatment of renal disease is extrapolated from studies involving pediatric patients. Prognosis in IgA vasculitis is dependent upon age and severity of renal involvement at presentation, with those who are younger and those who have minimal renal disease having more favorable outcomes.

### SEIZURES WITHOUT OVERT SYSTEMIC DISEASE

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#### Introduction/Background

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology that most frequently involves the lungs. Neurologic complications are estimated to occur in 5–10% of patients and more often occur in patients with known disease but can be the presenting feature. Sinonasal disease is less common occurring in an estimated 1% of patients.

#### Case Presentation

A 28-year-old male with no significant past medical history presents with new onset seizures. He reports being in his normal state of health until the morning of admission. He cannot recall the events leading to his hospitalization but was noted to be acting strange at work and subsequently had two witnessed generalized tonic-clonic seizures. In the emergency department, he had two additional generalized tonic-clonic seizures that resolved with lorazepam. On evaluation he was afibrile, non-tachycardic, tachypneic to 23 breaths per minute, normotensive, and non-hypoxic. Initially he was drowsy and confused. Over the course of several hours, he became more alert and returned to his baseline mental status. Physical exam was otherwise unremarkable. Laboratory evaluation revealed lactate 30 mmol/L, anion gap 43 mmol/L, creatine 1.82 mg/dL, creatine kinase 171,600 U/L, CRP 2.8 mg/dL, LDH 5,448 U/L. Urinalysis showed moderate blood, no red blood cells, no bacteria, and no casts. Chest radiograph showed bilateral perihilar infiltrates. CT head showed low density changes in the bilateral frontal lobes as well as loss of gray-white differentiation within the bilateral frontal lobe that was concerning for developing bilateral MCA distribution infarcts. MRI head showed diffuse nodular leptomeningeal enhancement underlying the orbitofrontal lobes bilaterally that was concerning for meningitis or cerebritis. This was likely contiguous with the opacified left frontal sinus and anterior nasal cavity given the dehiscence or thinning of the bilateral cribriform plate. Lumbar puncture showed 16 nucleated cells with 82% lymphocytes, protein 148 g/L, and glucose 105 mg/dL.

#### Discussion

This case highlights the importance in diagnosis so that appropriate treatment can be initiated. The etiology and pathogenesis of sarcoidosis remains unclear. Neurosarcoidosis can present as a diagnostic challenge given its diverse manifestations and ability to mimic other disease processes. Seizures are an uncommon complication of neurosarcoidosis and are associated with severe disease. In this case, the unique presentation of sinusonal disease and chronic rhinosinusitis heightened initial suspicions for an infectious process. Maintaining a broad differential of diagnoses and recognizing unique ways in which sarcoidosis can present is important in diagnosis so that appropriate treatment can be initiated.

### ANTIOXIDANT THERAPY RESTORES HEPATIC PHASE I & PHASE II METABOLIC ENZYMES ALTERED BY EXPOSURE TO MICROCYSTIN-LR IN A MURINE MODEL OF DIET-INDUCED NON-ALCOHOLIC FATTY LIVER DISEASE

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#### Introduction/Background

Cyanobacteria or blue-green algae are unicellular, autotrophic prokaryotes that thrive in the fresh and brackish waters. Colonies of these bacteria cause dense, noxious blooms that produce cyanotoxins as secondary metabolites. These blooms are an increasing economic and ecological problem worldwide. One of the most noted and potent toxin congeners produced by these bacteria is Microcystin-LR (MC-LR) which is also a known hepatotoxin. The current WHO guidelines for safe exposure to MC-LR have been extrapolated based on studies performed in healthy animal models. However, not much has been known about the effects of these toxins in settings of common pre-existing liver diseases such as Non-alcoholic Fatty Liver Disease (NAFLD). We have previously demonstrated that chronic or short-term exposure to low doses of MC-LR induce hepatotoxicity marked with significant hepatic micro-vesicular lipid accumulation and oxidative stress in mice with genetic or diet-induced NAFLD. Additionally, NAFLD mice exposed to MC-LR demonstrated impaired hepatic metabolism and excretion of MC-LR compared to MC-LR exposed healthy mice.

#### Objective(s)

In the current study we tested the hypothesis that augmentation of hepatic drug metabolism pathways with targeted antioxidant therapies would improve MC-LR metabolism and reduce hepatic injury in NAFLD mice exposed to MC-LR. Antioxidants included augmentation of the glutathione detoxification pathway with N-acetylcysteine (NAC) and interruption of specific Src kinase-mediated oxidant signaling pathways with a novel peptide (pNaKtide).

#### Methods

Six-week-old C57Bl/6J male mice (n=5–8 mice per group) were administered a choline-deficient 0.1% methionine containing high-fat diet (CDHFD) to induce NAFLD over a period of 6 weeks. During the 5th and 6th week, the mice continued to be fed on CDHFD and were gavaged every 24 hours (15 total doses over the 5th and 6th week) with vehicle and methenamine silver stains were negative, further supporting the diagnosis. CT chest showed mediastinal hilar lymphadenopathy and few scattered enlarged intrapulmonary nodes consistent with sarcoidosis. Echocardiogram showed no evidence of cardiac sarcoid. The patient improved clinically and was discharged home on corticosteroids with plans to transition to steroid sparing therapy.
(Control group, 300 µl of vehicle of water, n=5); 100 µg/kg of MC-LR (MC-LR only group, n=6), 100 µg/kg MC-LR and 25 mg/kg of the pNaKtide via intraperitoneal injection once a week at the end of week 5 and 6 (MC-LR+pNaKtide group, n=7); 100 µg/kg MC-LR and 40 mM NAC administered in drinking water (MC-LR+NAC group, n=8). At the end of the study, livers were assessed both histologically and by quantitative real-time PCR for drug transporters as well as Phase I and II drug metabolism enzymes. Protein carbonylation, a typical reactive oxygen species (ROS) induced protein modification of the side chain amines into aminoacyl carbonyls was observed and quantified in the liver sections. 24-hour urine was collected to quantify the 8-hydroxy 2-deoxyguanosine (8-OHGD), a marker of oxidative stress, using a colorimetric ELISA method as well as LC-MS/MS determination of both MC-LR and MC-LR-Cysteine (MC-LR-Cys), an adduct formed during hepatic detoxification of MC-LR.

**Results** Liver weight was not significantly different between the 4 groups; however, histologic analysis revealed a significant increase in hepatic inflammation with MC-LR exposure which was attenuated in both the MC-LR+pNaKtide and MC-LR+NAC antioxidant treatment groups (p<0.05 vs MC-LR for both). 8-OHGD levels in urine and protein carbonylation in liver, both markers of oxidative stress, were significantly upregulated upon exposure to MC-LR but significantly downregulated upon antioxidant treatments after exposure to MC-LR, indicating reduction in oxidative stress. We then investigated the changes in the expression of key drug transporters as well as Phase I and Phase II enzymes using quantitative PCR (qPCR). We observed that exposure to MC-LR significantly upregulated expression of the drug transporter Abcb1a by 248% compared to Vehicle treated. Cyp3a11, a Phase I enzyme belonging to the Cytochrome P450 family, was significantly upregulated by 125% in the MC-LR exposed group as compared to Vehicle. Phase II markers, namely, Pkm (Pyruvate kinase, muscle) was upregulated by 163% whereas Pklr (Pyruvate kinase, liver, and red blood cell) was significantly downregulated by 142% and Gad1 (Glutamic acid decarboxylase) was downregulated by 117%. Antioxidant therapy with both pNaKtide and NAC significantly attenuated these changes (p<0.05 vs MC-LR). LC-MS/MS analysis of 24-hour urine samples revealed that MC-LR+pNaKtide mice had a 2-fold increase in urinary excretion of the MC-LR-Cys metabolite (p=0.09 vs MC-LR) while MC-LR+NAC had a 2.2-fold increase in urinary excretion of the MC-LR-Cys metabolite (p<0.05 vs MC-LR).

**Conclusion** These Results suggest that in a diet-induced model of NAFLD, exposure to MC-LR significantly alters expression of key hepatic drug transporters and Phase I & II enzymes involved in microcystin metabolism. Importantly, MC-LR induced alterations in drug metabolism can be reversed with targeted antioxidant treatment and Results in augmented detoxification of MC-LR.