Abstracts

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Title: Machine learning prediction of visual field defects after stroke using tract disconnection information

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Visual field deficits (VFDs) are a disabling effect of stroke and other acquired brain lesions. Early identification of VFDs is important: patients may not be aware of their presence, which can have important safety implications (e.g. driving). Screening of VFDs on neurological exam has an estimated sensitivity of 50% - 70%. As such, tools to augment traditional screening of VFDs could improve identification of individuals that would benefit from more comprehensive visual field testing. In this study, we evaluated whether imaging-derived lesion location information could be used to identify individuals with VFDs. Lesion data from two stroke cohorts was used: Washington University (N=110) and the University of Padua (N=113). Random forest models were trained on lesion-derived measures from one cohort and used to predict the presence of VFD in the other cohort, with model training and out of sample testing performed in both directions. Specifically, models were trained on atlas-based measures of damage to gray matter regions and disconnection of white matter tracts. Additionally, we performed five-fold cross-validation on a merged dataset to assess the models' performance when trained on larger patient samples. All models were able to produce robust out-of-sample predictions of VFD, regardless of whether they were trained on estimates of regional damage, tract disconnection, or a combination of these measures, andract disconnection measures tended to provide the most predictive power. Together, our results indicate that lesion location information, which can be acquired from routine clinical imaging, can be utilized to identify individuals at higher risk for VFDs. This study provides a promising proof-of-concept illustrating the potential for imaging-based models to supplement neurological examination for the detection of VFDs in patients with acquired brain lesions.

Seizure-induced mortality and CO_2 chemosensitivity in mice lacking the clock gene *Bmal1*

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Epilepsy is a neurological condition causing recurring, unprovoked seizures. Those with epilepsy are at risk of sudden, unexpected death in epilepsy (SUDEP), a fatal complication of epilepsy in which no other cause of death is found. Serotonin system dysfunction has been implicated in the pathophysiology of SUDEP, which is more likely to occur at night when serotonin levels are lowest. *Bmal1* is a clock gene that helps maintain the body's circadian rhythm. When studying these *bmal1* mice, we discovered an additional, unknown mutation that had been mistakenly introduced into the *bmal1* mice. These mice exhibited much lower seizure-induced mortality than what was expected. The purpose of this study was to establish the control mice for this unknown mutation. To do this, we measured their CO_2 arousal response by recording how long it took the mice to wake-up after being exposed to high CO_2. We also measured their hypercapnic ventilatory response (HCVR) by measuring breathing frequency, tidal volume, and minute ventilation in high CO_2 conditions. Lastly, to determine seizure-induced mortality, we induced maximal electroshock seizures at 50 mA. The control mice had expected CO_2 arousal responses, hypercapnic ventilatory responses, and 50% seizure-induced mortality at 50 mA. We conclude that these are effective control mice for this unknown mutation. In the future, we want to generate unknown mutation knock-out mice and repeat these same trials. Overall, we want to further understand the mechanisms and pathophysiology of SUDEP to help with prevention and treatment.

Delivery of Dexamethasone via Pump after Cochlear Implantation to Reduce the Foreign Body Response

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Background: Cochlear implants (CIs) are a neural prosthetic device used to restore hearing ability to individuals with hearing loss. Despite advancements in cochlear implantation techniques and technology, some patients experience delayed residual hearing loss after implantation, which is attributed to several factors, including a foreign body response to the implant, resulting in fibrosis and neo-ossification around the implant. A mouse model shows reduced macrophages infiltration in the cochlea when comparing a dexamethasone-eluting CI and conventional CI. Current dexamethasone elution strategies involve a burst release of dexamethasone from the implant followed by a slow, low-level elution over months. It is not currently understood the long-term impact of dexamethasone elution in the cochlea and if the long-term release is necessary for the therapeutic mitigative effect on reducing the CI foreign body response. This is clinically relevant as long-term immune suppression in the cochlea from dexamethasone could negatively impact tissue remodeling and neuroprotective immune processes.

Purpose: The aim of this study is to determine the efficacy of short-term cochlear dexamethasone delivery in preventing the post-CI foreign body response.

Methods: 3 CX3CR1$^{+/GFP}$ mice were implanted with a cochlear implant and intracochlear pump on the left ear, and an additional 3 CX3CR1$^{+/GFP}$ mice were implanted with just a cochlear implant. The intracochlear pump was programmed to deliver 2 nanograms of dexamethasone over the course of 1 week. At 28 days, the subjects were euthanized and cochleae harvested for histologic preparation, with the contralateral non-implanted sides serving as controls. Cochleae will be perfused fixated in 4% paraformaldehyde and decalcified in EDTA prior to preparation of mid-modiolar 30mm frozen sections on a cryostat. Immunohistochemistry will be performed to compliment the CX3CR1-GFP reporter, including primary antibodies for a-SMA and DAPI and subsequent immunofluorescent secondary antibodies. Next, confocal z-stack images will be obtained on a Stellaris 5 confocal microscope from 3 adjacent mid-modiolar sections. Cell counts will then be obtained using Imaris software, and analysis will be performed in GraphPad Prism using one-way ANOVAs (a=0.05).

Results: Mice that were implanted with CI and osmotic pump showed no decrease in macrophage or neuron density when compared to mice with CI and no dexamethasone.

Discussion: These results indicate that long-term dexamethasone delivery is necessary for reduction of the foreign body response. However, suspected complications could have prevented adequate dexamethasone delivery through the pump catheter, and further study is required in order to confirm dexamethasone delivery.

‘Histopancreatosis?’: A Case of Chronic Granulomatous Pancreatitis

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Keywords: histoplasmosis, histoplasma capsulatum, pancreatitis, IgG4-related disease, interdisciplinary

Case Presentation: A 23-year-old woman from rural Iowa with a history of chronic pancreatic mass of unknown origin (discovered in 2021), chronic pancytopenia, and portal vein thrombosis presented to the emergency department with recurrent RUQ pain and difficulty tolerating oral intake. Vital signs were within normal range. Physical exam revealed mild jaundice, abdominal distension, diffuse tenderness (worst in the RUQ), and palpable splenomegaly without rebound or guarding. Lab results showed elevated total bilirubin (3.0, later 1.8), direct bilirubin 0.3, amylase 34, lipase 80 (later 58), low white blood cell (3.1), low platelets (45, later 28), hemoglobin 12.0 (later 10.2), histoplasma antibody complement fixation 1:8 (previously 1:128 in 2021), negative histoplasma urine antigen, IgG4 of 140, smooth muscle antibody IgG 1:40. Imaging (MRCP/MRI abdomen) revealed a 22x22mm pancreatic head lesion, subacute SMV thrombosis, massive splenomegaly (22.5 cm), and varices in paraesophageal, gastroesophageal junction, perigastric, gastrohepatic ligament, and perisplenic regions. All other labs, including a thorough infectious and autoimmune workup, were unremarkable.

The pancreaticobiliary consult service suggested that the patient's symptoms were likely due to chronic granulomatous pancreatitis caused by histoplasmosis, worsened by pregnancy (the latest in 2022). This conclusion was based on the patient's history, previous positive histoplasma antibody test (treatment was delayed in 2021 due to breastfeeding), necrotizing granulomas on an earlier biopsy, and imaging results. Interventional Radiology declined to perform splanchnic recanalization because of the chronic thrombosis and portal vein collaterals. SMV thrombosis resolved with a heparin drip, and the patient was transitioned to long-term anticoagulation with apixaban for at least six months. This was recommended by Hematology, with Gastroenterology’s approval, as upper endoscopy showed small esophageal varices not requiring banding. The Complex Disease Service recommended starting empiric itraconazole for possible histoplasmosis, repeating an upper endoscopic ultrasound with a biopsy of pancreatic head lesion, and conducting an immune dysregulation workup for potential IgG4-related disease. Infectious Disease agreed with empiric itraconazole due to a lack of better diagnostic explanations, though they noted the presentation was atypical for histoplasmosis-related chronic granulomatous pancreatitis since there were no signs of pulmonary or disseminated histoplasmosis. Hepatology recommended a transjugular liver biopsy with pressure measurements because of the patient’s intermittent hyperbilirubinemia, positive smooth muscle antibody, and portal hypertension signs, suspecting IgG4-related disease. The liver biopsy showed no signs of pathology or IgG4 staining, with normal pressure readings. The patient had four prior biopsies of the pancreatic head lesion at different hospitals, all showing necrotic and histiocytic inflammation suggesting necrotizing granulomas. The Complex Disease Service recommended a fifth biopsy focusing on the lesion's edge for IgG4-related disease, but it showed necrotic material with rare yeast forms and no IgG4-related disease evidence.

Discussion: Histoplasmosis is a fungal disease caused by *Histoplasma capsulatum,* endemic to the Midwestern United States, including Iowa. It spreads through bird and bat droppings in the soil, which can be inhaled by humans. Most cases are pulmonary, but the disease can spread to the CNS, adrenal glands, GI tract, and reticuloendothelial system, especially in immunocompromised individuals, such as pregnant women or those using glucocorticoids. This patient was on prednisone for pancytopenia and hypocellular bone marrow (50-60%) in 2023, which might have been due to undetected histoplasmosis or chronic massive splenomegaly. While histoplasmosis in the pancreatic head is rare, the presentation is more typical of IgG4-RD, which is unlikely in this patient due to inconsistent histopathology and no response to steroids.

Conclusions: Yeast forms of *H. capsulatum* can infect and inflame extrapulmonary organs even without full disseminated histoplasmosis. Atypical presentations of common diseases like endemic histoplasmosis can complicate diagnosis. Interdisciplinary healthcare can improve differential diagnoses, highlighting the debate between Hickam’s Dictum and Occam’s Razor.

Fenfluramine administration and a diet supplemented with whey reduces mortality in Dravet syndrome mice while increasing brainstem serotonin concentrations.

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Rationale: Patients with refractory epilepsy have a high risk of Sudden Unexpected Death in Epilepsy (SUDEP). Dysregulation of the serotoninergic system has been associated with respiratory dysfunction such as respiratory arrest induced by seizures and SUDEP. Knowing this, drugs such as Fenfluramine (FFA) and diets that increase serotonin levels have been approved for Dravet Syndrome (DS) to reduce seizure burden. These data support the idea that a high level of serotonin can prevent seizures and may prevent mortality in epilepsy patients.

Hypothesis: The goal of this study was to explore how the administration of Fenfluramine and a Whey Supplemented Diet (WD) affects (1) spontaneous mortality, (2) heat induced seizure mortality, and (3) brainstem serotonin content in *Scn1a*$^{R1407X/+}$ DS mice.

Methods: The first cohort of mice was used to analyze the effects of a WD. DS mice were provided a regular mouse diet or a diet supplemented with 13% whey beginning at the age they were weaned (P21). One group was video monitored until P60 to measure the rate of death caused by spontaneous seizures. In a second cohort of mice, mortality was determined in response to generalized convulsive seizures induced by hyperthermia (mimicking febrile seizures) .

A second cohort of mice was used to analyze the effects of FFA. DS mice were chronically administered FFA (0,1,3,10, and 30 mg/kg/day) FFA via an intraperitoneal osmotic mini-pump implanted at the age they were weaned (P21). The mice then underwent 10 days of video monitoring to document spontaneous death due to seizures. For those that survived, a Racine scale 5 (R5) seizure was induced by hyperthermia on day 11, and the probability of survival was determined.

A third cohort of mice was used to measure serotonin content in the brainstem. In one group wild type mice were placed on a normal mouse diet or a WD on P21. In a second group, DS mice were treated with 0 or 30 mg/kg/day of FFA by mini-pump and/or placed on a control or WD at the age of weaning. All mice in this cohort were placed under video monitoring for five days followed by rapid brainstem extraction. For all groups, high pressure liquid chromatography was used to measure brainstem serotonin content.

Results: A WD reduced the rate of spontaneous mortality in DS mice. The survival rate at P60 for mice provided a normal diet was 34% (n=66) compared to 58% of mice that were provided a WD (n=69). In addition, mice provided a WD were observed surviving more severe seizures than control mice. A WD also reduced mortality from heat induced seizures, with 100% of mice on a WD surviving R5 seizures (9/9) as compared to 33% on a normal diet (2/6).

Chronic administration of FFA reduced the rate of spontaneous mortality and was protective against heat-induced seizure mortality in a dose dependent manner. For mice receiving the highest dose of 30mg/kg, 78% of mice survived to P27 (n=9) compared to control mice where 63% survived (n=16). Furthermore, 86% of mice survived a heat induced R5 seizure (n=17) while only 20% (n=10) of control mice survived.

FFA and WD increased brainstem serotonin concentrations in a possibly synergistic manner. For wild type mice provided a WD, the average serotonin concentration was 24.03 pg/ul (n=12) compared to 21.56 pg/ul (n=12) for mice on a normal diet. This is an 11% increase in concentration through diet alone. When serotonin content was measured in DS mice placed on WD and/or FFA, the results were very similar. Serotonin content increased by 6-8% with either the WD or FFA alone. In addition, when mice were administered FFA plus WD, the serotonin content was 16% greater than control mice. This suggests an additive effect from FFA and WD on serotonin content.

Conclusion: A WD prevents spontaneous death. WD and FFA prevents heat induced seizure mortality likely in part by increasing brainstem serotonin levels. Also, WD and FFA administered together increased the serotonin level possibly synergically giving us a possible tool to control seizures and prevent death in epilepsy patients.

Modulating Hydrogel Stiffness to Understand the Role of Endothelial-to-Mesenchymal Transition in Age-Related Macular Degeneration

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In the United States alone, more than nineteen million people have developed age-related macular degeneration (AMD) as of 2019. Of this group, 1.49 million people suffer from a more severe stage of the disease known as wet AMD, which is characterized by invasive blood vessel growth. There are many environmental and genetic risk factors for the development of AMD such as smoking and polymorphisms of the *ARMS2/HTRA* genes. Currently, the gold-standard treatment for wet AMD involves anti-VEGF injections, which target and decrease excess blood vessel growth in the subretinal space. Unfortunately, this treatment does not address the scarring due to subretinal fibrosis, a complication of wet AMD. New evidence posits that epithelial/endothelial-to-mesenchymal transition (EMT) of choroidal endothelial and retinal pigmented epithelial cells may be implicated in the progression of AMD. However, the causes of EMT in AMD are still poorly understood. During EMT, cells de-specialize, migrate, proliferate, and contribute to fibrosis and inflammation. In other tissue systems, EMT is often triggered by inflammatory cytokines, and can also be initiated by increases in the stiffness of the surrounding matrix. Because tissue stiffness increases with age and in those who smoke, we hypothesize that matrix stiffness contributes to EMT in the context of AMD.

To further elucidate how stiffening of the local tissue impacts the development of EMT, we seeded choroidal endothelial cells (ChECs) on gelatin methacrylate (GelMA) hydrogels. To simulate tissue stiffening, we subjected these hydrogels to a combination of riboflavin and UV light, which increases the number of crosslinks and thereby stiffens the hydrogel. We measured the compressive modulus of the hydrogels before and after stiffening. We also monitored cell viability using a live/dead imaging kit and characterized gene expression using qPCR of several EMT and ChEC markers. Although some of our data suggest that modulating riboflavin concentration and light exposure time may be used to adjust hydrogel stiffness, these results were inconclusive due to our use of an insufficiently sensitive instrument. The viability of cells seeded on GelMA was not drastically different than on tissue culture plastic, which aligns with previous evidence that cells can attach to and survive on protein-based hydrogels. However, analysis of live/dead images from the stiffened sample group was hindered by the presence of auto fluorescent riboflavin, so we identified an appropriate far-red nuclear dye for future studies. We also found that the presence of GelMA complicated the extraction of high-quality RNA, so we developed several strategies to enhance the extraction process to enable robust qPCR in the near future. Eventually, this in vitro model of tissue stiffening could enhance understanding of the mechanism behind EMT, which could allow for the development of new therapies to slow or treat AMD.

Red- & Near-Infrared Light Therapy Post-Craniectomy Improves Recovery Timelines in Rodent TBI Model

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Traumatic Brain Injury (TBI) poses a complex challenge for both surgical and medical treatment as well as its rehabilitation. Current therapeutic strategies often fall short, and TBI outcomes are often neurologically devastating, with many experiencing persistent motor, cognitive, and sensory deficits. The surgical management of TBI involves decompressive craniectomy (DC) to remove the hemi-cranium, which mitigates rising intracranial pressures and subsequent cortical injury. Long-term outcomes of DC are plagued by permanent neural deficits and other morbidities as it fails to address the brain's intricate recovery process. However, this surgical procedure provides an opportunity to apply adjuvant treatments that would not be feasible with an intact cranium.

Photobiomodulation (PBM), consisting of red and near-infrared light therapy, has emerged as a noninvasive modality with potential neuroprotective and neurorestorative benefits. Light ranging from 600 to 1100 nm has been reported to improve mitochondrial function, reduce inflammation, and promote cell survival and neurogenesis. Recent Studies have demonstrated the efficacy of PBM in improving cognitive function, reducing symptoms of neurodegeneration, and enhancing recovery from neurological injuries. This study investigates the impact of red light (660 nm) and near-infrared light (850 nm) therapies applied to the site of craniectomy post-TBI and hemicraniectomy in a rodent model. We hypothesize that rats receiving red and near-infrared light interventional therapy post-TBI will recover from injury quicker than rats receiving TBI with no intervention.

Long-Evans rats were randomly assigned to one of five groups: (1.) sham control group receiving incision only; (2.) sham control group receiving incision, TBI, and hemicraniectomy; (3.) treatment group receiving TBI, hemicraniectomy, and red-light therapy (660 nm); (4.) treatment group receiving TBI, hemicraniectomy, and near-infrared light therapy (850 nm). Rats were trained to perform a beam walk task to assess motor function pre- and post-TBI and/or therapeutic intervention. TBI-arm rats received a global cortical impact via piston and underwent a standardized decompressive craniectomy procedure to emulate standard of care on Day 0. Red and near-infrared light arms received light therapy in two 30-minute sessions (AM and PM) for five consecutive days. A wavelength of 660 nm (power density to be determined) was applied to the craniectomy site for the red-light therapy group. A wavelength of 850 nm (power density to be determined) was applied to the craniectomy site for the near-infrared light therapy group. To assess fine motor coordination and balance, subjects performed the Beam Walk Test where the number of forelimb and hindlimb foot slips, and time to traverse the beam were recorded to evaluate motor deficits.

The application of PBM therapy using red light (660 nm) and near-infrared light (850 nm) significantly improved motor function recovery in rats post-TBI with hemicraniectomy. Beam walk test results revealed that rats treated with red light (660 nm) demonstrated a marked reduction in total foot slips by Week 2, outperforming all other groups. Similarly, the near-infrared light group (850 nm) exhibited substantial improvement, showing fewer foot slips compared to the control groups. These findings suggest that PBM, particularly red-light therapy, may enhance neurorehabilitation following TBI, potentially offering a non-invasive adjuvant therapy to traditional surgical interventions like hemicraniectomy. Further studies are warranted to optimize the parameters of PBM therapy and confirm its long-term benefits in neural recovery post-TBI.

Unlike conventional treatments that primarily focus on mitigating acute damage, PBM offers a dual benefit by not only reducing inflammation and supporting cell survival but also actively promoting neurogenesis and enhancing functional recovery. The significant reduction in motor deficits, as evidenced by improved performance in the beam walk test, suggests that PBM could be integrated into standard post-operative care following decompressive craniectomy, potentially reducing long-term morbidity associated with TBI.

Title: Incidence of Hydrocephalus in Myelomeningocele Patients in Zambia

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Introduction:
Hydrocephalus has a known association, but variable reported incidence (40-90%) in infants born with myelomeningocele (MMC) in high income countries. The incidence of hydrocephalus in many low-and-middle income countries (LMICs) is unknown, including Zambia.

Purpose: To determine the hydrocephalus incidence in children born with MMC in Lusaka, Zambia.

Methods: This prospective observational study at the major tertiary care center in Lusaka, Zambia included all infants less than 1 year of age born with MMC from May 31 – August 5, 2024. The primary outcome is the development of hydrocephalus at 90 days of life. Hydrocephalus was diagnosed based upon radiographic findings and physical exam findings of elevated intracranial pressure. The secondary outcome is development of surgical complications within 14 days postoperatively.

Results:
25 patients (52% male) presented with MMC during the study window with a median age at initial neurosurgical evaluation of 8 days [IQR 3,19]. The diagnosis of hydrocephalus at 90 days of life was 68% (N=17/25). 84% (N=21) underwent MMC repair at median age 30 days [IQR 15.5,125.8]. Follow-up data was available for 20 patients at two weeks post-operatively. 80% (N=16/20) were diagnosed with hydrocephalus prior to MMC repair and 20% (N=4/20) developed hydrocephalus postoperatively. Of the patients with hydrocephalus, 55% (N=11/20) underwent ventriculoperitoneal (VP) shunt insertion, 10% (N=2/20) underwent endoscopic treatment, and 35% (N=7/20) have had no treatment. The 14-day postoperative overall complication rate was 40% (N=8/20). 25% (N=5) developed wound infection or dehiscence. The mortality rate was 15% (N=3).

Conclusion:
The incidence of hydrocephalus in Zambian infants born with MMC in our cohort is 68% at 90-days of life. A larger study to evaluate hydrocephalus outcomes in these children over the first year of life is in progress.

Analysis of Tibiotalar Joint Contact Stresses in Patients with Cavovarus Foot Pathology

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Introduction

Cavovarus foot deformity affects up to 8-15% of the population. It has mainly been studied in the setting of Charcot-Marie-Tooth (CMT) disease, an inherited neuropathy, but there are a variety of presenting pathologies. Altered biomechanics from cavovarus foot place the ankle at increased risk for developing osteoarthritis (OA). Patients affected by ankle OA experience significant pain, loss of joint function, and inability to bear weight on the ankle. Recent studies have leveraged weight bearing CT (WBCT) to help better characterize joint biomechanics using computational modeling. WBCT enables the creation of 3D models to better analyze joint interactions in the setting of functional loading. The models support the estimating of joint contact stress using discrete element analysis (DEA). We aim to test if these computational techniques can assist in identifying patients at-risk of developing ankle OA secondary to cavovarus foot deformity.

Purpose

Various studies have indicated a link between changes in the morphology of the tibiotalar joint and the development of ankle OA. We hypothesize that a relationship exists between anatomic positioning of the ankle joint and increased asymmetric loading in the setting of cavovarus hindfoot alignment. Associated chronic increases in contact stress would increase the risk of ankle OA.

Methods

Deidentified WBCT scans were obtained in accordance with established IRB protocols. We studied three distinct patient cohorts: healthy controls with no underlying ankle deformity (39 feet), patients diagnosed with idiopathic (IDPATH) cavovarus deformity (24 feet), and patients diagnosed with cavovarus deformity in the setting of CMT disease (22 feet). WBCT scans obtained were segmented using commercial software (DISIOR, Paragon28, Colorado) to generate 3D surface models of the loaded tibia and talus. These models were then aligned and smoothed using Geomagic Design X. Opposing cartilage surfaces were then imported into MATLAB for analysis using previously developed DEA code. DEA treats subchondral bone as a rigid body and articular cartilage as an isotropic linear elastic material, idealized as a bed of springs. DEA was performed in MATLAB over 13 loading instances from the gait cycle with boundary conditions consistent with anatomic loading. Contact stress overexposure (CSTE) was analyzed using previously established methods (Figure 1). Statistical differences between each group were analyzed using a two-tailed Wilcoxon rank-sum test with a significance level of 0.05 ($p < 0.05$).

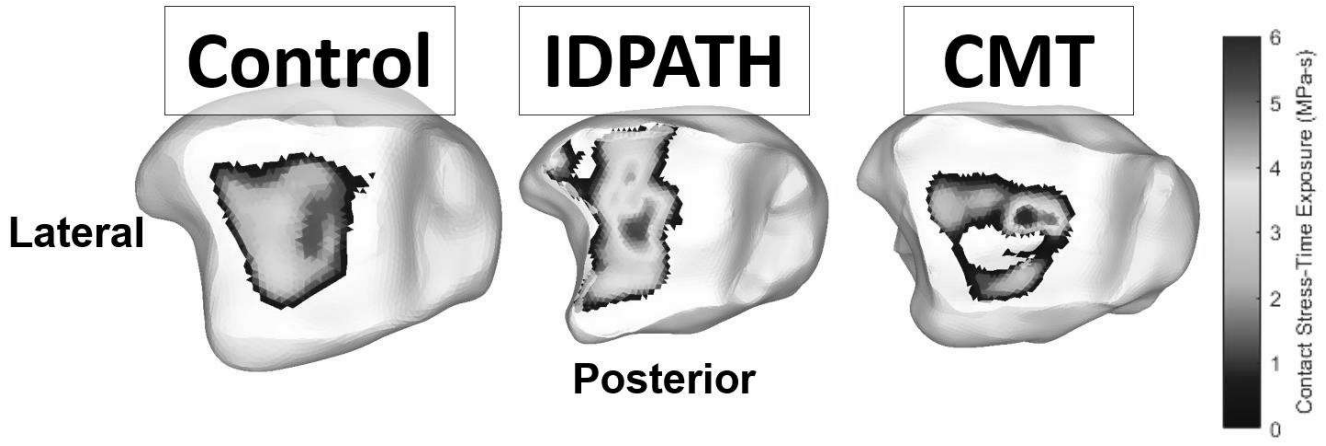
Results

Significant differences were observed between the control group and idiopathic group for both the area over the damage threshold (0.87 mm^2 vs 17mm^2, $p < 0.0001$) and the maximum contact stress overexposure (4.17 MPa•s vs 7.08 MPa•s, $p < 0.0001$). Significant differences were also observed between the control group and the CMT disease group for both the area over the damage threshold (0.87 mm^2 vs 7.39mm^2, $p = 0.01$) and the maximum contact stress overexposure (4.17 MPa•s vs 5.53 MPa•s, $p = 0.007$).

Conclusion

We hope that the development of this model will enable patient-specific prediction of progression to ankle arthritis, leading to subsequent identification, arthritic degeneration prevention, and management of at-risk patients.

Figure 1: Representative Patient Contact Stress Time Exposure Maps



Utilizing Weight Bearing CT to Evaluate ACL Reconstruction Success in Resisting Anterior Tibia Translation

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INTRODUCTION: The anterior cruciate ligament (ACL) helps stabilize the tibiofemoral joint by resisting forces that would otherwise shift the tibia anteriorly, medially, into valgus, and into external rotation relative to the femur. When the ACL is injured, excessive anterior tibial translation (ATT) is the primary clinical diagnostic feature. ATT contributes to knee laxity and puts an individual at elevated risk for additional injury. Amongst measures developed to understand the influence of mechanical forces around the ACL-deficient knee, the ATT appears to be the most reliable. Weightbearing imaging showed positive correlation between ATT and ACL injuries, but it was initially limited to plain radiographs. A recent study introduced weight bearing CT (WBCT) methods to assess knee laxity in five ACL-injured knees. The objective of the present study was to use WBCT to measure knee laxity after ACL reconstruction (ACLR) at timepoints of 3 months and 12 months after surgery. We hypothesized that ACLR knees of patients will show ATT comparable to that in their intact contralateral knee.

METHODS: Sixty individuals (29M/31F, age: 23.4±9.2 years) with a unilateral isolated complete ACL tear reconstructed by one of four surgeons with at least seven years of experience were recruited to participate in this IRB-approved study. A bone-patellar tendon-bone (BTB) graft was used in 12 cases, quadriceps tendon in 39 cases, and hamstring tendon in 9 cases. Bilateral WBCT scans of the knee in flexed and extended poses were acquired at 3 and 12 months post-ACLR. In both flexed and extended poses, absolute values of lateral compartment ATT (LATT) and medial compartment ATT (MATT) were measured for each patient in the ACLR and the non-injured (Control) knee. WBCT images were all analyzed by one orthopedic sports medicine fellowship-trained physician for average flexion angle and ATT. ACLR measurements were then compared to Controls, by follow-up time and type of graft used, using two-tailed t-tests with an α set to 0.05.

RESULTS: All 60 subjects presented to the 3-month WBCT post-operative follow-up, and 23.3% (14/60) have to date received a 12-month WBCT postoperative follow-up in this ongoing study. Mean flexion angles were 22.6° both in the Control and ACLR groups at 3 months, and by 12 months they were 24.1±5.1° in the Control and 25±5.1° in the ACLR. No difference was found between Control and ACLR groups regarding all lateral compartment measurements, whether at 3 or 12 months. In the medial compartment, at 3 months, the MATT in the ACLR group (0.7±1.7mm) was significantly greater than in the Control group (0.3±1.4mm) in flexion (p=0.047). At 12 months, the MATT in the ACLR group (2.0±1.2mm) was significantly greater than in the Control group (1.2±1.6mm) in extension (p=0.048). By 12 months a trend toward an increased LATT was apparent, but it failed to demonstrate significant difference. When evaluating different grafts, ACLR done with quadriceps tendons demonstrated comparable results in all parameters, except for MATT at 3 months, which showed a significantly smaller mean MATT measurement in the Control group (0.3±1.2mm) than the quadriceps ACLR group (0.9±1.6mm) in flexion (p=0.028). However, at the 12-month follow-up, this parameter showed no difference between groups. ACLR performed with BTB grafts appeared to demonstrate a trend of over-reduction (i.e., less MATT in extension) compared to the contralateral Control by 3 months and still appeared comparable by 12 months. Hamstring grafts demonstrated comparable ATT up to 12 months. It showed, however, an increased LATT trend in flexion by the 12-month follow-up that was not significantly different.

DISCUSSION: To our knowledge, this is the first case-series using WBCT to evaluate knees after ACLR. A previous study suggested that there was increased LATT in flexion in the ACL deficient knee, but our study concluded that LATT is comparable to the contralateral intact knee after ACL reconstruction both at 3- and 12-month follow-up. ATT measurements still reveal possible medial laxity that was not addressed by the surgery. In comparing different grafts, our study suggests BTB provides smaller ATT values when compared to the contralateral intact knee, suggesting an over-reduction by 3 months and comparable results by 12 months. Quadriceps autografts also provide comparable ATT with 12-month follow-up. On the other hand, hamstring autograft, although not statistically significant, appears to increase ATT by the 12-month follow-up. Those findings go along with clinical impressions since an increased tibial translation can be noticeable in the physical examination using different graft types.

SIGNIFICANCE/CLINICAL RELEVANCE: WBCT is a promising tool for use in evaluating ATT after ACLR. This study provides evidence that WBCT can be used as a high-quality imaging modality that will be valuable for orthopedists, radiologists, and biomechanical specialists determining the success of ACLR. The ATT measures might be used to understand how the mechanical forces impact the different types of grafts over-time to help reduce re-tear rates.

Platelet-Poor Plasma: A Novel Treatment for Acute Quadriceps Muscle Injuries

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Background: Quadriceps muscle injuries are common and can be associated with a prolonged recovery and high reinjury risk. Platelet-rich plasma (PRP) has been used to help augment recovery and healing after acute muscle injuries. However, the clinical evidence supporting the use of PRP for acute muscle injuries is mixed. Platelet-poor plasma (PPP) has been shown to aid in muscle repair primarily in basic science studies, with limited current clinical evidence.

Hypothesis: PPP is an effective and safe treatment for acute quadriceps muscle injuries

Study Design: Case series; Level of evidence, 4

Methods: Patients with an acute quadriceps muscle injury treated with an ultrasound guided PPP injection were included. All patients were evaluated and treated by the senior author, and the diagnosis of a quadriceps muscle injury was confirmed utilizing sports ultrasound. Following the PPP procedure, patients underwent a structured course of rehabilitation followed by a gradual return to play. The primary outcome of interest was time until unrestricted return to play.

Results: 37 consecutive patients were included with an average age of 22.5 (+/- 4.68) years old. 25 (68%) patients were male. The most commonly injured muscle was the rectus femoris (73%). On average, patients returned to full, unrestricted participation in sport 30 (+/-15) days post-injury. 1 (2.7%) recurrent injury was recorded within 6 months. Patients also reported a significant decrease in Visual Analog Scale (VAS) score at all measured timepoints ($p<0.05$).

Conclusion: PPP may be a safe and effective treatment for acute quadricep muscle strains and may potentially expedite time to return to play.

Identifying admission predictors of poor outcomes in midlife and older trauma patients with rib fractures

Colleen Bloeser, MPH, Colette Galet, PhD, Dionne Skeete, MD.

Introduction. As the US population continues to age, healthcare providers face a new set of evolving challenges. Older trauma patients (≥65 y) historically experience worse outcomes. Today, age alone is not an adequate marker of physiologic fitness and reserve. Thus, additional health predictors must be identified to guide the care of older patients. Evidence suggests that identification of risk factors for adverse outcomes such as pre-injury frailty, may contribute to poor outcomes in patients as young as 50 years old. Frailty scales such as the modified Frailty Index-5 (mFI-5) or the Canadian Study of Health and Aging clinical frailty scale (CSHA CFS), and the Charlson Comorbidity Index (CCI) are possible indicators of health outcomes in these populations. Literature suggests the potential for polypharmacy defined as taking 5 or more oral prescriptions, malnutrition, allergies, influenza immunization, mental illness, and history of fractures to predict health outcomes in adult populations. Determining which predictors are most accurate in determining trauma patient risk will aid health care providers in triage and adaptation of care.

Purpose. Herein, we aimed to identify admission predictors in trauma patients 50 and older with rib fractures.

Methods. This is a retrospective cohort study. The University of Iowa Trauma Registry was queried to identify all trauma patients 50 and older admitted for rib fractures from July 2015 to June 2020, including patients with minimal injuries in other body regions (AIS less than 2). Frailty was assessed using the mFI-5 and CSHA CFS, and defined as an mFI-5 score ≥3 or CSHA-CFS score ≥ 5. Additional data collected included demographics, number of rib fractures, injury severity score (ISS), body mass index (BMI), CCI, polypharmacy, malnutrition as defined by dietician assessment, allergies (drug, food, or seasonal), immunizations, mental illness—anxiety/depression and severe mental illness (bipolar disorder, schizophrenia, or other psychotic disorder), and fracture history. Multivariate analyses were performed to identify predictors of adverse outcomes. Primary endpoints were in-hospital mortality, the development of pneumonia, respiratory failure, and mechanical ventilation or supplemental oxygen. Secondary outcomes were hospital length of stay (LOS), ICU LOS, and discharge to a higher level of care. $P < 0.05$ was considered significant.

Results. A total of 627 patients were included. The median age of the population was 66 (IQR 57, 76); 71.9% of patients were male and 95.5% were white. The median number of rib fractures was 4 (IQR 2, 7) and the median BMI was 28.0 (IQR 24.8, 32.6). Based on the CSHA CFS, 19.0% were frail and, based on the mFI-5, 9.73% were frail. Overall, 60.93% of the population presented with polypharmacy, 7.18% presented with malnutrition, 47.1% had allergies, and 24.9% had an influenza vaccination within the past year. Overall, 24.9% of patients had anxiety/depression and 3.2% had severe mental illness; 19.6% of the population had a history of any fracture, 3.4% had a history of a fragility fracture,1.9% had a history of previous rib fracture; 4.8% of patients had an in-hospital mortality, 3.5% developed pneumonia, 8.8% developed respiratory failure, and 14.7% required mechanical ventilation. At discharge, 41.4% required a higher level of care and 23% were discharged to a skilled nursing facility (SNF). The median hospital LOS was 5 days (IQR 2, 9), ICU LOS was 3 days (IQR 2, 6), and days on a ventilator was 2 (IQR 1, 6). Upon adjustment for demographics, ISS, BMI, and number of rib fractures, CCI was significantly associated with mortality (OR: 1.46, 95% CI: 1.20, 1.77), need for mechanical ventilation (OR: 1.21, 95% CI: 1.03, 1.40), pneumonia (OR: 1.61, 95% CI 1.14, 2.28), and respiratory failure (OR: 1.30, 95% CI: 1.11, 1.53). Polypharmacy was associated with admission to SNF (OR: 1.61, 95% CI: 1.14, 2.28). Presence of allergies was predictive of pneumonia (OR: 3.15, 95% CI: 1.22, 8.09). Upon adjustment for multiple variables, stepwise analysis showed that CCI was associated with mortality, (OR: 1.56, 95% CI: 1.35, 1.82), pneumonia (OR: 1.27, 95% CI: 1.06, 1.53), respiratory failure (OR: 1.27, 95% CI: 1.12, 1.44), mechanical ventilation (OR: 1.14, 95% CI: 1.02, 1.28), total hospital LOS (IRR: 1.04, 95% CI: 1.02, 1.06), and ICU LOS (IRR: 1.14, 95% CI: 1.10, 1.19).

Conclusion. CCI, polypharmacy, and presence of allergies are each associated with poor outcomes in patients 50 y and older with isolated rib fractures. CCI was associated with most outcomes Collecting this admission information may serve as an efficient aid in the triage and adaptation of care for trauma patients 50 y and older.

The Impact of Perioperative Nutrition and Baseline Albumin Levels on Wound Healing in Mohs Micrographic Surgery Patients

Authors: Emma Blomberg, BS, Grace Haugstaud, BS, Sydney E. Rand, BSBA, Morgan Samson, RN, Jessica Flanders, BS Linda Snetsellar, PhD, Nicole Negbenebor, MD, Kelly Messingham, PhD, Jennifer Powers, MD

Background: Malnutrition is a significant predictor of mortality and can increase a patient's susceptibility to poor clinical outcomes. Serum albumin can be used in clinical settings as a marker of nutritional status among patients without significant comorbidities. Malnutrition and inadequate protein consumption can lead to hypoalbuminemia with associated delays in wound healing. Overnutrition can also impact healing due to inflammation, altered immune function, and other physiologic changes associated with obesity. Elderly adults are at heightened risk of malnutrition as they are less likely to obtain adequate nutrients from their diet alone. Many patients undergoing Mohs Micrographic Surgery (MMS) for treatment of skin cancer are elderly, as skin cancer primarily affects patients between their sixth and eighth decade of life. Pre-operative serum albumin levels may be used to predict the quality of post-operative healing and surgical outcomes in these patients.

Purpose: We evaluated the prevalence of malnutrition in the MMS patient population and assessed the relationship between serum albumin levels, nutritional status, and surgical outcomes. We hypothesize that malnutrition as well as diets that are deficient in specific macro- and micro-nutrients in MMS patients leads to both challenges the day of Mohs surgery as well as greater incidence of wound healing complications.

Methods: Following the first stage of their Mohs procedure, serum albumin levels were collected, and the Mini Nutritional Assessment (MNA-SF) was administered to subjects to assess their risk of malnutrition. A food frequency questionnaire (FFQ) and the State-Trait Anxiety Inventory (STAI) were administered to assess subject's dietary habits and emotions regarding their surgery. Chart review was conducted to collect data regarding age, sex, body mass index (BMI), smoking status, current medications, chronic medical conditions, surgical history and insurance status. Subjects returned for follow up visits at 1 week and 2-3 months post-operatively where the Patient Observer Scar Assessment Scale (POSAS) was used to evaluate wound healing from the perspective of both the patient and surgeon. Skin erythema was measured via colorimetry using a CR-400 Chroma Meter for those attending in person follow up. Photographs of the surgical site were scored by the surgeon using the Visual analog scale (VAS). If subjects did not return in person for follow up, the POSAS and VAS measurements were obtained via phone call using photographs.

Results: Subjects were 41 patients (25 White males, 16 White females) with the average age of 69.8. 94% of albumin levels were within normal range (3.5-5.5 g/dL). Similarly, 84% of our subjects scored within "normal nutritional status" on the MNA-SF. Only 1 subject was "malnourished". Albumin levels ($p<0.01$), BMI ($p=0.05$), and Charleston Comorbidity Index (CCI) ($p=0.05$) were significantly associated with the mean MNA-SF score. Albumin ($p<0.01$) was significantly associated with the mean MNA-SF score after accounting for BMI ($p=0.15$) and CCI ($p=0.73$). 75% of subjects met BMI criteria for overweight (25-30 kg/m^2) or obese (>30 kg/m^2). No subjects were underweight according to their BMI. 85% of subjects showed "no or low anxiety" according to STAI scores, which did not correlate with patient or disease characteristics. After 1 week of healing, albumin levels, nutrition assessment scores, and patient/disease characteristics were not associated with healing outcomes provided from POSAS and VAS scores.

Conclusions: This study was limited by its small sample size and relatively homogenous patient demographics. Only short-term healing outcomes have been analyzed at this time. Our results support albumin as a valid marker of nutritional status. Given the high rates of obesity in our patients, the effects of diet control and weight loss on postoperative wound healing are unknown. FFQ data will be analyzed to determine diet quality and identify macro- or micro-nutrient trends associated with healing and surgery tolerance. This study could provide valuable knowledge about indications for perioperative nutritional supplementation to optimize postoperative healing and may be relevant to other surgical outcomes beyond the scope of dermatology.

Block or No Block? Regional Anesthesia and Return-to-Sport Outcomes in Quadriceps Tendon Autograft ACL Reconstruction

Seth M. Borchard, MHA; Nicholas J. Pitcher, BS; Elle M. McCormick, BBA; Robert W. Westermann, MD

INTRODUCTION: Existing research on ACL reconstruction involving patellar tendon (BTB) and hamstring autografts indicate a link between nerve blocks and decreased functional strength at six months in return-to-sport (RTS) testing. There has been a growing usage of quadriceps tendon (QT) grafts in ACL reconstruction in recent years with studies showing increased hamstring stability and improved graft durability, while the effect of nerve blocks on post-operative muscle strength is unknown. This research aimed to compare RTS muscle strength testing in athletes six months following a quadriceps tendon ACL reconstruction performed with or without a nerve block.

PURPOSE: The goal of this research is to determine whether it is in the best interest of young athletes undergoing ACL reconstruction to have an intraoperative nerve block or not. We are seeking to better understand how an athlete's muscle strength is affected by the usage of a block in ACL reconstruction using a quadriceps tendon graft.

METHOD: This was a retrospective analysis of RTS strength testing in competitive or recreational athletes who had a QT ACL reconstruction at a Midwest academic referral center. There were 182 participants ranging from 12 to 29 years of age with a mean age of 16.9 years old. Patients were stratified into two groups based on whether they received an intraoperative nerve (adductor canal) block. Relevant tests performed during RTS testing included isokinetic quadriceps and hamstring strength (ISOK) in addition to limb symmetry and self-reported psychological readiness. Most patients underwent multiple RTS tests; for this study we used the data from their initial test typically done in the six months post-operative timeframe.

RESULTS: 43 patients had an intraoperative nerve block, while 139 did not have a block. There were no statistically significant differences in quadriceps or hamstring strength when comparing the median scores of the nerve block and no-block groups across the major quantitative categories of isokinetic muscle strength or limb symmetry. Isokinetic quadriceps strength performed at 60 degrees/second showed a marginally significant increase in no-block patients though this was not seen when tested at 300 degrees/second.

CONCLUSIONS: No significant differences in functional strength testing at six months were seen in ACL reconstruction involving quadriceps tendon grafts based on block status. There is marginally significant data indicating that there may be increased quadriceps strength at 60 degrees/second for patients not receiving a block. This research strengthens the case for leveraging an adductor canal block in QT ACL reconstruction involving young athletes as an effective tool for pain management without compromising muscle strength or RTS readiness.

Title: Screening Rates of HIV, Hepatitis C, and Syphilis During Acute Stroke Hospital Admissions at The University of Iowa (2016-2020)

Name: Samuel J. Braza, BA, BS

Mentor: Julie C. Gudenkauf, MD

Other Collaborators: Angela Lewis, RN; Heena Olalde, RN; Caroline Lang, BS; Noah Knosp, BA, BS

Introduction: Stroke is a leading cause of death and disability in the USA. Effectively addressing the root causes of stroke and managing patient comorbidities are crucial for optimal stroke care. Infections including HIV, Hepatitis C (HCV), and syphilis are associated with significantly increased risk of stroke and other major adverse health outcomes, and stroke may be the initial clinical manifestation of these infections. Knowing the infectious status of a patient could drastically change acute stroke management, secondary prevention strategies, and patient prognosis. This study aims to examine rates of screening of HIV, HCV, and syphilis in acute stroke hospitalizations at the University of Iowa, a Comprehensive Stroke Center in the United States, between 2016-2020, and determine whether age and other demographic factors predict screening.

Hypothesis: We hypothesize that the overall screening rates for individual infections (HIV, HCV, and syphilis) in acute stroke are low compared to guideline-concurrent screening rates for diabetes and high cholesterol for the period of 2016-2020, and that annual screening rates of these infections will increase over time. We also hypothesize that screening for these infections will occur more often in younger patients compared to older patients, in minority populations, and in those with poorer socioeconomic indices.

Methods: For each admission to the University of Iowa Stroke inpatient service between 2016 and the end of 2020, we reviewed the electronic medical record of the associated patient. Information about HIV, HCV, and syphilis testing were collected. We also abstracted stroke-related diagnostic codes (ICD 10) and patient demographic information (age at time of admission, sex, race, zip code, and insurance type). We analyzed screening rates for HIV, HCV, and syphilis for each year and in total among patients who did not already have known chronic infections. Logistic regressions were performed to analyze whether age and minority racial status were related to infectious screening performance. Additionally, the relationship between age and known chronic infection was also analyzed via logistic regression. Planned analyses will examine the relationships between infectious screening and sex and socioeconomic status.

Results: From 2016-2020, there were 5704 stroke admissions, of which 7 had previously known chronic HIV, 42 had known HCV, and 4 had known syphilis infections. Of the patients who were not known to have these infections at the time of admission, 86 were screened for HIV, 122 for HCV, and 68 for syphilis. Annual screening rates from 2016-2020 for all three diseases were low and did not show consistent increases per year. Rates ranged from 1.06% to 2.25% (mean = 1.51%) for HIV, from 1.31 to 2.74% (mean = 2.14%) for HCV, and from 0.53% to 2.50% (mean = 1.19%) for syphilis. Age was not available for 66 admissions, but among the patients with accessible data, age at admission was found to be inversely correlated with screening rate for HIV ($p < 0.001$), HCV ($p < 0.001$), and syphilis ($p < 0.001$). Increased age was also inversely correlated with likelihood of having known chronic infection of HCV ($p = 0.018$) and syphilis ($p = 0.036$) but not HIV ($p = 0.055$). Minority race was also associated with screening rate for HIV ($p < 0.001$), HCV ($p = 0.015$), and syphilis ($p < 0.001$), though race was not available for 767 admissions.

Conclusion/Overall significance: Screening rates for treatable infectious diseases remain low among stroke patients. Patients who are young or belong to a minority group are more likely to be screened. While Iowa has a lower prevalence rate of HIV compared to the national average, Iowa has worse than national rates of late HIV screening, such that 25% of new diagnoses occur in patients who already have AIDS related illnesses. Any chance for screening vulnerable populations should thus be taken to prevent further disease progression and sequelae, and stroke patients should be included within this category since infectious diseases relate to stroke risk and their presence may change management. Future work will examine if enhanced infectious screening practices in acute stroke hospitalizations can be used to inform the clinical management of stroke and patient outcomes.

Correlating Operating Room Noise during Cesarean Sections with Maternal Stress and Outcomes

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Mentor: Unyime Ituk, MBBS, FCARCSI, MBA
Additional Contributors: Erik Anderson, MD, Carl Skoog, MD

Introduction:
Noise in the operating room (OR) is a recognized hazard, known to impair communication among staff and increase stress levels. While its effects on healthcare personnel have been studied, little is known about patient perception of noise, particularly during cesarean delivery (CD) under neuraxial anesthesia, where patients are fully conscious. This study aimed to investigate if patients undergoing CD perceive OR noise as stressful and to examine the correlation between actual noise levels and patient-reported stress.

Methods:
This prospective observational study was conducted on women undergoing CD at the University of Iowa Hospitals and Clinics. Eligible participants had sound levels recorded in the OR and completed three questionnaires 24 hours post-surgery: the Weinstein Noise Sensitivity Scale (WNSSF), a noise perception questionnaire, and a noise-related stress questionnaire. Noise levels were measured using a Spartan model 730 noise dosimeter, and the study analyzed the correlation between noise sensitivity, perception, and stress, as well as the effect of surgery urgency on noise levels.

Results:
Out of 70 participants, 67 were included in the final analysis. The ambient noise levels in the ORs were 53.4 dB and 58.5 dB, with peak levels of 82.7 dB and 88 dB, respectively. The mean noise sensitivity score was 17.6 (± 3.9). Noise was perceived as very soft or soft by 23% of patients, comfortable by 67.8%, and loud or unpleasant by 9.2%. A significant association was found between noise sensitivity and stress (OR 1.15 [95 CI 1.03 – 1.31], $p = 0.038$).

Discussion:
The study found that a subset of patients experienced noise-related stress during CD, particularly those with higher noise sensitivity. These findings suggest the need for interventions to reduce OR noise or manage patient perceptions of noise. Limitations include the study's single institution setting and the potential for recall bias. Future research should explore strategies to mitigate noise-related stress in surgical environments.

Exploration of Interdisciplinary Treatment for Substance Use and Mood Disorders in Pregnancy

Caroline Brown, Dr. Stacey Pawlak PhD, Xinyu Zhang, Sarah Hambright, Caroline Boyd-Rogers

Introduction: Mental health and substance use disorders during the perinatal period can jeopardize the well-being of both the parent and the offspring, underscoring the critical importance of screening and intervention during this time. The effectiveness of treatment is often hindered by stigma, socioeconomic factors, and limited research into these complex issues. Integrating interdisciplinary care that combines substance use and mental health treatment within standard obstetric practices may enhance outcomes for this vulnerable patient population.

Purpose: This study details the establishment of a maternal substance use disorder (MSUD) clinic within an outpatient obstetric setting at an academic medical center located in a predominantly rural state. Descriptive statistical analyses are provided, delineating maternal and infant variables for 97 individuals receiving care at this clinic. Additionally, the report examines potential associations between these variables and patient outcomes.

Methods: Patients were screened for substance use at both 12-week and 28-week visits using a brief, patient-affirming assessment tool. This tool not only evaluates the patient's own substance use but also collects information regarding the substance use behaviors of the patient's parents, peers, and partner. When a patient screened positive for current substance use or a problematic history of substance use, a brief intervention was conducted by the medical provider. This intervention involved a discussion of the risks associated with substance use. Referrals to treatment facilities were provided as necessary.

Findings/Results: Methamphetamine use and PTSD diagnoses were significant predictors of the total number of perinatal MSUD visits, after adjusting for rurality and substance use (tobacco, marijuana, opioids, alcohol), as well as depression and anxiety diagnoses. Methamphetamine use was negatively associated with perinatal MSUD visits ($B(1) = -0.665$, $P < .001$), with users attending fewer visits ($M = 2.09$) compared to non-users ($M = 3.59$). Conversely, PTSD was positively associated with the number of perinatal MSUD visits ($B(1) = 0.416$, $P = .032$), with individuals diagnosed with PTSD attending more visits ($M = 3.32$) than those without PTSD ($M = 2.75$). Additionally, methamphetamine use and anxiety diagnosis were predictive of total perinatal visits, even after adjusting for the same variables. Methamphetamine use was again negatively associated with the number of visits ($B(1) = -0.567$, $P < .001$), with non-users attending more visits ($M = 7.53$) compared to users ($M = 4.48$). Anxiety diagnosis was positively associated with perinatal visits ($B(1) = 0.319$, $P = .018$), with individuals diagnosed with anxiety attending more visits ($M = 6.76$) compared to those without anxiety ($M = 4.57$).

Conclusions/Overall Significance: This study exemplifies and supports previous research underscoring the benefits of a multidisciplinary approach to perinatal mental health and substance use care. While the current analysis primarily facilitated the exploration of fundamental descriptors and variable associations, future quantitative studies may build upon this research through examining treatment modalities aimed at optimizing outcomes for both the birthing patient and the infant. Future studies may also investigate strategies to enhance patient follow-up and quality of treatment among individuals with methamphetamine dependence.

Alignment of Patient Expectations with Care Provided in the Emergency Department: A Study on Patient Satisfaction

Paisley Bryant, Todd Sexton DO, Alexander Wittry MD, Hayden Smith PhD, MPH

INTRODUCTION: Patient satisfaction in the Emergency Department (ED) is a predictor of the likeliness to return to the ED, post-care health outcomes, and reported quality of care. An understanding of factors contributing to patient satisfaction can provide information to improve satisfaction and care. Additionally, a better understanding of patient expectations at ED arrival may help to reduce miscommunications and wastefulness stemming from providers attempting to fulfill expectations which may or may not be accurate. Collecting data on patient expectations, satisfaction, and the relationship between them offers a starting point for improving communication.

OBJECTIVE: To investigate patient expectations at arrival to the Emergency Department, and to determine if ED factors and alignment of expectations with the care received increases patient satisfaction.

METHODS: A cross-sectional, survey-based study was designed to evaluate patient expectations when they arrive at the ED and how met or unmet expectations factor into patient satisfaction with their experience.
Data collection was conducted at two affiliated hospitals in Iowa from June to August 2024. One hospital was a level I trauma center in an urban setting and the other was a level IV trauma center situated in a nearby suburb. Patients who were under the age of 18, obtunded, incarcerated, had pre-existing cognitive disorders, presented with imminent life-threatening conditions (e.g., cardiac arrest, respiratory failure, etc.), or did not speak English with no translator available were excluded from the study. If a patient could not complete the survey on their own (paralysis, hand injuries, etc.) the person accompanying them, or the researcher completed the survey with permission and supervision from patient.

The study included three forms of data collection: a Pre-Care Survey to assess expectations, retrospective chart review to determine if expectations for testing and intervention were met, and a Post-Care Survey to assess satisfaction. The Pre-Care Survey consisted of multiple-choice questions, whereas the Post-Care Survey was free response questions and a scaled satisfaction question (i.e., 1-5).

RESULTS: Four hundred and twenty-five patients were eligible for the study. Ten patients declined participation and thirteen were unable to complete the Post-Care Survey, resulting in four hundred and two completed surveys. One hundred and ninety-four surveys came from the level I hospital and two hundred and eight from the level IV hospital. Of the total surveys, 73.6% patients reported a satisfaction score of 5 (satisfied) while only 2.99% of patients reported a 1 or 2 (dissatisfied or somewhat dissatisfied).

Two hundred and thirty-two patients (57.7%) waited less than forty-five minutes before being roomed, while the other 42.3% waited longer. Across all patients there was no association between wait time and satisfaction, even though faster timing was one of the top improvements study patients suggested. Additionally, for blood work, imaging, and medications there was no significant decrease in satisfaction when a patient expected a test or intervention and did not receive it. Patients most commonly attributed their satisfaction scores to wait times, staff attitudes, and quality of care. Communication, attentiveness, and kindness were common keywords for patients who reported satisfaction with their visit.

CONCLUSIONS: Patient satisfaction was not associated with wait time increases. Patients who did not receive and expected test or intervention (i.e., blood work, imaging, medication) were approximately as satisfied with their care as patients whose expectations align with received care. Patient satisfaction is complex and likely depends on several factors including more nuanced qualities of care. Ultimately most patients reported being satisfied with their ED visit with many citing staff attitudes, kindness, or communication as reasons why.

“Surgery was a Rotation that I Dreaded:” Medical Student Perceptions of Surgeons

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Introduction: Negative stereotypes of surgeons permeate the media and lay culture. Consequently, medical students may bring biased, unfavorable attitudes about surgeons to the surgical clerkships. These preconceived ideas can negatively impact the surgical clerkship experience - making students less likely to pursue careers in surgery and more likely to maintain negative attitudes toward their surgical colleagues when they enter practice. Given recent trends in declining numbers of surgeons and the impact of workplace conflict on physician burnout, these stereotypes are especially concerning. Developing a more nuanced understanding of medical student perceptions of surgeons may help clerkship directors and surgeon educators use a data-driven approach to prophylactically address common misconceptions during preclinical and clinical medical student didactics to ensure students receive an accurate portrayal of surgeons. The purpose of this study was to qualitatively analyze essays written by medical students during their surgical clerkship and assess students’ perceptions of surgeons as expressed in these essays.

Methods: Qualitative study using essays required to be written by all medical students on the surgical clerkship at a university hospital from 4/2017 to 5/2023. First, we performed summative content analysis and scored each student reflection for their perception of surgeons (positive, negative, or not mentioned). Then, we conducted thematic analysis to identify negative and positive themes related to student perceptions of surgeons. Two investigators reviewed each reflection, and a third investigator ensured consistency and arbitrated disagreements.

Results: Of the 626 student essays reviewed, 308 (49%) included student’s perception of surgeons: 141 students (46%) perceived surgeons positively, and 167 (54%) perceived surgeons negatively. Thematic analysis of the essays identified the following themes: (1) Traits of a good surgeon; (2) Stereotypes- confirmed or debunked; (3) Surgeons as decision makers; (4) Surgeons as communicators; (5) Honesty and disclosure; (6) Patient-centric (or not!); (7) Trust; (8) Informed consent; (9) Negative traits of a surgeon; (10) Professionalism in the operating room; and (11) educators.

Conclusion: Many medical students have negative perceptions of surgeons. Identifying how students justify these perceptions will allow surgical educators to provide targeted guidance to clinical and pre-clinical students to help ensure accurate depictions of surgeons and surgery as a profession. These efforts may improve recruitment of students into the surgical workforce and subsequent multidisciplinary interactions with colleagues.

Impact of the COVID-19 Pandemic on Poison Center Teleconsultation Services for Healthcare Facilities

Student: Zachary Case

Mentor: Priyanka Vakkalanka, PhD **Collaborators**: Eliezer Santos Leon, Daniel McCabe, MD

Background: Consultation with Poison Control Centers (PCCs) by healthcare facilities (HCF) has been shown to decrease potentially avoidable Emergency Department (ED) visits, hospital costs, and length of stay. During the COVID-19 pandemic, EDs and mental health care were significantly impacted, especially in rural HCFs with limited resources and logistical challenges. The aim of this study was to evaluate the impact of the COVID-19 pandemic on PCC teleconsultations with HCF providers for intentional exposures, and to examine if those differences varied between urban and rural HCFs.

Methods: We used a mixed-methods approach with explanatory sequential design. Using quantitative data for intentional exposure cases reported to the National Poison Data System between 2018 and 2022, we analyzed admission type (to critical care [CCU], non-critical care, psychiatric facility) by time period (pre-COVID-19 or COVID-19 era) and geography (urban vs rural). We conducted a sub-group analysis of Midwestern-serving states. After quantitative analyses, we gathered information about the experiences of PCC staff (medical directors and Specialists in Poison Information [SPI]) in managing intentional exposures by qualitative interviewing. We performed qualitative analysis of interview transcripts and identified common codes. We grouped the codes into broader themes and examined urban-rural differences within each theme.

Results: Compared to pre-COVID-19 urban HCFs, rural HCFs had lower non-CCU (aOR: 0.69; 95%CI: 0.67-70) and psychiatric admissions (aOR: 0.80; 95%CI: 0.78-81) in the pre-COVID-19 era, and the COVID-19 era (non-CCU [aOR: 0.66; 95%CI: 0.65-0.67]; psychiatric [aOR: 0.77; 95%CI: 0.76-79]). CCU admissions during the COVID-19 era were lower in both rural (aOR: 0.53; 95%CI: 0.51-0.55) and urban HCFs (aOR: 0.66; 95%CI: 0.64-0.68). Qualitatively, we identified four major themes: Admission/ED Processes, Nature of Calls to the PCC, Operations and Logistics, and PCC to Hospital Communication. With the onset of the COVID-19 pandemic, participants noted admission delays, overwhelmed hospitals, increased strain on PCC staff, and unexpected barriers to follow-up, such as nurse unavailability. Urban-rural differences within each theme had mixed responses.

Conclusions: The COVID-19 pandemic significantly impacted clinical care processes for patients presenting with overdose, with greater disparities in admissions among rural HCFs**.** Challenges identified by PCC staff that contributed to the decrease in psychiatric admissions during the COVID-19 era included the necessary prioritization of COVID-19 transmission and cases. This is concerning as intentional exposure cases and mental health treatment may have been incomplete with sub-optimal clinical care for these patients, suggesting the need to further investigate the impact of unresolved mental health conditions. Despite these trends, PCCs provide a strong public health and clinical infrastructure for providers in HCFs. Future studies should examine the potentially synergistic impact of the COVID-19 pandemic on mental health conditions and the integration of PCC staff with clinical management.

The Effect of FGF21 on Bone Marrow Mesenchymal Cells in Duchenne Muscular Dystrophy

David Chang
Mentor: Hongshuai Li

Abstract

Introduction: Duchenne Muscular Dystrophy (DMD) is a genetic condition caused by mutations within the gene encoding the connective protein dystrophin. Patients with DMD present early on in life with a spectrum of symptoms, including both muscle and bone degeneration. While the muscle loss in DMD has been heavily studied since the condition was first described, the skeletal abnormalities, including osteoporosis and bone deformations have only recently been analyzed. A recent publication by Li et al. characterized a significant increase in levels of FGF21 produced ectopically by dystrophic muscle in mice with DMD; subsequent study showed increased adiposity of bone in mice with elevated FGF21 levels. For a cell to be able to detect FGF21, it requires expression of Beta-Klotho and the FGF21 receptor; in bone, this would include both bone marrow adipocytes and bone mesenchymal stem cells, both of which have bone regulatory capabilities via secretion of various hormones. In this study, we seek to analyze the effect that high concentrations of ectopic FGF21 has on the secretome of these stem cells.

Methods: To further elucidate the effects that high levels of FGF21 has on bone, we isolated Bone Mesenchymal Stem Cells (BMSC's) from human femur marrow and cultured immortalized mouse ST2 cells, treated half with 10nm FGF21 and analyzed RNA expression of a panel of genes after 24 hours of treatment using qPCR.

Results: Initial results showed no significant changes in gene expression between the FGF21-treated and controls in the immortalized line but did seem to reveal significant increases in production of adiponectin in FGF21-treated primary human BMSCs. However, attempts to replicate this experiment have been unsuccessful.

Conclusion: FGF21 may increase production of adipogenic factors in BMSCs, which supports our initial hypothesis that ectopically produced FGF21 contributes to osteoporosis in patients with DMD. Further study is needed, particularly in early passage primary BMSCs and *in vivo*, to accurately describe the effect of FGF21 on BMSC secretomes.

Very Low-Calorie Diet for Metabolic Dysfunction-Associated Steatotic Liver Disease in Obesity

Ethan Chen BS, Leon Sun BS, Marcelo Correia MD MSc PhD

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) has become the leading cause of liver disease in the wake of the obesity epidemic. MASLD is defined as fat infiltration of at least 5% of hepatic volume and is a common complication of obesity that can progress to liver cirrhosis. The management of MASLD relies on interventions that promote weight loss of at least 10%, however, traditional low-fat/low-calorie diets produce weight loss of 5-10%. Very-low calorie diets (VLCD) are manufactured replacement meals used to limit calorie intake to 800 kcal/day. Individuals with obesity who consume VLCD can lose more than 10% of their baseline weight over the course of 2 months. We hypothesized that VLCD can acutely reduce liver steatosis measured with transient elastography (FibroScan) in subjects with obesity and MASLD.

Methods

We treated 7 women [Age 42 years ± 2.2] with obesity [BMI 43.2 kg/m^2 ± 1.7] and MASLD [Controlled attenuation parameter (CAP) 333.3 dB/m ± 16.5] for 8 weeks with VLCD. FibroScan data was obtained before and after the intervention along with vital signs, waist circumference, body fat percentage measured by bioimpedance, and pertinent blood tests.

Results

Across the 8 weeks, adherence to VLCD ranged from 65% to 90%, with a mean of 76%. Weight decreased by a mean of 14.1 kg [± 0.9] or 12% from baseline ($p < 0.0001$). Waist circumference decreased by a mean of 11.6 cm [± 1.8] ($p = 0.001$). Neck circumference decreased by a mean of 2.6 cm [± 0.2] ($p = 0.002$). Body fat percentage decreased by a mean of ~2% [± 0.7] ($p = 0.02$). Systolic and diastolic blood pressures decreased by 12 mmHg [± 2.8] and 11 mmHg [± 1.4] respectively ($p = 0.0002$ and 0.006). HbA1c decreased by 0.27% [± 0.08] ($p = 0.02$) and HOMA-IR declined by 2.17 [± 0.62] ($p = 0.02$). Fasting glucose, triglycerides, ALT, AST and creatinine did not show significant change. Notably, FibroScan showed a substantial decrease in CAP of 97.6 dB/m [± 22.2] ($p = 0.0046$), indicating substantial reduction of liver steatosis. Liver stiffness score did not show significant change.

Conclusions

These results suggest that VLCD is effective for acute reduction of liver steatosis. In addition, this study confirms that VLCD safely and effectively reduces weight, blood pressure, HbA1c, and insulin resistance, at least in the short term. Historically, weight regain commonly occurs after completion of VLCD; however, potent anti-obesity medications may help with the prevention of this weight regain, a hypothesis that needs to be tested in future studies. In conclusion, VLCD can acutely improve MASLD, but its chronic effect on fat liver content remains to be established.

Assessment of prognostic value of baseline hematologic profile in cutaneous T-cell lymphoma

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Background: Cutaneous T-cell lymphomas (CTCL) pose a unique challenge to diagnosis and management due to their protean clinical manifestations, variety of pathologic findings, and lack of reliably effective and durable treatments. Occupying the intersection between oncology and dermatology, CTCL encompasses both primarily skin disease as represented by mycosis fungoides (MF) and leukemic disease, as represented by Sezary syndrome (SS). Optimal management of CTCL requires accurate staging, and currently the NCCN (National Cancer Consortium Network) recommends TNMB integration. With respect to the blood category in staging for CTCL, stratification is based upon peripheral blood flow cytometry (PBFC), which quantifies absolute counts of either $CD4^+CD7^-$ or $CD4^+CD26^-$ cells and stratifies patients into B0 [<250 μL cells], B1 [>250/μL to <1000/μL cells], and B2 [>1000/μL cells]. Although PBFC currently serves effectively as the gold standard for measuring blood involvement in CTCL staging, whether other blood parameters, including complete blood count (CBC) and lactose dehydrogenase (LDH), offer predictive value in staging and prognosis in CTCL patients has not been definitively explored.

Purpose: This study investigated whether complete blood count and lactate dehydrogenase baseline measurements are associated with staging and prognosis of patients with cutaneous T-cell lymphoma, specifically mycosis fungoides and Sezary syndrome.

Methods: This study was approved by our institution's IRB. We performed a retrospective analysis of our multidisciplinary Cutaneous Lymphoma Program registry for all MF/Sezary patients. CBC and LDH data were collected for patients at the time of maximum staging (determined by PBFC). Patients with a lack of appropriate CBC, LDH, or flow cytometry data were excluded. All patient charts were manually reviewed to ensure they met the inclusion criteria, and a profile of clinical, laboratory, and pathologic information were collected. The patient cases were analyzed for the presence of association between each hematologic profile parameter and maximum B stage (determined by PBFC). The frequency of incidental findings by initial bloodwork was also recorded and analyzed. Two-sample t-tests with unequal variances were used to evaluate differences in CBC and LDH biomarkers across maximum B-Stage from PBFC.

Results: 35 CTCL patients met the inclusion criteria. Demographic data show average patient age at diagnosis was 58.2 years, (range 31-89 years), with a sex distribution of 26% females and 74% males and a disease distribution of 89% MF only, 3% SS only, and 9% both MF and SS. Twenty-six patients (74%) were stage B0 at maximum PBFC while 9 (26%) were stage B1/B2. Patients with Stage B1/B2 were noted to have elevated levels of white blood cell count (Mean 16.4 v. 7.5) and LDH (mean 310.3 v. 236.3) when compared to B0, though no hematologic parameters were found to significantly differ according to maximum B-stage ($p>0.05$). Incidental findings were uncommon (2.9%).

Conclusion: While we gather additional patients for a more statistically robust analysis, this study can potentially demonstrate the utility of cheap, relatively easy-to-obtain laboratory parameters in adding value to staging and prognosis in CTCL. The study also documents the frequency that bloodwork can incidentally discover underlying medical conditions such as monoclonal B-cell lymphocytosis or anemia. These results may help further tailor care for CTCL patients according to more refined predictive tools. Future directions for analysis include evaluations of pre-diagnosis CBC and LDH parameters in their association with short- and long-term outcomes, including overall survival, disease-specific survival, and responsiveness to therapy (as reflected by number of systemic therapies instituted).

Evaluation of Systemic and Tissue-Specific Immunotolerance Mechanisms in Patients with Autoimmune Bullous Pemphigoid.

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Background: Bullous pemphigoid (BP) is an autoimmune blistering disease of the elderly (> 60 years of age) that is characterized by an autoantibody-mediated attack on structural proteins in the skin. Since the mechanisms of disease are not well understood, standard treatments consist of broad-based immunosuppression with steroids, which is associated with significant morbidity.

Autoimmunity originates when immune tolerance mechanisms fail. Tolerance in tissues, also known as peripheral tolerance, depends on a balance of activating and inhibitory signals provided by specialized T-cell subsets. Autoreactive T cells are usually suppressed by regulatory T cells (Tregs). Although the target antigens are present in other tissues, the autoimmune response is confined to the skin. This suggests that immune changes leading to BP occur in the skin itself.

Purpose: We hypothesize that the development of BP lesions is associated with tissue-specific alterations in T-cell subsets associated with a loss of immune tolerance.

Methods: Perilesional biopsies of intact skin and peripheral blood mononuclear cells (PBMCs) were collected from prospectively enrolled patients through the dermatology clinics at the University of Iowa. From banked cell and tissue samples, PBMCs were utilized from 20 BP patients and 24 control patients (~40% females and an average age of 77 ± 2 years). CD4+ T cells were purified, and RNA was extracted and reverse transcribed into cDNA. RT-qPCR was performed, and a PCR array was used to detect functional differences in T cell activation and immune tolerance. T-cell subsets and their expression of various activation and exhaustion markers were quantified and analyzed by multicolor flow cytometry. CD4+ FoxP3+ Tregs were evaluated in skin cryosections via immunofluorescent staining and confocal microscopy.

Results: Gene expression of immunotolerance markers, IL2RA, CTLA4, and CD40L, was downregulated in peripheral CD4+ T cells from BP patients ($p<0.05$). The frequencies of T cell subsets, CD4+ T cells, and FoxP3+ Helios+ Treg cells, were similar in BP and controls. Other immunotolerance markers like CTLA-4 and IL4 were similar in BP and controls. In contrast, immunofluorescent staining of FoxP3+ cells in skin cryosections identified a decrease in the percentage area of FoxP3+ cells in BP patients compared to controls ($p < 0.01$).

Conclusion: This study revealed decreased expression of immunotolerance genes but no difference in the frequency of CD4+ T cells or Tregs in the PBMCs, while a significant difference in FoxP3+ cells was identified in perilesional skin biopsies in BP patients versus skin from controls. This suggests that the loss of immune tolerance in BP may be confined to the skin and/or associated with qualitative differences in skin T cell subsets. Further study is needed to evaluate the phenotype and functional changes in cutaneous immune cell subsets in BP.

Comparison of two micro-invasive glaucoma surgeries

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Background:

Glaucoma is a progressive eye disease associated with increased intraocular pressure (IOP). Without treatment, glaucoma can lead to optic nerve damage, constriction of the visual field, and blindness. Glaucoma can be treated using medical and surgical means. Traditional surgical techniques are highly effective at reducing IOP but come with risks and complications including lifelong infection risk. Microinvasive glaucoma surgery (MIGS) techniques such as the gonioscopy-assisted transluminal trabeculotomy (GATT) and goniotomy using the Kahook Duel Blade (KDB) were developed as less traumatic methods to reduce IOP. MIGS procedures work via modification of the trabecular meshwork and provide IOP reduction with decreased risk of complications when compared with traditional surgical methods.

Objective:

Although MIGS procedures are popular for treating glaucoma, the rapid expansion of their usage has drawn scrutiny from health insurance payors including Medicare. This research will be valuable in providing evidence for the efficacy of the procedures that will guide both clinical decision-making and Medicare's reimbursement policies.

Methods:

A retrospective cohort study was conducted comparing outcomes in open-angle glaucoma patients who received a GATT procedure vs those who underwent excisional goniotomy using the KDB tool. The primary outcome measure for this study was postoperative IOP. Secondary outcomes included postoperative medicated eye drop usage, percent IOP decrease, and best-corrected visual acuity (BCVA). Exclusion criteria for this study included age less than 18 years old, previous glaucoma surgery, MIGS procedures other than GATT and KDB, intraoperative procedure failure, and closed-angle glaucoma. The KDB group contained 67 eyes from 48 patients and the GATT group contained 54 eyes from 43 patients. Treatment failure was defined as post-operative IOP greater than 22 mmHg, no reduction in glaucoma medications on post-operative day 30, or second glaucoma surgery.

Results:

At 24 months post-operation, a significantly increased success rate was observed in the GATT procedure group when compared with the KDB group (55.80% vs. 18.18%, $p<0.001$). Additionally, medication burden was reduced from 3.26 medications pre-operation to 1.00 medications post-operation, compared to a reduction of 1.9 to 1.72 medications in the KDB group. A similar pattern was observed in IOP changes, with GATT procedure reducing the average IOP from 24.76 mmHg to 14.35 mmHg compared to a reduction of 15.7 mmHg to 14.84 mmHg in the KDB group at 2 years post-op.

Conclusions:

These data suggest that the GATT procedure more effectively reduces IOP, minimizes the medication burden, and results in a higher overall success rate when compared to goniotomy using KDB. However, these results must be replicated on a larger scale and in a randomized controlled trial.

Metallosis in Posterior Lumbar Fusion: Investigating Corrosive Susceptibility based on Rod Metal Type and Bending Method

Samantha Corman, Catherine Olinger, MD, MS, Douglas Fredericks, Nicole Watson, PhD

Metallosis is an adverse event associated with metal on metal (MoM) implants, identified clinically by tissue discoloration by metal debris. Metal debris is understood to promote a type IV hypersensitivity response, and in the context of spinal implants, can result in loosened or failed devices. There is insufficient understanding of the factors that contribute to metallosis in posterior lumbar fusions (PLF). We investigate how rod material type (Titanium vs Cobalt Chromium) and bending method (pre-bent vs surgeon bent) affects production of metal debris produced in a wear/corrosion test. This project follows a modified ASTM F1717-21 fatigue testing protocol to stress spinal constructs. Resultant wear is analyzed using Inductively Coupled Plasma Optical Emission spectroscopy (ICP-OES) to measure the mass of Ti, Co, and Cr and with stereomicroscopy to localize wear. Preliminary results will be available mid-August focusing on comparing pre-bent cobalt chromium rods and surgeon-bent cobalt chromium rods.

Addressing Tumor Hypoxia through Intratumoral O_2 Injection

Student: Ryan Courtney, BA
Mentor: James Byrne, MD, PhD

Background: Hypoxic conditions are found in and around tumors of all cancer types, making it a popular therapeutic target. Rapid tumor growth can lead to atypical vascularization of tumors, creating areas of hypoxic stress. This hypoxic stress can drive resistance to many conventional cancer therapies, including radiotherapy. Further, the hypoxic stress can drive malignant progression by increasing invasiveness and metastasis. Thus, tumor hypoxia is associated with poorer patient survival. Despite efforts to mitigate tumor hypoxia as a therapeutic strategy, altering the tumor microenvironment has proven difficult. Challenges include optimizing intratumoral oxygen pressures, safety, and treatment logistics. Here, we report on a system for direct intratumoral O_2 injection that synergizes with radiotherapy and demonstrate that tumor oxygenation using this system slows tumor growth and improves survival in a mouse model of sarcoma.

Aim: The aim of this project is to evaluate the efficacy of an oxygen infusion pump to overcome tumor hypoxia in malignant peripheral nerve sheath tumors (MPNSTs).

Methods: Murine MPNST cells were injected subcutaneously in the right flank of female C57BL/6 mice. At two weeks post injection, tumors were catheterized with an 18-gauge needle. Oxygen was injected via a syringe pump at a flow rate of 500 µL/minute up to a pressure of 50 mmHg and maintained at this pressure for 5 minutes. Directly after these 5 minutes, the catheter was removed and a single fraction of 15 Gy radiation was administered to each tumor. Control groups included no gas catheterization + radiation, radiation alone, catheterization alone, and no treatment. Following treatment, tumor volumes were measured 3 times weekly using calipers. Tumor volumes were approximated using the formula V = 0.5 x length (L) x width (W)^2, with length and width corresponding to the x and y measurements of the tumor in mm. Animals were euthanized once a terminal endpoint of the study was reached, which included ulceration around the tumor, tumor volume > 2000 mm^3, weight loss > 20% of initial body weight, and body composition score < 2.

Results: Mice that received O_2 catheterization + radiation demonstrated significant slowing of tumor growth and increased survival compared to all control groups. There were no significant differences in mouses weight between the groups.

Conclusion: Here, we demonstrate that direct intratumoral oxygenation can radiosensitize MPNST tumors in a mouse model. This work is clinically translatable and may be used in combination with current standard-of-care therapies to treat hypoxic tumors.

Abstract Title: Modeling phase I post-anesthesia care unit patient transport times among multiple destinations

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Objective: Previous research has shown that transporter availability for phase I Post-Anesthesia Care Unit (PACU) patients is vital. It is well-known that when the patient census is high, queues for transporters increase rapidly when all transporters are unavailable. As such, days with ≥1 delay in PACU admission can have many such delays. Despite >20 years of subsequent PACU operations management research, there have been **no** publications with PACU transport times analyzed. We describe an implementation of Epic's Rover Transport application for PACU transports, including destinations and round-trip transporter times.

Methods: The University of Iowa IRB determined that the study did not meet the regulatory definition of human subject research. Epic's Rover Transport application at the University of Iowa main hospital's PACU has had complete use July 2022 through April 2024, when analysis began. That interval was 670 calendar days. Epic's SlicerDicer tool was used for data extraction. Transport destination categories were created based on comparable distances from hospital engineering blueprints, all with one elevator transport except the phase II PACU.

All transporters were assigned automatically by the Rover Transport application. The queue of available patient transports was matched to the queue of available PACU-specific transporters, with the transport that had waited in queue for the most minutes automatically assigned to the transporter who had been idle (not transporting) for the most minutes. When the assigned transporter returned to the PACU after the transport, they used their transport app to log completion of the job, at which point they were placed back in the queue of available transporters.

Results: The N =22,846 transport times differed between phase II recovery and each of the other destination categories (all Holm-Šidák adjusted P ≤0.0017). The distribution of the number of transports to each destination category differed among four-hour periods (P <0.0001), as did the distribution of hours of transport time (P <0.0001). The number of transporters beginning shifts of ≥4 hours varied among four-hour periods (P <0.0001). There were relatively few transports in the morning, higher in the afternoon and evening, and then lower in the nighttime (P <0.0001). Total hours of transport time also differed among periods (P <0.0001).

There was a high concordance correlation between actual total transport time and transport times predicted from the number of PACU patient exits, compared pairwise using combinations of four-hour periods and workdays (r=0.97). Even using conservative 95% confidence limits for the limit lines, the pairwise differences were -1.04 hours to +1.05 hours, for a prediction range of 2.09 hours. These limit lines were considerable compared to the mean 57 minutes a transporter spends transporting per four-hour period. Validity of the Bland-Altman analysis was supported by the absence of significant correlation between the differences and the number of transports, examined pairwise among combinations of four-hour period and workday (P =0.21). Validity was also supported by correlation between the differences and the proportion of transporters' turnarounds that were quick (<2 minutes) during the workday's four-hour period (P <.0001). Applying these results, staffing would be based on total hours of transport time per four-hour period, those total hours being approximately normally distributed (Shapiro-Wilk W's >0.98).

We also evaluated whether sample sizes would be feasible for manual data collection (e.g., tracking transport data by hand one day every two weeks). Pairwise comparisons were generated between each workday's "light" periods (08:00–11:59 versus 20:00–23:59) and "busy" periods (12:00–15:59 versus 16:00–19:59). Both pairwise comparisons were normally distributed (Shapiro-Wilk W >0.99). At Type I α = Type II β =0.05, differentiation of hours of PACU transport workload between four-hour periods required total transport data from at least 18 out of every 100 workdays for the "light" four-hour periods, or 44 out of every 100 workdays for the "busy" four-hour periods. Rounding the time of each transport up to the nearest 15 minutes to represent inaccurate manual recording increased the days required to differentiate to 80 between "busy" periods and to 33 between "light" periods. Alternatively, restricting the error rate α=β=0.01 required 80 and 32 days of data for comparisons, respectively.

Conclusions*:* PACU transport times differ significantly among destinations. Therefore, when more than one patient is waiting for transport, target the patient waiting who will generally have the briefest transport, especially if transporting to the phase II PACU. Do not base transporter staffing and scheduling on the distribution of PACU discharges by time of day, rather by the mean and standard deviation of the workday's total transport times during the hour period. Hospitals with Epic should use the Rover Transport application for this purpose if even just for the resulting data collection to optimize staffing.

Melanoma diagnostic revision following pathologic review at an Iowa referral academic medical center

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Background & Purpose: Cutaneous melanoma is affecting Iowans with increasing incidence (5th nationally age-adjusted 2016-2020), escalating the necessity for accurate and precise diagnosis. Given interobserver variability, however, there is potential for discordance, or lack of agreement, in the diagnosis made by individual dermatopathologists on the same glass slides. Literature reports discordance rates of 25-26% for classifying a benign nevus versus malignant melanoma. These substantial reported discordance rates call for increased investigation to inform public health work, as even slight differences in melanoma diagnoses and staging can lead to significant treatment changes including larger surgical excision, invasive sentinel lymph node biopsy procedures, and decisions about immunotherapy. Major histopathologic criteria such as Breslow thickness determine T-staging, which largely determines the treatment plan. Minor criteria such as mitotic rate provide further prognostic information. In Iowa, a largely rural state, many melanoma diagnoses are referred to the dermatology or oncology departments at Iowa Health Care (IHC) in Iowa City which by protocol prompts a repeat pathology interpretation. The frequency and nature of discordance in this re-review, and its impact on patient care has not yet been formally assessed.

Materials & Methods: In this retrospective cohort study, the histopathologic revision of melanoma diagnoses of 243 cases referred to IHC during a 5-year period (2016-2021) was reviewed. In each case, IHC dermatopathologists re-examined glass slides prepared and previously interpreted by pathologists at outside institutions. Diagnoses of melanoma-in-situ and choroidal melanoma were excluded. The frequency of histopathologic revision for both major and minor criteria was examined, with major criteria including Breslow thickness and ulceration, and minor criteria including mitotic rate, histological subtype, Clark level, and the presence of lymphovascular and/or neural invasion, tumor infiltrating lymphocytes, and microsatellitosis. Further analysis was performed to ascertain any effect of biopsy type and margin status on diagnostic revision.

Results: 11.5% (n=26/226) of cases had a discordance in T-staging, which was impacted by Breslow thickness and ulceration status. Of the discordant cases, 34.6% (n=9/26) were due to differences in Breslow thickness measurement, 15.4% (n=4/26) due to differences in ulceration status, and 30.1% (n=8/26) due to IHC upgrading a referring center's diagnosis from stage 0 (melanoma in situ) or unspecified atypical melanocytic proliferation to invasive melanoma (T1a/T1b). Breslow thickness had a discordance of 23.1% (n=54/234). The total percentage of discordance for major criteria, including T-stage, Breslow thickness, and ulceration, was 22.1% (n=27/122). We identified 6.2% (n=14/225) discordance in reporting no mitotic activity versus at least 1 mitosis/mm^2. The total level of mitotic rate discordance was 38.2% (n=86/225). Additional minor criteria included tumor infiltrating lymphocytes, Clark level, and melanoma subtype, which had discordance levels of 21.6% (n=35/162), 14.4% (n=30/208), and 13.0% (27/207), respectively, with 65.6% (n=80/122) of total cases showing discordance in at least one minor element. Margin status was discordant in 6.3% (15/138) of cases. Specifically, referring centers identified transected margins in 30.5% of cases, while IHC only identified transected margins in 23.5% of cases ($p<0.01$). The type of biopsy had a statistically significant association with discordance in identifying transected margins: shave biopsies (17.7%), punch biopsies (12.9%), and excisional biopsies (0%) ($p<0.01$).

Conclusion: Significant discordant elements exist in re-readings of melanoma cases in the state of Iowa, including Breslow thickness, ulceration, and margin status, often influencing staging and therefore treatment decisions. The discordance levels in this study are comparable to the high levels of discordance reported in the literature, including a study performed at Emory University Hospital which documented discordance in pathologic stage (19%), Breslow thickness (65.8%), ulceration (5.1%), and mitotic figures (56%). Whether these second diagnostic reviews translate to improved patient outcomes invites further investigation.

Implementation of an Ultrasound-Based Return to Play Protocol Following Muscle Injury: Effect on Same-Season Recurrent Injury Rate

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Background:

Return to play (RTP) decisions following athletic injury can be extremely difficult due to a constant tension between athlete safety and competitive demand. For these reasons, there has been much interest in assessing techniques for improving RTP diagnostics so that athletes with low-risk injuries can be allowed to return to play as soon as possible while athletes with higher risk injuries can be held out to facilitate further healing. However, this task has proven to be quite difficult as few imaging or clinical measures seem to reliably predict recurrence risk. Ultrasound imaging has been slowly gaining attention in this conversation due to its unique capabilities such as economical serial imaging, Doppler flow, dynamic contraction visualization, and easy facilitation of interventions such as PRP injections and hematoma evacuation. The University of Iowa Sports Medicine Department began implementing a novel RTP protocol for the Track and Field and Women's Soccer teams that utilizes these features in the fall of 2019. This study aimed to evaluate the efficacy of this new protocol in improving recurrent injury rates.

Hypothesis:

We hypothesized that there would be a decrease in recurrence rate in thigh muscle injuries on the University of Iowa Track and Field and Women's Soccer teams when comparing the 2014-2019 and 2019-2024 seasons. We also predicted that athletes who were adherent to the protocol from 2019-2024 would have a lower recurrence rate than those who were non-adherent during the same time period.

Methods:

Injury data was collected from both the SIMS and Smartabase athletic training databases along with clinical data from EPIC. Recurrent rates from 2014-2019 were compared to 2019-2024. Recurrence rates within the 2019-2024 group were also analyzed based on adherence to the new protocol. In order to account for inter-patient correlation, statistical models were used to calculate odds ratios for each of these comparisons.

Results:

When comparing the cases adherent to the protocol to the cases from 2014-2019 for recurrence rate, there was an odds ratio of 0.13 (95% CI: 0.01-1.15, p=0.068). The comparison between adherent and non-adherent cases from 2019-2024 yielded an odds ratio of 0.12 (95% CI: 0.01-1.24, p=0.072).

Conclusion:

Our results showed sizable reductions in recurrence rate as a result of protocol implementation, although these results did not meet our threshold for statistical significance. However, the results are encouraging given the small sample sizes available. As a retrospective pilot study, these findings warrant further evaluation of the novel ultrasound RTP protocol with a well-powered prospective experimental design, perhaps with multi-site involvement to more definitively determine its efficacy in clinical practice.

Cystic fibrosis transmembrane conductance receptor as a mediator of oxidative stress in pancreatic ductal adenocarcinoma

John Davelaar, Yunxia O'Malley, Anna Prouty, Zachary Campbell, Aliye Uc

Background: Reactive oxygen species are highly reactive molecules that are biproducts of natural cellular processes, such as aerobic respiration. ROS generation and elimination are closely regulated and in circumstances where ROS concentration exceeds the body's ability for elimination, cellular and systemic damage can occur. One disease that is closely associated with elevated ROS is cystic fibrosis (CF) due to mutations in the cystic fibrosis transmembrane conductance receptor (CFTR) gene that, in addition to other outcomes, limits CFTR-mutated cells' ability to efflux glutathione yielding decreased endogenous antioxidant capabilities and increasing ROS concentration. In 2019, a combination of elexacaftor, tezacaftor, ivacaftor (ETI) received FDA approval to target the F508del mutation in CFTR to restore function and outcomes for CF patients. CFTR's function in oxidative stress is relevant beyond the primary CF disease, as increased life expectancy in CF patients has revealed associations between CFTR mutations and other diseases such as pancreatic ductal adenocarcinoma (PDAC). PDAC is one of the deadliest malignancies among all cancers and is being projected to become the second-leading cause of cancer-related death by 2030. Increased oxidative stress biomarkers are known to be negatively correlated with overall survival in PDAC. ETI has been revolutionary in the treatment of CF; however, the effects of ETI on *CFTR* function in the pancreas, oxidative stress levels, and cell proliferation in PDAC has not been elucidated and warrants investigation.

Hypothesis: We hypothesize that oxidative stress and cell proliferation in pancreatic ductal epithelial cells derived from a CFTR-mutated PDAC cell line (CFPAC1) will be mediated by CFTR.

Methods: In our cell culture experiments, the effects of ETI were assessed against DMSO as DMSO is utilized to solubilize ETI into solution for treatment. In our first experiment, CFPAC (F508del mutated CFTR) and Panc1^{cftr-} cell lines were cultured for 3 days in the culture media containing ETI or DMSO. Following the treatment period, flow cytometry was utilized to analyze median cellular fluorescent intensity of ROS (dichloro-dihydro-fluorescein diacetate), mitochondrial superoxide (mitosox red), and the mitochondrial transmembrane potential (tetramethylrhodamine methyl ester). In our second experiment, a cell proliferation assay was conducted in which each cell line was plated and grown in the presence of ETI or DMSO with cell counts recorded daily to assess growth and treatment effects over time. In our last experiment, cells were grown to form a fully confluent monolayer, then scratched with a 3D-printed wound-making tool, and finally the area of the wound was assessed each day using ImageJ.

Results: We found that ETI treatment significantly decreased total ROS ($p<.001$) in CFPAC cells compared to DMSO while Panc1 cells exhibited significantly increased ROS ($p=.011$) following ETI treatment. In both cell lines, mitochondrial superoxide increased following ETI treatment (CFPAC - $p=.053$, Panc1 – $p<.001$) with no decrease in transmembrane potential suggesting that mitochondrial integrity is maintained. In the proliferation assay, ETI slowed cell growth in both cell lines (CFPAC – $p=.002$, Panc1 - $<.0001$). Additionally, we found that in CFPAC cells, ETI slowed wound closure in the scratch assay at both 1 and 2 days ($p<.0001$, $p=.0001$, respectively) compared to DMSO treatment.

Conclusions: In a cell culture model of PDAC, CFTR therapy decreased total ROS levels and slowed cell growth while increasing mitochondrial superoxide levels. Further investigation into the role of CFTR in PDAC and cellular metabolism is warranted.

Cytokine Responses to Blood Transfusion in Premature Infants: Neurocognitive Performance and Sex Differences

Neena Deshpande
Mentor: Amy L. Conrad, PhD
Collaborators: Henry Feldman, PhD, Peggy Nopoulos, MD, Amanda Benavides Mostek, MD

Introduction: Anemia is commonly seen in preterm infants and is usually treated using RBC transfusions. However, transfusion also carries risks due to an immunomodulatory role on infant development, so it is critical that it is used appropriately. Emerging evidence regarding sex as a biological variable in disease pathophysiology and treatment response supports the need for further investigation into appropriate treatment for preterm infants. In recent studies, female preterm infants with anemia appeared to benefit most from receiving fewer transfusions and tolerating a greater degree of anemia, while best outcomes in male infants were seen when anemia was minimized through liberal utilization of transfusions. Also, there were sex differences observed in inflammatory responses to transfusion. MCP-1 increased with number of transfusions in only female preterm infants and was associated with worse cognitive and motor performance at 12 months. TNF-β was the only cytokine identified that was higher in males compared to females after transfusion and was associated with better cognitive outcomes at 12 months.
Purpose: In this secondary analysis of the Transfusion of Prematures (TOP) clinical trial, we investigated the relationship between pretransfusion hemoglobin (ptHb), cytokine markers, and cognitive performance in preterm infants at 24 months. We hypothesized that the sex differences found in the relationship between ptHb, cytokine levels, and cognitive outcomes would be replicated (i.e., higher ptHb and higher MCP-1 levels will be associated with worse outcomes for females, while higher ptHb and higher TNF-β levels will be associated with better outcomes for males). Further, we hypothesized that the relationship between ptHb and cognitive performance would be mediated by cytokine levels.
Methods: This study used a subset of the participants enrolled in the multicenter TOP trial who received care at the University of Iowa. Infants enrolled in the trial were under 1000g at birth, gestational age at least 22 weeks but less than 29 completed weeks, and less than 48 hours of age at enrollment. Standard 15ml/kg RBC transfusions were administered, and blood samples were collected at least once per week as clinically indicated per NICU policy, not timed in relation to blood transfusions. Samples were scavenged for cytokines using the Three Meso Scale Diagnostic LLC multiplex kits. Infants returned for a follow-up visit at about 24 months corrected age. The Bayley Scales of Infant & Toddler Development, 3rd Edition (BSID) were used to evaluate cognitive status. We assessed the influence of ptHb on neurodevelopment at 24 months using repeated-measures regression analysis, conducting separate analyses for males and females. Mean cytokine levels during the TOP hospitalization (TNF-β, IL-6, IP-10, MCP-1, log-transformed to reduce skew) were added individually to the regression model to test for mediation of the predictor effect.
Results: 80 infants had transfusion data, cytokine analysis, and 24-month BSID completed. 21 infants were excluded due to sepsis or necrotizing enterocolitis. Three other male outliers identified through iterative reweighting were excluded. Male and female groups did not have significant differences in gestational age, birth weight, ptHb, cytokine levels, BSID scores, age at BSID testing, or incidence of ROP or IVH. Mean SNAPPE score was significantly lower in males (40) than females (54), though both were above the threshold for high risk of mortality (37). For females, higher mean ptHb was significantly associated with lower BSID scores, with an over a 4-point decrease in BSID per g/dL increase in ptHb. When controlling separately for levels of each cytokine, the relationship between ptHb and BSID was not significantly diminished, indicating a lack of cytokine mediation. After the variability accounted for by ptHb, IL-6 had significant predictive value. Specifically, there was a 1.5-point decrease in BSID for each 25% increase in IL-6. TNF-β, IP-10, and MCP-1 did not add significantly to the prediction of BSID at 24 months after controlling for ptHb. For males, ptHb was not significantly associated with BSID, with or without controlling for TNF- β, IL-6, IP-10, and MCP-1. After accounting for ptHb, TNF- β significantly contributed to the prediction of BSID, and there was roughly a 2-point increase in BSID scores for each 25% increase in TNF- β.
Conclusion: This data supports the existing body of evidence showing best outcomes in female infants treated using lower ptHb thresholds and male infants treated using higher ptHb thresholds. This study also builds upon the previous analysis at 12 months to demonstrate an association between TNF- β levels and increased BSID scores in males, as well as inflammatory cytokines and poorer BSID scores in females. Although cytokines do not appear to be mediating the effect of transfusion on BSID scores in males or females, specific cytokines do appear to have independent effects on neurodevelopmental outcomes.

Gut Microbiome Composition and its Association with Multiple Sclerosis Relapse: A Shotgun Metagenomic Study Correlated with MRI Findings

Sandeep Dhingra, MS; Sudeep Ghimire, PhD; Nicolas Wasko, MD; Ashutosh Mangalam, PhD

Multiple Sclerosis (MS) is a chronic autoimmune disease with inflammatory demyelination of the central nervous system. Studies have displayed the role of gut microbiota dysbiosis and gastrointestinal disorders and their link with the pathobiology of multiple sclerosis. However, there is no consensus on specific gut bacteria, potential mechanisms that contribute to disease pathogenesis, or disease severity and progression over time. Specifically, data correlating MS relapse based on MRI imaging is lacking. To address this, we evaluated whether there is a correlation between MS patients' microbiome and future disease and disease relapse. Electronic medical records (EMRs) of patients diagnosed with MS and enrolled in the study at the University of Iowa Health Care (UIHC) Department of Neuroimmunology were analyzed. A total of 190 patients were enrolled in the study, but shotgun-metagenomic sequencing of the stool microbiome was performed on 45 MS patients and 51 healthy controls (HC). Recent MRI imaging results categorized stable disease versus active disease with relapses. Patients with relapses were further divided into one or more than one over the course of the study. Thus, there were three groups: no MRI activity (mostly quiet or clinical remission), one relapse, and more than one relapse. Shannon diversity analysis showed a significant difference ($p = 0.041$) between patients with quiet disease versus those with relapse; however, beta-diversity (Bray Curtis dissimilarity based PCA) was not different among groups ($p = 0.3$). Lefse-based differential analysis showed the enrichment of multiple bacterial taxa in each group. Patients with relapses showed an abundance of Methanobactera species. Those with quiet disease as per MRI results showed an enrichment of Parabacteroides and Bacteroides species. Our study characterized the diversity of gut microbiota species in active MS versus quiet MS, shedding light onto the role of the gut microbiome in MS relapses and severity.

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Oxidative Stress and Inflammation in Posterior Cruciate Ligaments of Bariatric Arthroplasty Patients

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INTRODUCTION: Total knee arthroplasty (TKA) is standard of care for end-stage osteoarthritis. Obese patients have worse outcomes and higher complication risks compared to non-obese patients, and these outcomes may be due to increased inflammation associated with increased adipose tissue rather than merely additional mass. 3-nitrotyrosine (3-NT) is a marker on cellular proteins produced by iNOS via addition of nitric oxide and radical oxygen species during states of oxidative stress. CD68 is a marker of activated monocytes (primarily macrophages). Together, these markers can indicate the M1 inflammatory potential of certain tissues. In this study, we aimed to quantify the presence of these two inflammatory markers in posterior cruciate ligament (PCL) specimens of patients undergoing TKA to assess their role in degenerative joint disease (DJD).

METHODS: PCL specimens were obtained intraoperatively from 39 TKA patients. The average age was 64.5 (SD = 9.8), the average BMI was 34.9 (SD = 6.1), and 54% were female. Formalin fixed, paraffin-embedded tissue was sectioned and stained for 3-NT and CD68 macrophages using immunohistochemistry. Slides were scanned and then analyzed using Olympus OlyVIA and ImageJ/FIJI. 20 regions of interest (ROI) were randomly selected on each slide. We used color deconvolution and particle analysis to identify nuclei and DAB staining. The percentage of positively stained cells per ROI was calculated. These values were compared to BMI (overweight, obese class I, obese class II, obese class III) and age (45-55, 56-65, 66-75, 75+) using ANOVA, and compared to sex (male or female) via t-test. Two slides were excluded from the study due to inability to analyze from slice preparation error.

RESULTS: 3-NT production was significantly elevated in all patients greater than 55 years old (n=29), and CD68 macrophage infiltration was significantly increased in patients 66-75 years old (n=13). Males had both significantly higher 3-NT production and CD68 infiltration compared to females (n=14). The number of percent positive 3-NT cells significantly decreased between overweight and obesity class I patients ($p<0.0001$). However, an increase in 3-NT production is then seen as BMI progresses from class I to class III. The overall difference in percent positive 3-NT cells was statistically significant between all BMI groups except between obesity class I and class II ($p<0.0001$), with the highest percentage of 3-NT in the overweight and obesity class III populations. The difference in percent positive CD68 infiltration between BMI groups was statistically significant in all groups except between overweight and obesity class II, and between obesity class I and class III ($p<0.0001$). When comparing the ratio of the percentage of CD68:3-NT, we found that 50% of the 3-NT was being produced by CD68 macrophages in the overweight population, while nearly 100% was being produced by CD68 macrophages in the obesity class II population. However, every BMI category showed at least one patient with greater than 100% 3-NT production from CD68.

DISCUSSION: Interestingly, there is a stark increase in 3-NT production in all our patient specimens after the age of 55 years old, which begins to diminish upon reaching the 76+ age group. This may be indicative of an increased oxidative or inflammatory process occurring in these patients that begins to decline as metabolic health slows and overall aging occurs. Contradicting our hypotheses, we also found male subjects to have both increased 3-NT and CD68, which was surprising due to literature supporting pro-inflammatory phenotypes to be more genetically prevalent in females. The initial decrease in 3-NT production between overweight and obesity class I populations may be associated with lower overall NO production in obese patients, thus resulting in lower 3-NT formation. However, the subsequent increase in 3-NT production from obesity class I to class III may be indicative of increased radical oxygen species production independent of NO in these populations. In addition, although CD68 macrophage infiltration decreased in higher BMI populations, the CD68:3-NT ratios exceeding 100% in all BMI populations suggests persistent 3-NT production from an alternative radical oxygen species-producing cellular source. Overall, we show statistically significant differences in an unexplored area of inflammatory characteristics of the bariatric arthroplasty population. Future directions of this study aim to address its limitations, such as quantifying 3-NT in a non-obese control group to assess whether the levels of 3-NT in obese patients differ from baseline. In addition, we would like to use immunohistochemical analysis to stain for fibroblasts and neutrophils to locate the primary cellular source of inflammation in soft tissues of the knee, as well as staining for IL-1β, TNF-α, and MMP's to further investigate the inflammatory activity in these tissues. CD206 macrophage staining should also be considered to explore the possibility of an M1 to M2 macrophage transition, which, in combination with adiposity and histologic architecture analysis, could help identify areas of fibrosis and weakening of these ligamentous knee structures. Biomechanical analyses of cadaveric knee ligaments (including PCL) are currently being performed to investigate mechanical differences in these tissues across BMI categories. Ultimately, we aim to determine whether these inflammatory changes lead to differences in surgical outcome of TKA or disease progression among patients with differing BMI's and body composition.

SIGNIFICANCE: While literature has primarily focused on inflammation's effects on cartilage and subchondral bone in the progression of DJD, we aim to focus on the lesser explored topic of its effects on the biomechanically important ligamentous structures of the knee. Hypothesizing that different patient populations may have different inflammatory characteristics in these structures, we hope that these findings will impact pre-, post- and intraoperative decision making when choosing constraint and construct options when performing bariatric arthroplasty surgery and treating bariatric arthroplasty patients.

Development of Gene Therapy Vectors to Treat Cerebellar Disorders

Student: Amanda Dougherty, M2
Mentor: Samuel M. Young, Jr., PhD

Introduction: Cerebellar degeneration is associated with various genetic disorders that gradually cause the loss of Purkinje cells. The Purkinje cell is the neuron responsible for the sole output of all motor information from the cerebellar cortex and is essential for coordinating movements, maintaining balance, and fine-tuning motor control. Viral vector gene therapy has emerged as a possible strategy for addressing cerebellar degenerative disorders as it enables the expression of functional genes through the delivery of therapeutic transgenes. While adeno-associated virus vectors (AAVs) and Lentiviral vectors (LVV) have had success, many of the disease-related genes have a cDNA size that exceeds the packaging limits of those vectors. For Adenoviruses (Ad), the most common vectors utilize the Group C Ad5 serotype capsid proteins, which rely on the Coxsackievirus-Adenovirus receptor (CAR) to infect cells. However, these Ad5 vectors are unable to transduce many neuronal cell types that are dysfunctional in many CNS disorders, including Purkinje cells. The human CD46 (hCD46) receptor is widely expressed throughout the human CNS and is the primary attachment receptor for many other Ad serotypes. To overcome the current limitations of Ad vectors to treat CNS disorders, we created chimeric first-generation Ad vectors that utilize the hCD46 receptor.

Hypothesis/Purpose: We hypothesized that by swapping the fiber and knob domain of the Ad5 vector with the same domain from other Ad serotypes that use the hCD46 as their primary attachment receptor, we could transduce Purkinje cells and expand the current utility of Helper Dependent Adenovirus (HdAd) vectors for cerebellar disorders.

Method: Two novel chimeric adenoviral vectors were produced containing the serotype 5 capsid and the fiber and knob domains of serotypes 35 or 50. These vectors expressed the fluorescent reporter protein mClover3 under the control of the cytomegalovirus (CMV) promoter, creating Ad5/35 CMVmClover3 and Ad5/50 CMVmClover3, respectively. The chimeric vectors were co-mixed with a red fluorescent protein expressing Ad5 CMV mCherry vector and stereotactically injected into the cerebellar cortex or deep cerebellar nuclei of wildtype and “humanized” transgenic mice that express the hCD46 receptor. One week after the injection, the brain tissue was collected, sliced, immunostained for PCP2, a Purkinje cell-specific marker, and imaged using confocal microscopy.

Results: Both Ad5/35 and Ad5/50 were effective in transducing Purkinje cells in a hCD46-dependent manner upon injection into the cerebellar cortex and deep cerebellar nuclei. Expression of mClover3 in Purkinje cells for both viruses was only observed in the hCD46 transgenic mice. Expression of mCherry from the Ad5 vector was not observed in any Purkinje cells for either the WT or hCD46 animals. Furthermore, we found that both Ad5/35 and Ad5/50 can undergo retrograde transport upon entry from the axon terminals due to the expression of mClover3 in Purkinje cells far from the DCN injection site.

Conclusion: We aimed to enhance the utility of HdAd vectors for treating cerebellar disorders by developing novel chimeric adenoviral vectors that exhibit altered tropism for Purkinje cells. By swapping out the fiber domain of Ad5 with those from Ad35 and Ad50, we were successful in transducing Purkinje cells in our humanized transgenic mouse model. Future studies to optimize the delivery and test on a larger scale may contribute to finding a gene therapy cure for cerebellar neurodegenerative disorders.

Optimizing Suturing Pressure in Aortic Valve Replacement: A Prototype for Color-Releasing Compression Pods to Reduce Paravalvular Leak

Cody J. Dvorak, Arun K. Singhal, Suresh M.L. Raghavan, Ned Bowden, Shanari M.R. Wickremasinghage

Background: Paravalvular leak (PVL) is a known complication of aortic valve replacement (AVR) in which retrograde blood flow occurs between the implanted valve and native tissue. An improper seal of the replacement valve can be the result of inadequate suturing pressure or calcification buildup. Clinical consequences of PVL may include prolonged surgical time, infection, anemia, heart failure, and in extreme cases, death.

Purpose: Current AVR technique requires the completion of valve replacement before PVL can be tested for and identified, ultimately leading to prolonged operation times. Real-time identification of locations with increased PVL risk would offer advantages in heart valve replacement operations. This research presents the design and development of a color-releasing polymer compression pod that indicates optimal suturing pressure, aiming to reduce the risk of PVL during valve replacement operations.

Methods: Initial designs focused on a colored, liquid-like polymer contained within an outer coating of a stiffer, biocompatible polymer. When compression force between the native tissue and replacement valve is applied to the polymer pod, the outer coating breaks, releasing the inner colored polymer into the surrounding environment. Prototypes utilized Polylactic Acid (PLA) dissolved in Dichloromethane (DCM) as the outer polymer coating of the compression pod. Limitations due to manual construction required the PLA outer coating to be applied in 2 layers, a top and bottom. PLA was poured onto glass slides, leveled off to a pre-set thickness and cooled. A pre-measured drop of Polyethylene Glycol (PEG) mixed with food dye was placed on the PLA bottom layer. The PEG center was then covered with PLA and cooled, allowing for a complete seal between the PLA layers. Several variables were tested, including PEG molecular weight (MW), temperature during pod construction, and PLA bottom layer thickness. Other prototypes were made with a mold, giving pre-determined boundaries for the PEG to set in. Alternatives for both PLA and DCM were also tested for their effectiveness in pod prototype construction.

Findings: A 3:1 ratio of 600:8,000 MW PEG proved to be the most stable PEG for compression and pod construction. Tetrahydrofuran (THF) was found to be a more effective solvent than DCM. Compression testing of a prototype using these parameters saw proper leakage of the PEG through the PLA outer coating. Results were repeatable with no evidence of delamination or PLA breakdown.

Conclusion: The development of an effective prototype successfully demonstrates the potential of a color-releasing compression pod. Once the pod design is adjusted to break at an ideal compression force, it can serve as an accurate indication of optimal suturing pressure being applied to a replacement valve. This could help ensure proper seal of the implanted heart valve and ultimately reduce the occurrence of PVL during AVR operations.

Gabe Ewert
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Investigating Outcomes and Predictors of Response to Transcranial Magnetic Stimulation for Treatment-Resistant Depression Using the NIH Toolbox Emotion Battery

Introduction/Purpose:

Depression is a widespread mental disorder hallmarked by low moods, low energy, and the inability to enjoy life. Unfortunately, about 30% of people do not respond to typical antidepressant medications, in a condition called treatment-resistant depression (TRD). Transcranial Magnetic Stimulation (TMS) is one of the treatments which has been developed for TRD. In TMS, the patient receives trains of magnetic pulses, typically to the left dorsolateral prefrontal cortex. Several sham controlled trials have demonstrated the efficacy of TMS for TRD treatment. However, the treatment is not universally helpful. Literature regarding the mechanism of TMS points to the treatment helping correct aberrant connections of the brain's cortical networks. Drysdale et al. (2017) found four fMRI "biotypes" of depression, based upon brain network connectivity, two of which were reliably related to response to TMS treatment. Other studies have identified specific personality traits, demographic factors, and illness-related factors that are predictive of treatment response.

Here we investigate whether other predictive factors could be found for TMS response. For this study, we utilized the NIH Toolbox Emotion Battery (NIHTB-EB), a set of rating scales designed to measure the totality of a participant's emotional health. No prior study has utilized the NIHTB-EB for studying TMS treatment of TRD. Our purpose for this analysis was two-fold. First, we investigated what emotional changes were observed in TMS for TRD. Second, we explored whether any pretreatment NIHTB-EB scales were predictive of TMS response as a first step in determining if the depression "biotypes" related to observable emotional differences which could be clinically utilized in the future.

Methods:

90 participants receiving clinical TMS treatment for MDD were included in the University of Iowa Interventional Psychiatry Patient Registry. Participants signed consent and the study was IRB-approved. All participants received between 20 and 36 daily TMS treatments. Participants completed the PHQ9 depression rating scale along with the NIHTB-EB on the dates of their first and final visits to assess changes in symptoms. Subjects with a 50% or greater reduction in PHQ9 over the treatment course were deemed responders to TMS. Statistics were run to assess what changes in NIH TB-EB measures occurred over the treatment course. Participant data was also input into a random-forest machine-learning model to assess the pre-treatment NIHTB-EB categories most predictive of response to TMS treatment.

Results:

Across all participants, 14 of the 17 NIHTB-EB rating scales had a significant change between the first and last visit. Ratings of "positive" emotions increased, and "negative" emotions decreased throughout treatment. Both TMS responders and non-responders demonstrated the same directionality of emotional change, with the magnitude being higher in the responder category. The magnitude of the changes were not uniform among emotion scales - higher amounts of change were noted with emotions such as sadness and perceived stress, and less change was noted for other emotions such as hostility and physical aggression.

Using machine-learning, the model could predict responders vs. non-responders with 62.5% accuracy, which is significantly above chance ($p = 0.027$). Higher scores in the self-efficacy and general life satisfaction rating scales were found to be the most predictive factors of TMS response. Most other factors, such as pre-treatment PHQ9 symptom burden or perceived stress, were not found to be major predictors of response.

Discussion:

The differences in NIHTB-EB ratings before and after treatment demonstrate changes that reflect PHQ9 changes and capture additional symptom categories that improve with TMS for TRD. These additional categories of improvement could inform potential target symptoms in future clinical trials of TMS for other neuropsychiatric conditions. Additionally, there were no emotion measures that showed worsening of symptoms after a TMS course. The effect of pre-treatment self-efficacy and general life satisfaction scores on antidepressant efficacy of TMS could also be clinically useful. Future studies should investigate the relationship between NIHTB-EB scores and previously published depression fMRI biotypes. This research suggests that psychotherapeutic techniques which enhance one's self-efficacy and general life satisfaction may also augment the antidepressant efficacy of TMS. Ultimately, more research is required to further investigate why this predictive link exists between TMS response in TRD and ratings of pretreatment self-efficacy and general life satisfaction.

Title: Examining the Clinical and Complement Biomarker Profiles in C3 Glomerulopathy Patients Treated with Targeted Complement Inhibitors

Authors: **Lauren Fergus,** Jillian Hall, Nicole Gerot, Matthew Allen, Monica D. Hall, Patrick D. Walker, Yuzhou Zhang, Richard J. H. Smith, **Carla M. Nester**

Introduction

C3 Glomerulopathy (C3G) is defined by dominant C3 deposition on kidney biopsy and persistent alternative complement pathway dysregulation. As complement inhibitors progress through clinical trials, their impact on disease processes compared to current drugs remains a subject of inquiry.

Purpose

In this single-center study, we aim to describe and compare changes in clinical and complement biomarkers pre- and post-initiation of complement inhibitors or standard treatments.

Methods

43 patients from the University of Iowa's C3G Natural History Study were included in the cohort. 26 were enrolled in complement inhibitor (CI) trials. These trials included Novartis APPEAR (NA-FBi), Novartis Extension (NE-FBi), MAP-LNP023 (NC-FBi), Apellis VALIANT (AV-C3i), MAP-APL2 (AC-C3i), Avacopan ACCOLADE (C5aRi), and Achillion (FDi). Guideline-recommended treatment groups included Eculizumab (C5i) and Mycophenolate Mofetil ± Prednisone (MMF±P). Controls were placebos in the Novartis APPEAR trial. Biomarkers were collected 0-6 months prior and 6-12 months after initiation. Complement biomarker testing included C3 and soluble C5b-9. Clinical biomarkers included eGFR and Urine Protein/Creatinine Ratio (UPC). The mean percent change from baseline was calculated and compared across all treatment groups.

Results

NA-FBi, AV-C3i, and C5aRi groups showed small mean increases in eGFR (+1-23%), while FDi had the greatest mean decline (-17%). Standard treatment and control groups demonstrated small changes in eGFR (MMF±P -6%, Control +4%), with similar variability to CI groups over this period. All CI groups had a mean reduction in UPC after initiation, ranging from -1% (C5aRi) to -65% (NC-FBi), compared to little change in the control group (-2%), and generally worsening proteinuria with MMF±P (+37%). C3 showed little mean change in standard treatment and control groups (MMF±P, +7%, Control +9%), while CI groups ranged from decline (C5aRi -54%) and little change (C5i, +7%), to large increases, as was the case for most CI trials (+116-4523%). Soluble C5b-9 dropped in all CI groups besides C5aRi (+56%), with the largest declines observed in C3i (-80%- -75%) and FBi (-79%- -46%) trials. Standard treatment and control groups had modest (MMF±P, 13%) to no effect (Control, +1%)

Conclusion

In our cohort, clinical and complement biomarker impact are mixed. NA-FBi and AV-C3i demonstrated improvement in all biomarkers measured. In several other CI groups, improvements were seen in three of four biomarkers and as a whole, had improved outcomes when compared to standard MMF±P and controls. In aggregate, although these results are derived from small cohort data, provide promising evidence of the efficacy of complement inhibitors on alternative pathway activity and clinical disease in C3 patients.

Disparities in the Management of Low Back Pain

Student: Chase Fifield, M2

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Other collaborators: Franklin Dexter, MD, PhD

Background: Pain carries a significant burden both at the individual level as well as across the healthcare system. Unmanaged or poorly managed pain can have a variety of negative consequences ranging from a loss of productivity and work absences to psychological difficulties and a lower quality of life. Low back pain in particular is a frequently encountered complaint by pain management specialists. It is imperative physicians in this space recognize and understand the effects demographic and other socio-economic factors may have on the treatment course for patients with low back pain.

Purpose: Patients with low back pain should receive with equal frequency a variety of interventions and recommendations. Disparities in the management of low back pain associated with race, insurance, primary language, or county of residence should not occur and must be identified to eliminate differences in outcomes for patients.

Methods There were 2,452 new patient encounters screened at the Iowa River Landing Pain Management Clinic resulting in 1,348 patients with a low back pain related diagnosis to be included in further analysis. A low back pain related diagnosis was broadly defined as any diagnosis related to lumbar or sacral dysfunction. This cohort was then screened for any procedures performed for the treatment of low back pain within 180 days of the initial patient visit. Procedure rates were then compared based on various factors including age, gender, race, insurance, primary language, and county of residence, grouped into health districts based on geographic location.

Results: Data from the 1,348 patients with low back pain was analyzed. This cohort was 42% male and 58% female. Procedural interventions for the treatment of low back pain occurred in 40% of the study population. The majority of patients were white (87%), spoke English as their primary language (97%), and were from Iowa (95%). A private health insurance plan was most frequent (37%), followed by Medicare (24%), Medicare Advantage Plans (17%), Medicaid (16%), or “Other” (6%). The median age for those who underwent a procedure was 61, while the median age for those that did not receive a procedure was 56. A p-value of <0.001 was deemed significant. On this basis, differences in procedure rates based on gender, race, and English as a primary language were deemed not significant ($p = 0.037$, 0.3716, and 0.3824 respectively). When comparing Medicaid vs all other insurance types, there were significantly less procedures performed in the Medicaid group ($p<0.001$). Patients from southeastern Iowa were significantly more likely to receive a procedure than all other areas ($p<0.001$).

Conclusion: This analysis demonstrates that differences in procedure rates for the treatment of low back pain exist for patients with Medicaid insurance compared with all other insurance types. Geographic factors also demonstrated a strong correlation with procedure rates as patients from the southeastern part of the state were significantly more likely to receive a procedure. These findings are an initial step in identifying differences in outcomes for patients and generating future quality improvement research aimed at alleviating those variances.

Development of Histological Measures of Metallosis in a Novel Model of Spinal Fusion

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Disclosures: None

Introduction:

Metallosis is a complex complication of joint revision surgery resulting from metal-on-metal articulations. Thought to be underdiagnosed, metallosis may contribute to unexpected failure of surgical fusion procedures. Research of metallosis in total hip arthroplasty has been shown to cause inflammation and toxic effects to surrounding soft tissues. Despite having more metal-on-metal articulation, spinal implants have not received adequate research on the implications of metallosis. To catalyze this effort, our group has incorporated physiologically relevant surgery and metal deposition similar to what is seen in clinical presentations of metallosis into an animal model of posterolateral lumbar spinal fusion. Because hematoxylin staining is known to turn dark black in the presence of excess metal, we hypothesized that this common histological stain applied to tissue containing metal particles would allow for quantification of metallosis. To test this hypothesis, we developed and applied an image processing approach to identify, measure, and stratify particles staining black during hematoxylin staining because of reactions of hematoxylin with metals. We further hypothesized that oxidative stress might be induced in these areas, and examined this using immunohistochemical staining of markers of oxidative damage, protein glutathionylation (PSSG) and 3-nitrotyrosine (3-NT).

Methods:

All animal experiments were done with approval of the University of Iowa IACUC. Twelve rabbits received an iliac crest bone graft (ICBG) surgery of their posterolateral lumbar spine. Bilateral grafts were placed intermediate to adjacent transverse processes (TPs). Six-weeks after ICBG placement, dorsal injections were administered directly perpendicular to the center of the graft of either a high, low, or no concentration of a Ti/Cr/Co alloy. After another six-week period, these animals were euthanized and an area spanning the width and depth of the TPs, including graft and injection, was collected for histological processing for paraffin embedding. Samples were sectioned in the sagittal plane in three increments labeled medial, central, and lateral, corresponding to their position along the graft. Histological staining of the structure and metal particles was done with hematoxylin and eosin (H&E). Immunohistochemical staining was done with the Roche Discovery Ultra automated staining system using antibodies against oxidative damage markers PSSG and 3NT. Both PSSG and 3NT utilized 3,3'-diaminobenzadine (DAB) counterstained with hematoxylin. Stained sections were then scanned using an Olympus VS200.

Image analysis to quantify metal particle presence in H&E-stained tissue utilized FIJI Image J software, incorporating novel aspects of color deconvolution technology and classification of pixels by both size and color intensity. Resulting data included both labeled and color coordinated images of the tissue and numerical data of each present particle, deemed "positive pixels" by the analysis. Total positive pixel data for each analyzed section were then divided by the total particles present in the entire field, including all surrounding tissue. This resulted in a measurement of number of positive pixels present per section, abbreviated to "percent area". Graphical analysis of this data was then performed using GraphPad software, comparing the percent area values of groups which received a high concentration of metal injection compared to those that received a low concentration injection. Statistical analysis via an unpaired t-test was then performed and presence of statistical significance was evaluated. A qualitative analysis was also applied to 3NT and PSSG-stained tissue to assess levels of oxidation present proximal to metal particles.

Results:

High (100x) magnification of H&E-stained tissue from an animal injected with a high concentration of Ti/Cr/Co alloy reacts with hematoxylin to produce this black/brown staining pattern distinct from typical blue-stained cells, Figure 1a. Nearby purple and pink staining identifies cells and tissue containing no metal particles. Figure 1b shows the post-analysis image regions produced from the image in Figure 1a. Areas labeled with distinct color are considered positive pixels containing metal particles. Figure 2 is the resulting graphical comparison of particle presence, in terms of percent area, in high and low concentration recipients. Using this analysis, we were able to identify significantly more particles in the high concentration group. Figure 3a is a representative image of PSSG positive cells (brown) in an area containing metal particle debris. Figure 3b is a representative image from the same region stained for 3NT positive cells.

Discussion:

Statistical analysis suggests a statistically significant difference in the amount of metal particles present between high concentration and low concentration injection groups, supporting the hypothesis that differences in metallosis can be detected using hematoxylin staining. This will be invaluable for evaluating metallosis and its biological effects. Future studies will include the effects of the high and low concentration injections upon bone formation in this model. Analysis of 3NT and PSSG staining reveals that oxidative stress is not overt in these specimens. 3NT staining displays a negligible signal in areas containing particles, with only trace amounts of brown staining present, meaning little to no oxidation is occurring due to 3NT formation. Moderate staining for PSSG was identified (brown), but local differences will need to be investigated with a second marker to ensure cell type specificity in any analyses, i.e. to ensure T-cells or macrophages or fibroblasts are being appropriately compared between groups. Thus, oxidative stress from metallosis was not overt, but future studies may refine any redox biological changes resulting from this condition.

Significance/Clinical Relevance:

As spinal surgery has some of the highest surgical complication rates, developing a method to accurately identify and measure metal deposition in coordination with surgical fusion models has the potential to gain insight into prediction of fusion failure. The animal model utilized provides a system for testing and evaluating the effects of metallosis. Our early results demonstrate that not only does our approach identify particles, but that we will be able to study local biological responses to these metal particles. Further use of this model could provide key descriptions of metallosis helping to define and diagnosis patents with this condition.

Figures

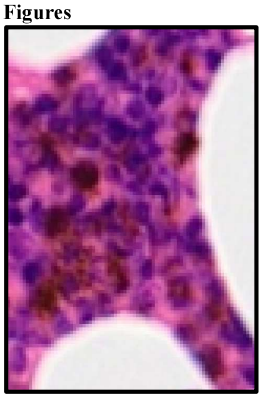

Figure 1a

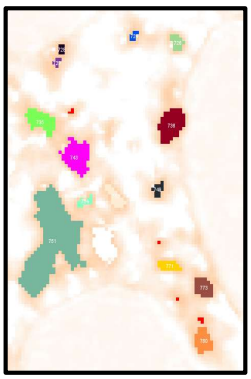

Figure 1b

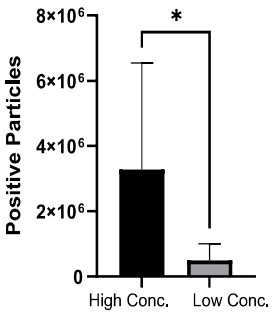

Figure 2

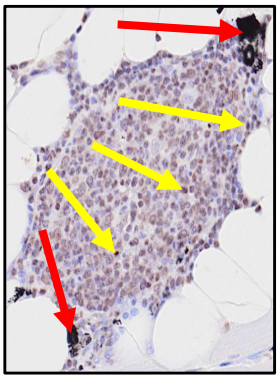

Figure 3a

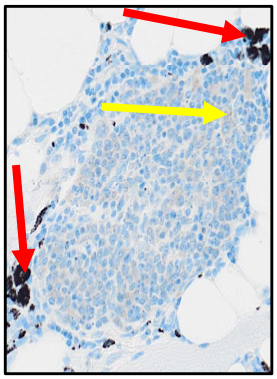

Figure 3b

**Red arrows denote metal particles, yellow arrows for positive staining of oxidation*

International acid burn violence: A systematic review of prevalence and the demographics of survivors

Student Author: Julia Fleecs
Mentors: Dr. Kanwal S. Matharu, Dr. Femida Kherani, Dr. Erin M. Shriver

Background: Vitriolage, intentional burning with acid, has been reported globally yet no international system exists to document its prevalence and outcomes. These crimes often target the face and eyes resulting in extensive facial and ocular involvement, disfiguring and isolating survivors and leading to devastating morbidity. Ocular and periocular burns from acid assault are distinct from accidental burns in their severity and bilateral nature. Burns to the eyelid can cause cicatricial eyelid retraction and lagophthalmos with vision threatening exposure. Vision preservation after an acid attack is something survivors report as having the greatest impact on their quality of life, demanding the attention of ophthalmologists globally. International NGOs supporting survivors of acid assault estimate that 80% of acid attacks target women. True demographic data is difficult to obtain due to underreporting associated with fear of retaliation, shame, and lack of access to care.
Purpose: This study analyzes peer-reviewed cases of acid assault from the medical literature to better understand the demographics of survivors in relation to gender and geography, as well as how these results compare to statistics reported by non-governmental organizations (NGOs). The goal of this review is to bring attention to the reality of international acid violence, its impact on vision, and lay the foundation for future work focusing on the ophthalmic and periocular management of these complex cases.
Methods: A search of PubMed and Scopus databases identified case series, case reports, and cohort studies of chemical burn injuries and acid burn violence published in the English language between 2000-2024. Search terms included "vitriolage," "acid assault," "chemical burns," "corrosive attack," and "acid violence." Reference lists of literature reviews identified in the search were manually analyzed. Inclusion criteria required at least one report of intentional chemical violence and identification of the country where the attack occurred. This review focused on assault by acid, although identifying the offending agent is not always possible and cases where the chemical was not disclosed were also included. Data on alkali burns were excluded with the exception of articles where demographic data was reported as a combined statistic for alkali and acid cases, and the majority of the reported cases in the study were acid. Information collected included the data source, study period, number of cases, chemical used, country, age, gender, reported motivations, and reported visual impairment. Precise terminology on visual impairment or documentation of vision was not consistently found and authors' descriptions of "partial blindness," "complete blindness," or "total loss of vision in one eye" were recorded. Countries were sorted into economic classifications as determined by The World Bank Group assignment based on income level per capita. For comparison, a secondary search using the Google search engine identified NGOs with published statistics on acid violence cases.
Results: Fifty-four publications describing 1,553 cases from 21 countries met the inclusion criteria. 77.14% of these cases were from lower-middle income countries, as compared to 11.27%, 10.62%, and 0.97% in high-income, upper-middle income, and low-income countries, respectively. Thirty-two articles describing 1,219 cases of chemical attack from 17 countries reported on the gender of the survivor. 55.21% of cases involved female survivors. The average age was 25.23 years old and 28.24 years old for female and male survivors, respectively. Six countries had male predominance in survivors, 6 countries had female predominance in survivors, 1 country had an equal gender ratio, and 4 countries had only 1 case report. Percentage of survivors who were female in high-income countries was 36.08% compared to 67.44%, 57.40%, and 46.67% female cases in upper-middle, lower-middle, and low-income countries, respectively. Five countries (Bangladesh, Cambodia, India, Pakistan, and Uganda) were found to have established NGOs, with published statistics on gender of survivors. All NGOs reported a higher proportion of female survivors with an average female to male ratio of 2:1 over 5,129 total cases. Fourteen studies documented vision loss with 17.65% of cases reporting "blindness" in at least one eye.
Conclusions: Vitriolage exists globally with the highest number of reports in lower-middle income countries. While typically publicized in the media as affecting predominately women, the role of gender differs significantly based on geographic location. Compared to statistics reported by NGOs, the peer-reviewed literature has less difference in the number of female survivors as compared to males. Significant vision loss is reported in intentional acid burning and insufficient detail on ophthalmic injuries from acid violence and management of these injuries exists in the medical literature. More research is needed to understand the severity of ophthalmic injury in acid burn cases and how they relate to gender.

Title: Exploring the Peripheral Auditory Impacts of Alzheimer's Disease Before and After Cochlear Implantation: Preliminary Results

Presenter: Logan Flom
Mentors: Rachel Scheperle, Marlan Hansen
Collaborators: Brian Mostaert, Shakila Fatima, Ibrahim Razu, Muhammad Rahman

Introduction:
Alzheimer's disease (AD) is the most common form of dementia and represents one of the greatest public health concerns worldwide. Hearing loss is the most widespread modifiable risk factor for dementia, contributing up to a five-fold increased dementia risk. Although cochlear implants (CIs) are one option for hearing loss rehabilitation, dementia may lead to less successful implant outcomes. It is uncertain whether suboptimal outcomes are reflective of cognitive impairments, peripheral neural involvement, or a combination of factors. Few studies have explored the impacts of AD on the peripheral auditory system with cochlear implants, and previous studies have been confounded by the co-occurrence of sensory hearing loss. As this relationship may inform hearing loss rehabilitation in patients with underlying neurodegenerative disease, this study aims to elucidate the role of AD in peripheral auditory status using specific AD mice models that reduce the impact of sensory hearing loss. We hypothesize that AD mouse models will demonstrate more pronounced degeneration of spiral ganglion neurons (SGNs) compared to controls, resulting in impaired neural responses to acoustic and electrical stimulation before and after cochlear implantation.

Methods:
Three mouse strains (5XFAD, AD-Tau, CBA/J) were utilized in this experiment. The CBA/J strain will serve as a baseline as it retains hearing better than more commonly used Black6 strains. The 5XFAD and AD-Tau experimental groups are defined by mutations in human microtubule-associated protein tau (MAPT) and five Familial Alzheimer's Disease (FAD) genes, respectively, serving as apt models for AD and its characteristic neuropathology. Acoustically-evoked auditory brainstem responses (ABRs) and distortion product otoacoustic emissions (DPOAE) were elicited with 8k, 16k, and 32k tone bursts/paired tones from 90-20 dB SPL to allow for visual threshold determination (based on wave I of the ABR and 2f1-f2 frequency for DPOAEs). These acoustic tests were conducted between 3-7 days prior to implantation to assess auditory nerve and outer hair cell function, respectively. Left ears were implanted with a CI and electrically stimulated intraoperatively. Electrically-induced compound action potentials (eCAPs) were elicited using charge-balanced, biphasic square-wave pulses with an interphase gap (IPG) of 7 μs and 42 μs to assess auditory nerve function. For each IPG, an input/output (I/O) function was obtained by incrementally adjusting the current level, allowing for estimates of eCAP threshold, maximum N1 latency, maximum amplitude, amplitude-growth function slope, and IPG effect. Refractory recovery functions were also obtained by incrementally adjusting the masker-probe interval within a forward masking paradigm, allowing for estimates of absolute and relative refractory periods. I/O functions were constructed by considering peak-to-peak response amplitudes as a function of current level. Researchers were blinded during data collection and subjective data analysis (e.g. visual detection, peak marker placement).

Results
Data collected for seventeen mice (10 males, 7 females) will be presented; data collection is ongoing. Ages at the time of surgery ranged from 8-123 weeks. Average left-sided ABR thresholds were 42 ± 14 dB (8k), 29 ± 12 dB (16k), and 38 ± 13 dB (32k). Average left-sided DPOAE thresholds were 59 ± 11 dB (8k), 48 ± 9 dB (16k), and 56 ± 10 dB (32k). There is a trend suggesting increasing ABR thresholds with age. Correlations between DPOAE thresholds and age and between ABR thresholds and DPOAE thresholds were not observed. Most of the electrically evoked data appears to be without substantial variation across ages, but a greater sample size and genotype data is necessary to definitively make conclusions given the small differences expected. Due to genotyping backlog and unblinding times, more robust analysis that includes group effects will be presented in person.

Discussion
While our current sample is limited due to its acute acquisition and small size, it appears that ABR threshold across subjects increases with age, which may be a potential confounder or indicative of AD status; more robust analysis is required once genotypes are obtained. Work in this area is ongoing to better establish mechanistic links between AD neuropathology and auditory dysfunction in the setting of CI, including histological investigation and more in-depth analysis of electrophysiological parameters.

Title: Liquid Biopsy in Pediatric Brain Tumors Using Nanopore Sequencing

Authors: Nolan S Ford [1], Janice E Cook-Granroth, [2], Brian J Dlouhy [3], Rebecca Reynolds [3], John M Buatti [4], Moon Ley Tung [5], Andrew Groves [5]

Introduction: Primary brain and central nervous system (CNS) tumors are the most frequent solid tumors in children[1] and the leading cause of cancer-related mortality in those aged 0 to 14 years[1]. The high mortality rate can be attributed to delayed diagnosis, difficulty in obtaining an accurate histological diagnosis due to the inaccessible anatomical location and heterogeneous nature of these tumors, and the lack of response to treatment in aggressive tumor subtypes. The current gold standard method of diagnosis, monitoring of treatment response and long-term follow-up of pediatric brain tumors (PBT) is tumor tissue biopsy and magnetic resonance imaging (MRI). These approaches have significant limitations for longitudinal monitoring such as the inability to perform sequential tissue biopsies of PBT due to surgical risks and the limited biological insights offered from MRI studies alone. The updated 2016 World Health Organization Classification of Tumors of the CNS[2] emphasizes the importance of accurate molecular classification of these tumors as it has been shown that personalized treatment in a highly aggressive subtype of PBT, H3K27M-mutant pediatric diffuse glioma is associated with long term survival of greater than 2 years[3]. Thus, minimally invasive diagnostic tests are highly desirable in PBT to facilitate early and accurate diagnosis through the molecular profiling of these tumors to guide effective anti-cancer therapies and reduce cancer-related mortality and morbidity in PBT.

Hypothesis: Peripheral blood is an ideal sample source for liquid biopsy using the Oxford Nanopore (ONT) platform, and will enable minimally invasive, fast, and accurate diagnosis of PBT.

Methods: We identified and consented pediatric patients with primary brain tumors from the Stead Family Children's Hospital through our IRB approved protocol (ID# 202212193). Fresh brain tumor tissues were collected during surgery and sent for next generation sequencing (NGS) as per standard clinical protocol. Venous blood was collected in Streck Cell-Free DNA BCT collection tubes or Vacutainer EDTA tubes. Venous blood tubes was processed after collection or stored and processed within 24 hours. Plasma supernatant was aspirated without disturbing the buffy coat containing the germline genome DNA and transferred to a fresh centrifuge tube. Plasma was centrifuged to remove residual cells from plasma and aliquoted to a 15mL conical tube. CSF was stored and centrifuged at 3000g for 5 at 4 degrees Celsius for 15 minutes. The supernatant was collected and stored until ready for further processing. Cell free DNA (cfDNA) was extracted from plasma or CSF supernatant using the QIAamp circulating nucleic acid kit. Eluted cfDNA was quantified using the Qubit Double Stranded DNA (dsDNA) High Sensitivity (HS) assay and quality controlled using the 260/280 ratio on the NanoDrop platform. Extracted cfDNA was used as input for nanopore sequencing until ready for further processing. Paired germline genomic DNA was extracted from the buffy coat to confirm any copy number variants and to correct for any method-specific artifacts. Whole genome sequencing (WGS) was performed on the PromethION 2 sequencing device using extracted cfDNA as described above. Input samples went through library preparation, barcoding, and adapter ligation as per the manufacturer's protocol and performed in triplicates. The results obtained from the nanopore sequencing were compared to the NGS results performed on the primary brain tumor tissue.

Findings: With the data collected, there was much inconsistency between the concentrations of plasma and CSF cfDNA among four patients each presenting with pilocytic astrocytoma. When collected six days after gross total resection, our first patient sample of plasma and CSF cfDNA was 14.25 and 152.6 ng respectively. When collected one day after gross total resection, the second patient sample of plasma and CSF cfDNA measured 1.5 and 111.6 ng. The third patient sample collected one day after gross total resection had 3.68 and 1.95 ng of plasma and CSF cfDNA respectively. The fourth patient sample collected one day before resection measured 2.08 and 2.1 ng of plasma and CSF cfDNA respectively.

Overall Significance: The Oxford Nanopore Sequencing (ONT) platform has shown some capability to sequence cfDNA in the peripheral blood of PBT patients and identify tumor-specific copy-number and methylation patterns. However, limitations remain such as collecting consistent volumes of sample and a frequently changing protocol through ONT. This non-invasive diagnostic strategy still has the potential to revolutionize care including at diagnosis (even prior to surgery), and monitoring of disease before, during, and after treatment. Lastly, the ability of this technology to establish and validate novel biomarkers will be crucial in the development of targeted therapies in the most aggressive tumor types.

Erica Fossee

Mentor: Dr. Allison Momany and Dr. John Dagle

Title

Amino Acids and Neonatal Morbidities in Preterm Neonates

Background

Preterm birth is the leading cause of mortality in children under 5 years old globally and has been increasing in the United States. Medical advancement has allowed preterm neonates to survive into child and adulthood, but this has also led to unique long-term health problems including delayed neurodevelopment. Early disease detection and intervention may mitigate some long-term health consequences of preterm birth. Previous research has demonstrated associations between amino acids and certain diseases of prematurity. This highlights how measuring amino acids in preterm infants may be used clinically for earlier detection of diseases. Furthermore, preterm infants have a unique metabolic profile compared to term infants, and thus, research specific to preterm neonates is necessary to improve clinical outcomes.

Purpose

The aim of this study was to examine the associations between physiological measures, amino acid levels, and common neonatal morbidities in preterm neonates.

Materials & Methods

47 preterm infants born before 31 weeks were included in this study. Infants were born at the University of Iowa or University of California San Francisco and are part of the PROMPT study, Predicting Maturity, Mortality, and Morbidity in Preterm Newborns. Infant physiology and disease data was obtained through EPIC charts. Blood spots from discarded samples were stored in a –80C freezer until being sent to the state hygienic laboratory to be analyzed via tandem mass spectrometry. Regression analyses were done to assess the associations between amino acids and physiological measures including respiratory rate, heart rate, systolic blood pressure, and diastolic blood pressure. Multilevel longitudinal models were used to analyze the association between amino acids and diseases of prematurity including intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), cytomegalovirus (CMV), and pneumonia. All analyses were completed in R.

Results

There were no significant associations between amino acids and physiological variables once adjusted for gestational age (GA) and infant birthweight (BW). In multilevel models, there were also no significant associations between amino acids and physiological variables after adjusting for GA and BW. There were significant positive and negative associations between amino acids and various diseases of prematurity in unadjusted multilevel longitudinal models. Alanine was positively associated with CMV and negatively associated with ROP. Citrulline, methionine, and methionine/phenylalanine were positively associated with IVH. Methionine/phenylalanine was also positively associated with ROP. Phenylalanine/tyrosine was positively associated with pneumonia.
Leucine/phenylalanine was negatively associated with CMV. Multiple associations were maintained when adjusted for GA and BW.

Conclusions

This exploratory analysis revealed negative and positive associations between amino acids and neonatal morbidities common in preterm neonates. Future studies should aim to replicate these findings in larger and diverse populations so that the findings may be utilized clinically to improve the health outcomes of preterm infants. Additionally, future research should examine continuous measures of physiology during NICU stay to better assess associations between physiology and amino acids.

Sensitivity and Specificity of Proton Density Magnetic Resonance Imaging With and Without Fat Suppression in Identifying Meniscal Tears

Student: Garrick Gama, BS
Mentor: D. Lee Bennett, MD, MBA

Introduction: Proton density (PD) weighted magnetic resonance imaging is a widely accepted method for evaluating meniscal tears. However, PD imaging increases the fat signals which is why using proton density with fat suppression (PD-FS) has become a new area of exploration. Minimal studies have been published assessing the comparisons between the PD and PD-FS, and no studies have been published that assess lateral meniscal tears.

Methods: Our retrospective study included all patients who underwent arthroscopy for possible meniscal tears at UIHC between July 1, 2020 and January 31, 2021. Three different radiologists independently reviewed the MRIs of each patient looking only at PD and PD-FS sequences. The radiologists provided a score ranging from 1 (definitely no tear) to 5 (definitely a tear) and defined whether the identified tear was medial, lateral, or both. If at least 2 out of the 3 radiologists gave a score of 4 or 5, this was considered a positive diagnosis of a meniscal tear based on imaging. The standard of reference was arthroscopic findings. Sensitivities and specificities for medial and lateral tears for both PD and PD-FS were calculated. Comparisons of the performance between PD and PD-FS were calculated utilizing the McNemar test in the setting of both medial and lateral tears.

Results: Within our sample of 98 patients, the prevalence of confirmed medial meniscal tears was 75.5% and confirmed lateral meniscal tears was 38.8% based on arthroscopic findings. When assessing for medial meniscal tears, PD-FS had a higher sensitivity (95.9% vs 93.2%) and lower specificity (79.2% vs 87.5%) in comparison to PD. A similar pattern was seen with lateral meniscal tears with PD-FS having a higher sensitivity (73.7% vs 68.4%) and lower specificity (83.3% vs 85.0%) when compared to PD. There were no significant differences in detecting medial meniscal tears (McNenar test statistic: 3.0, p=0.73) or lateral meniscal tears (McNemar test statistic: 10.0, p=0.83) between the PD and PD-FS sequences.

Conclusion: There is no statistically significant difference in identifying medial or lateral meniscal tears between the PD or PD-FS sequences. Given the similar performance between PD and PD-FS, PD-FS proves to be an adequate sequence that may be utilized in the detection of medial and lateral meniscal tears.

Optimized Recovery of Coronary Endothelial Cells for Aptamer-Based Discovery

Student: Jason Gao
Mentor: Jennifer Streeter

In the United States, someone has a heart attack every 40 seconds. Identifying molecules that bind to coronary artery endothelial cells (ECs) is a critically important step in the development of diagnostics and therapeutics that can specifically target ECs to better identify and treat heart attacks. However, the challenge in identifying potential molecules is being able to recover the ECs from coronary arteries. To address this challenge, we assessed the efficacy of three methods for recovering ECs from human and porcine coronary arteries exposed to RNA aptamer molecules. Visualization of EC pellets and confocal microscopy of vessels was used to assess EC recovery. EC recovery method 1 was excision of the coronary artery and opening it longitudinally, applying digestive enzymes to release ECs from the lumen of the vessel, and using forceps to scrape the endothelial cells from the lumen. Method 2 was encasing the artery in agarose gel, cannulating the vessel, infusion of digestion enzymes with a pump, and collection of flow-through ECs. Method 3 was encasing the vessel in superglue and plastic wrap, injecting digestive enzymes by hand, and collecting flow-through ECs. Method 1 did not yield a visible EC pellet, but EC denudation was confirmed by confocal microscopy, and aptamer recovery was confirmed by UV visualization of aptamer. Method 2 did not yield a visible EC pellet, but EC denudation was confirmed by confocal microscopy. Method 3 yielded a large, visible cell pellet, but the vessel was overly digested and lost structural integrity needed for confocal imaging. Although all three methods were successful at removing ECs from coronary arteries, method 3 yielded the highest cell recovery, which will enable identifying ligands that bind to coronary artery endothelial cells. Developing these methodologies has important implications including the ability to design diagnostics and therapeutics that can specifically diagnose and treat coronary artery disease.

E-cigarette exposure induces endothelial activation and alters the phenotype of circulating monocytes

Student: Matthew Gao
Mentors: Andrea Benavides, Josalyn L. Cho, MD
Collaborators: Anna Stanhewicz, PhD

Background:
The prevalence of electronic cigarette (e-cigarette) use in the United States has increased substantially over the past several years. However, the acute and long-term health risks associated with e-cigarette use remain incompletely understood. A growing body of literature suggests that exposure to e-cigarettes may increase the risk of cardiovascular disease in a similar manner to cigarette smoke, which mediates its effects through both direct damage to the endothelium and induction of pro-inflammatory monocytes. $CD14^+CD16^-$ classical monocytes are innate immune cells produced in the bone marrow and released into the bloodstream, where they migrate to tissue both during homeostasis and in response to inflammation. Classical monocytes also give rise to $CD14^-CD16^+$ nonclassical monocytes, which patrol the vasculature and play a vital role in maintaining endothelial health. In this project, we aimed to understand how exposure to e-cigarettes alters circulating monocytes. We hypothesized that chronic e-cigarette use promotes an inflammatory phenotype in circulating monocytes.

Methods:
We enrolled adult males and females between the ages of 18 and 24 years with either no history of e-cigarette use (healthy controls; HC) or ≥ 6 months of e-cigarette use (chronic e-cigarette users; EC). All study protocols were approved by the University of Iowa Institutional Review Board, and participants gave their written informed voluntary consent before inclusion. Participants underwent venipuncture, and peripheral blood mononuclear cells (PBMC) were isolated by density centrifugation using Lymphoprep (STEMCELL Technologies). $CD14^+CD16^-$ classical monocytes were isolated to >95% purity from PBMC by negative selection, then stimulated with 100 ng/ml lipopolysaccharide (LPS) or vehicle for 24 hours. TNFα production was measured by flow cytometry. Primary human umbilical vein endothelial cells (HUVEC) were grown to >85% confluency, then stimulated with either vehicle, cigarette smoke extract (CSE; 3% w/v) or JUUL pod e-liquid (3% w/v) in four 15-minute intervals to mimic the recurrent inhalation patterns of smokers and e-cigarette users or continuously for 24 hours. HUVEC phenotype was analyzed by flow cytometry.

Results:
We enrolled 12 HC (7F/5M) and 10 EC (5F/5M). There were no differences in the white blood cell (WBC) count or differential between groups. Compared to HC, EC had a lower frequency of $CD14^+CD16^-$ classical monocytes (live singlet $CD3^-CD19^-$: 33.2% vs. 16.6%, $p < 0.05$) and a higher frequency of $CD14^-CD16^+$ nonclassical monocytes (NCM; 10.4% vs. 20.5%, $p < 0.05$). $CD14^+CD16^+$ intermediate monocytes, which are a pro-inflammatory subset derived from classical monocytes, were not different between groups. There was a non-significant trend toward increased production of TNFα by classical monocytes isolated from EC in response to LPS (36.4% vs. 57.5%). Classical monocytes differentiate into non-classical monocytes upon interaction with the endothelium in a Notch-dependent manner. We therefore assessed whether exposure of endothelial cells to e-cigarette liquid altered expression of the Notch ligand Delta-like 1 protein (DLL-1). HUVECs exposed to JUUL pod e-liquid and CSE both expressed higher levels of DLL-1 compared to media controls (median fluorescence intensity [MFI]: media, 6275 (±749), JUUL, 9734 (±1120), CSE, 9628 (±1847); $p < 0.01$ for both comparisons vs. media). Similarly, the monocyte adhesion molecule CD62-P was upregulated in JUUL pod e-liquid exposed (MFI 12650 (±1585); $p < 0.001$) and CSE-exposed HUVECs (MFI 11037 (±1804); $p < 0.01$) compared to media controls (MFI 6999 (±739)).

Conclusions:
We found a lower frequency of classical monocytes and a higher frequency of non-classical monocytes in EC compared to HC as well as a trend towards higher production of TNFα in response to LPS stimulation. Furthermore, JUUL e-liquid exposure increased DLL-1 and CD62-P expression on endothelial cells to a similar extent as CSE exposure. These results suggest that e-cigarette exposure may promote endothelial adhesion and transmigration of classical monocytes into tissue and their differentiation into non-classical monocytes. Thus, e-cigarette exposure may be a risk factor for cardiovascular disease and further research into the specific effects of e-cigarettes on cardiovascular health is warranted.

Title: Computation model for predicting early clinical outcomes in children with vesicoureteral reflux integrating objective data from renal ultrasound and voiding cystourethrogram

Student: Bailey Garnica, M2
Mentor: Dr. Christopher Cooper, MD, Urology
Collaborators: Bridget Zimmerman, PhD and Jacob Clark, Biostatistician II

Introduction*:* Primary vesicoureteral reflux (VUR) is the retrograde flow of urine from the bladder to the upper urinary tract due to dysfunction of the ureterovesical junction (UVJ). VUR is a common pediatric urological condition that occurs in children with a history of urinary tract infections (UTIs). However, optimal management of children with VUR remains a challenge because many children spontaneously resolve VUR without serious complications, but others may develop significant problems such as pyelonephritis which may result in renal scarring, hypertension, and chronic kidney disease.

Previously, computational models from our institution were developed to help physicians and families predict if VUR was likely to resolve within 1 or 2 years and included variables such as, age, gender, presenting symptom, reflux grade, laterality, whether reflux occurred during filling or voiding, initial bladder volume at onset of VUR, and ureteral duplication. Subsequent research analyzed the distal ureter diameter ratio (UDR) as a prognostic factor. These results showed that increasing UDR was less likely to resolve spontaneously and increased the risk of UTI independent of VUR grade. Previous research also analyzed renal ultrasound (US) data and abnormal renal US's were associated with decreased VUR resolution. The goal of the current project was to create updated computational models that included the previous predictive variables in addition to UDR and renal US data to better predict reflux resolution.

Methods: We reviewed the medical records including the initial and subsequent voiding cystourethrography's (VCUG) of children diagnosed with primary vesicoureteral reflux between 1999 and 2023 at our institution. We also reviewed renal ultrasound data obtained within seven months of a patient's VCUG. The UDR was calculated by dividing the largest ureter diameter within the false pelvis (defined as the area below the most superior aspect of the iliac crest) by the distance from the bottom of L1 to the top of L3 vertebral bodies on the VCUG. Renal ultrasounds were considered abnormal if the refluxing kidney had was $\leq$ 1cm compared to the normal contralateral kidney or if there was moderate or severe hydronephrosis (SFU grade 3 or 4).

Results: We reviewed 432 VCUG's from 70 males and 225 females. We were able to identify 50 right kidneys and 61 left kidneys positive for moderate or severe hydronephrosis. We were able to identify 47 right ureters and 52 left ureters for hydroureter.

Conclusions: With the integration of distal ureter diameter ratio and renal ultrasound data, our computational model can accurately predict the chances of reflux resolution at 1- and 2- years as well as breakthrough UTIs post diagnosis on a more individualized basis. The accuracy, ease of use, and use of many clinical variables offers clinicians the chance to use our model to best predict vesicoureteral reflux management.

Medical Student Research Conference Presentation: Gehrmann Abstract

Title: Role of Intrinsically Disordered Regions in the Organization of the Herpesvirus Particle

Presenter Name: MaryTherese Gehrmann

Mentor Name: Dr. Richard Roller

Background and rationale - An estimated 67% of the population under 50 years old is infected with Herpes Simplex-1. Virions initiate infection in epithelial cells and spread to sensory neurons where they remain latent until environmental triggers activate their lytic cycle. HSV-1 virion is composed of a double stranded DNA core, icosahedral capsid, tegument, and outer membrane containing lipids and proteins. The tegument is a loosely ordered structure composed of more than 20 different proteins. The tegument is thought to be mostly held together by redundant interactions between the proteins, since only three of them are essential for formation. About 90% of the tegument proteins contain at least one intrinsically disordered region (IDR) of 30 amino acids or more. The loose arrangement, redundancy of interactions, and high density of IDRs in its protein components, suggest the hypothesis that the tegument is a biomolecular condensate formed by interactions between IDRs

Hypothesis/purpose - We tested the specific hypothesis that the IDRs of two of the tegument proteins, pUL46 and pUL47 are both necessary and sufficient to mediate their incorporation into the HSV-1 tegument. pUL46 and pUL47 were selected for their single terminal IDR and abundant protein expression.

Approach - To test for necessity of the IDRs for tegument incorporation, cells were infected with viruses that express intact pUL46 and pUL47 or mutant viruses from which the pUL46 or pUL47 IDRs were deleted. Virions were purified by density gradient centrifugation and the incorporation of wild-type or mutant proteins into the virions was determined by immunoblotting. To test for sufficiency of the IDRs for incorporation, viruses were constructed in which the IDRs of pUL46 and pUL47 were fused to a heterologous protein (EGFP).

Findings/Results – Deletion of the pUL46 and pUL47 IDRs did not diminish their expression in infected cells. Neither the UL46 nor the pUL47 IDR was strictly necessary for their incorporation into the virion tegument, although deletion of the pUL46 IDR reduced its efficiency of incorporation. These results suggest that the ordered domains of the protein are either partially (pUL46) or completely (pUL47) sufficient. Future studies will determine if the IDRs are sufficient for tegument.

Conclusion - These studies have identified sequences that are sufficient to mediate protein incorporation into the virus tegument. This should allow customization of the composition of the herpesvirus virion to include agents that modulate the innate and adaptive host response to the virus to improve the performance of vaccine or oncolytic therapy candidates.

Title: Assessing the effect of GPx1 inhibitors on colon cancer cells/organoids

Mahaasrei Ghosh, B.S., Sarah Short, Ph.D.

Introduction: Colorectal cancer (CRC) is a significant global health issue, often treated with 5-fluorouracil (5-FU) in FOLFOX regimens. However, FOLFOX response rates are moderate, and therapy resistance is common. Reactive oxygen species (ROS) play a complex role in CRC, with tumor cells exploiting antioxidant pathways for growth and survival. Notably, GPx1, a selenium-containing antioxidant protein, is upregulated in CRC, correlating with poor prognosis and therapy resistance. Due to previous in-lab studies showing that genetic deletion of GPx1 increased 5-FU sensitivity, we hypothesized that targeting GPx1 activity could enhance sensitivity to CRC therapies. Our proposed studies aim to understand GPx1's roles in tumor therapy and test the synergy between a panel of recently identified GPx1 inhibitors and standard CRC treatments. Ultimately, this research may identify strategies to improve therapeutic responses that reduce CRC mortality.

Hypothesis: We hypothesized that drugs reported to decrease GPx1 activity will increase sensitivity to 5-FU in colon cancer cells or patient-derived tumor organoids. We expect to see decreasing viability due to the cancer cells' inability to protect themselves from ROS.

Methods: We plated a 96-well plate with $5x10^3$ cells per well of either HCT116 or SW480 cells, two independent CRC lines. First, we tested viability of HCT116 and SW480 cells with varying concentrations of GPx1 inhibitors over 72 hours via the CellTiter-Blue assay. Next, we added serial dilutions of 5-FU (0.625 μM to 320 μM), with and without the reported GPx1 inhibitors, auranofin, 2,3-dimercaptosuccinic acid, cefoxitin, and ceftibuten. For these pilot studies, each inhibitor was used at IC50 concentrations again GPx1 activity as reported previously (PMID: 37244126). After 72 hours, we ran viability assays to determine therapeutic responses. For organoids studies, a similar strategy was used plating 5μl of organoids in Matrigel into the center of the well of a 96-well plate. Viability was established before and after treatment, with pre-treatment readings used to establish baseline well-to-well variability.

Findings/results: Here, we determined that most purported GPx1 inhibitors (2,3-dimercaptosuccinic acid, cefoxitin, and ceftibuten) had no effect on viability at baseline. These inhibitors likewise failed to induce significant changes in viability in conjunction with 5-FU treatment. However, auranofin improved the sensitivity of HCT116 cells and tumor organoids to 5-FU at the GPx IC50 concentration. Interestingly, while auranofin alone had no substantial effects on viability of HCT116 cells, we observed a pronounced decrease of SW480 cell viability at the GPx IC50 concentration with and without 5-FU.

Conclusion/Future directions: Despite the impact of genetic GPx1 deletion previously observed by the Short lab, the newly identified GPx1 inhibitors generally do not influence the response to 5-FU treatment in colon cancer cells or organoids. Positive results were obtained with auranofin, although this response may be mediated by other targets of this drug, such as thioredoxin reductase. Future studies will more clearly establish the effect of our drug panel on GPx1 activity in colon cancer cells and use this information to further optimize dosing strategies.

Racial disparities in lung cancer in Iowa

Lexie Golden, Madi Wahlen, Mary Charlton

Introduction: Racial disparities in lung cancer have been observed in the United States. Compared to White individuals, Black individuals have a higher incidence of lung cancer, particularly adenocarcinoma and squamous cell carcinoma, and are typically diagnosed at a younger age and at a later stage of disease. Black individuals also have a higher mortality than White individuals. There are many hypotheses which attempt to explain these disparities. Access to care may be a challenge and can be affected by many factors such as socioeconomic status or geographic location. Additionally, current screening guidelines may not factor in biological differences, such as tobacco metabolism, resulting in potentially inadequate screening of Black people. Finally, disparate care provided to Black and White individuals may drive these disparities. For example, it has been observed that Black patients are less likely to receive surgery than White patients at the same disease stage. Similar disparities likely also exist in Iowa. The 2021 Cancer in Iowa report indicated that Black individuals experience higher mortality than White individuals for several diseases including lung cancer. Disparities such as these are extremely concerning, so the aim of this project was to better understand what these disparities actually are and determine what drives them.

Purpose: The purpose of this project was to better understand disparities in lung cancer between Black and White individuals in Iowa.

Results: Using the data from the Iowa Cancer Registry we identified a cohort of 19,877 White patients and 454 Black patients diagnosed with lung cancer between 2010 and 2021. We found that black individuals are diagnosed at a younger age than white individuals. Over 17% of the Black patients in the cohort were diagnosed between the ages of 18-54 compared to only 8% of White patients. Given the observation that Black patients receive less surgery than White patients nationally, we also wanted to compare the surgery rates for Black and White patients in Iowa. We observed the same trend; at any stage of disease, Black patients received less surgery than White patients. For example, at stage II, 50% of White patients received surgery compared to only 33-36% of Black patients. Initial Kaplan-Meier survival curves suggest that stage of disease and age are the most important drivers of mortality, but within groups of similar stage and age there does appear to be a difference in mortality between Black and White patients.

Conclusion: This data is preliminary but suggests that disparities do exist between Black and White lung cancer patients in Iowa. Future directions include multivariable analysis to establish whether there are racial mortality disparities and to further investigate what drives these disparities.

Title: Playing Hide and Seek: Investigating Nav1.5 Expression Across Different Mouse Cardiomyocyte Fractions

Student: Sebastian Gomez (M2G)
Mentor: Barry London

It is estimated that between 1.5-5% of the general population is affected by arrhythmias. Sudden cardiac death and arrhythmias unfortunately account for 15-20% of all deaths. Understanding the mechanism by which cardiac arrhythmias develop can help scientists and clinicians alike better treat these lethal conditions. One area of interest is the cardiac sodium channel, Nav1.5. Nav1.5 is responsible for generating ~95% of the sodium current in any given cardiomyocyte, yet previous studies have shown that only a portion of Nav1.5 is expressed at the cell membrane. Nav1.5 is only physiologically functional at the cell membrane. Human mutations of Nav1.5 have been shown to predispose individuals to arrhythmias from conditions including Long QT Syndrome and Brugada Syndrome. Our lab and others have previously shown that altering post-translational modifications, including decreasing NAD+-dependent deacetylation by the Sirtuin1 (SIRT1) enzyme or increasing phosphorylation by the Protein Kinase C (PKC) enzyme, can reduce sodium current produced by Nav1.5, likely at least in part by impacting Nav1.5 trafficking to the cell membrane. However, it is unknown whether these two separate post-translational modifications are physiologically related to one another. We engineered double mutant mouse models with partial or complete knockout of acetylation and phosphorylation to investigate a possible relationship. Initial electrocardiogram (ECG) measurements of the new model found that both wildtype and homozygous double knockout mice have relatively normal ECGs, while the heterozygous partial knockout mice were the only ones producing an abnormal ECG. **I hypothesized that the heterozygous partial knockout of both the acetylation and phosphorylation of Nav1.5 reduces membrane Nav1.5 expression compared to wildtype and homozygous double knockout of acetylation and phosphorylation of Nav1.5.** To measure membrane Nav1.5 expression in mice with different levels of deacetylation/phosphorylation knockout, whole mouse hearts were harvested from young adult wildtype, heterozygous partial knockout, and homozygous complete knockout mice. The membrane protein fragments of the mouse cardiomyocytes were extracted using a protein compartmentalization kit, and protein concentration was qualitatively measured using Western Blot techniques. Western blots on two cohorts of double mutant mice showed little to no difference in membrane Nav1.5 expression between wildtype, heterozygous partial knockout, and homozygous complete knockout of acetylation/phosphorylation of Nav1.5. Additionally, after increasing the sample size of ECGs, there was no longer a significant impact to ECGs in heterozygous knockout mice as was previously suggested. **In conclusion, I was not able to find that the partial knockout of deacetylation and phosphorylation of Nav1.5 impacted Nav1.5 trafficking and expression to the cell membrane, which would have explained the initial abnormal ECG findings in the heterozygous partial knockout mice.** The next step would be to measure if the Nav1.5 channels that are expressed at the cell membrane across the different mice are indeed deacetylated and not phosphorylated. It is possible that Nav1.5 does not need to be deacetylated and dephosphorylated to reach the cell membrane and become functional. It could be that Nav1.5 may rely on other post-translational modifications to reach the cell membrane. Additionally, any Nav1.5 membrane expression changes found in acetylation/phosphorylation knockout mice may become more apparent after the mice have been stressed with either a simulated myocardial infarction or other ischemic injury. **Nevertheless, more efforts are needed to investigate Nav1.5 channel trafficking and function to help scientists and clinicians alike continue their battle against arrhythmias.**

Infection of Adipocytes with *L. infantum* Induces Changes to Cellular Phenotype

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Introduction: Leishmaniasis is a neglected tropical disease with several distinct disease phenotypes, all of which are caused by protozoan parasites of the genus *Leishmania*. Visceral leishmaniasis (VL), caused by *Leishmania infantum* or *L. donovani*, is a systemic infection causing hepatosplenomegaly and pancytopenia, which is often fatal if untreated. Leishmaniasis is primarily endemic to resource limited countries. As these countries become more modernized, high-fat and high-cholesterol diets are also becoming more common, and obesity rates are on the rise. Recent studies have evaluated the relationship between obesity and cutaneous leishmaniasis, revealing that obesity complicates disease progression and presentation, as well as leading to longer recovery times and greater chance of failing initial treatment. We previously reported that a high fat/high cholesterol leads to aberrant parasite trafficking and survival in a murine model of VL. Not much work has been done yet to investigate whether adipocytes, the main cell type in adipose tissue, is implicated in the pathologenesis of leishmaniasis. *Leishmania* are obligate intracellular parasites of phagocytic cells in mammals and survive long-term in tissue macrophages. Our lab made the surprising preliminary observation that *Leishmania* spp. promastigotes are internalized by adipocytes.

Purpose: To investigate whether adipocytes serve as host cells for *L. infantum* parasites *in vitro*, and whether adipocytes undergo phenotypic changes in response to the parasites.

Methods: A pre-adipocyte cell line was differentiated until mature (ten days), then infected with *L. infantum* metacyclic promastigotes with an MOI of 10:1. After 4, 24, 48, or 72hrs, cells were divided into one subset that was trypsinized, applied to slides, fixed and stained with Wright Giemsa. Another subset was lysed with TRIzol, and RNA was isolated using a phenol/chloroform extraction method. RNA was reverse transcribed, and cDNA was quantified by TaqMan qPCR. mRNA transcripts that are specific to cells with an adipocyte phenotype (adiponectin, PPAR-γ, lipoprotein lipase) and those specific to cells with an immune phenotype (interferon-α/β receptor 1, interferon-γ receptor 1, interleukin-6) were compared between uninfected and infected samples using a $\Delta\Delta C_t$ relative quantitation method. Additionally, RNA was purified and submitted to the Iowa Institute of Human Genetics for RNA-Seq analysis which is ongoing. All statistical analysis was conducted using GraphPad Prism software.

Results: Parasites were internalized by adipocytes and transformed to the intracellular amastigote stage. Amastigote burdens increased significantly between 24 and 48hrs, with a plateau at 72hrs. At 4hrs, most parasites were extracellular promastigotes. Most infected cells at 48 and 72hrs had several internal amastigotes, notably different from 24hrs. This implies that amastigotes may undergo a few rounds of intracellular replication inside these cells. TaqMan assays revealed all three markers of adipocyte metabolism that we tested were significantly downregulated in infected cells at the 48 and 72hrs timepoints. IL-6 expression was significantly upregulated in infected cells, although the two interferon receptors showed no significant difference after infection.

Conclusion: Adipocytes are suitable hosts for *L. infantum* parasites, able to support stage development and possibly replication, implicating them as possible cellular reservoirs for parasites during chronic infection. Adipocytes also undergo significant transcriptomic—and likely phenotypic—changes during infection with *L. infantum*, which would likely contribute to disruption of normal adipocyte metabolic functions and adipokine release and possibly promote a pro-inflammatory environment. These changes may cause more severe disease pathology, as well as aiding in systemic dissemination of parasites during VL. It is unclear if these cellular changes would be sustained long-term, or whether these phenotypic changes are driven by the host, pathogen, or both.

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The Predictive Value of Renal Medullary Pyramidal Thickness Post-Pyeloplasty

Ryan Grandgenett, Sarah Perry, Christopher S. Cooper

Abstract

Introduction

Ureteropelvic junction obstruction may cause hydronephrosis and thinning of the renal parenchyma. Therefore, hydronephrosis and thinning of the renal parenchyma are factors used to grade the degree of hydronephrosis. The greater the degree of hydronephrosis and thinning of the parenchyma, the more likely there is a ureteropelvic junction obstruction that will require surgical intervention (pyeloplasty). However, the grading of hydronephrosis and parenchymal thinning have been traditionally based on subjective impressions of sonographic images and have limited reliability when it comes to grading in a reproducible manner. The overall renal parenchymal thickness increases with age, making it less reliable to use for assessment compared to the medullary pyramidal thickness (MPT) which changes very little in the first 9 years of life. Recently, medullary pyramidal thickness (MPT) has been shown to be more reliable than traditional grading systems and also demonstrated to be predictive of obstruction and pyeloplasty as well as a predictor of the differential renal function (DRF) as assessed by nuclear renal scan in patients with unilateral hydronephrosis. An MPT ≤ 3 mm is associated with significantly increased risk of decreased differential renal function and and subsequent pyeloplasty in multiple studies. To date, the value of MPT in post-operative kidneys has not been reported. This project aims to determine if there is a change in MPT post-pyeloplasty, and if so, if this change is a reliable method for predicting differential renal function and kidney recovery.

Purpose

We hypothesized that there would be an increase in MPT thickness in the hydronephrotic kidney at a greater rate than the contralateral normal kidney's MPT change. We also hypothesized that an increased ratio (hydronephrotic:normal contralateral MPT) post-operatively would be significantly correlated to an increase in the DRF in the hydronephrotic kidney. In addition, having a better understanding of the typical/anticipated change in post-operative MPT after a successful surgery allows physicians to more effectively monitor recovery.

Methods

This study was a retrospective chart and radiographic review of patient data from patients undergoing pyeloplasty from 01/2006 -12/2023 at the UIHC (IRB #20200-5068). The data collected for this project included the following patient information: name, MRN, DOB, gender, date of surgery, last ultrasound before surgery date, MAG-3 nuclear renal scans before surgery, post-surgical ultrasounds, and post-surgical MAG-3 scans. The subjects included in this study had high grade (SFU grade 3 or 4) congenital unilateral hydronephrosis detected prenatally or within the first 3 months of life who underwent pyeloplasty before the age of 2 years. This study was completed by analyzing the multiple variables listed above including the ultrasound data and MAG-3 data that was collected to assess the MPT and DRF in patients post-surgery compared to pre-surgery. Data was analyzed from one pre-operative ultrasound and three post-operative ultrasounds. Statistical analysis was performed to identify associations between variables and post-surgical MPT.

Results

96 patients were included with grade 3 or 4 unilateral hydronephrosis that underwent pyeloplasty for UPJ obstruction. Median patient age at surgery was 139[IQR 79.5, 322] days. The median number of days after surgery that an ultrasound was performed was 90[IQR 76.75, 108.25] days. The median change in PT in the hydronephrotic kidney from the pre-op ultrasound to the post-op ultrasound was 1.3[IQR 0.8, 2.2] mm and the median change in AP diameter of the renal pelvis was -1.5[IQR -0.7, -2.5] cm at median 312[IQR 257, 452] days post-op. Significant negative correlations were shown between PT and AP diameter. No significant correlations were found between PT and DRF likely due to the small number of patients (42) who had post-op MAG-3 renal scans.

Conclusion

PT is expected to increase and the AP diameter of the renal pelvis is expected to decrease shortly after pyeloplasty. When post operative ultrasounds show a decrease in PT and increase in AP diameter, it is predictive of treatment failure. Renal medullary pyramid thickness and anterior-posterior renal pelvis diameter measurements may be useful ways to monitor kidney recovery post-pyeloplasty.

Effect of genetic background and shock tube generated blast waves on optic nerve structure and function

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Background/Introduction: Blast-mediated traumatic brain injury (bTBI) is both an acute and chronic spectrum disorder that is the most common type of head injury among military personnel. Depending on the severity of the injury, acute consequences of bTBI may be readily apparent at the time of injury, whereas chronic consequences are currently more difficult to detect, despite resulting in progressive, potentially debilitating symptoms. Chronic symptoms of bTBI can especially be difficult to identify due to overlap with those of PTSD, leading to an even more increased need for identifying pathobiological markers for bTBI early in the disorder in this population. It is possible to reproduce bTBI in mice using shock tube generated blast waves. Research has been done using mice models to demonstrate how these blast waves affects the retina, specifically regarding retinal ganglion cell structure and function. They demonstrated that increasing the blast intensity and number of blast exposures results in increased ocular injury and that the extent of ocular injury following bTBI is influenced by multiple genes, including those related to apolipoprotein E, brain-derived neurotrophic factor, the dopaminergic system, the serotonergic system, and interleukins. Due to the vision-impairing effects that shock tube generated blast waves have on retinal ganglion cells, it is important to investigate possible effects on the optic nerve and how structure of the optic nerve impacts retinal ganglion cell function. Mouse research has also implicated that the retinal ganglion cell response to shock tube generated blast waves is dependent on genetic background, so we will be investigating whether this response is observable in the optic nerve as well.

Aims/Hypothesis: The aims of this study are to study how genetic background affects structure of the optic nerve following bTBI and how the intensity and number of blast exposures affects optic nerve structure.

Methods: 90 mice were separated into 6 groups based on genetics and endured frequency and intensity of blast waves. Blast injury was induced in mice using an advanced blast simulator that generates a blast wave using compressed gas. In vivo structure of the retina was examined by OCT to measure the retinal nerve fiber layer (RNFL), the retinal ganglion cell layer (GCL), and the inner plexiform layer (IPL). RGC function was examined using the PERG and overall visual function was examined using the OMR. Mice were euthanized at either 3 or 6 months following blast injury, whole eyes were enucleated, and the posterior cups were dissected and fixed. 1 μm cross sections were cut on an ultramicrotome, transferred to glass slides, stained with 1% paraphenylenediamine (PPD) and mounted to glass slides. Light micrograph images were obtained with an Olympus BX-52 microscope to perform cell counts.

Results: Manual hand counts are being performed currently from the confocal images of the mouse optic nerves in order to have data. Statistical comparisons will be performed using both paired t-tests and ANOVA testing. We will compare blast exposed mice to sham blasted mice for inbred mouse lines. For outbred mouse lines, we will compare nerves that have been removed from a mouse prior to blast injury to nerves that were left and exposed to blast injury. For both groups, we will perform correlation analysis to determine if optic nerve damage correlates to retinal and brain damage.

Neuroinflammatory Biomarkers and Brain Volume Alterations in Hemophilia A

Kevin Gubner, Danielle York, Daniel Thedens, Eric Axelson, Dr. Yahya Almodallal, Dr. Janice Staber

Background: Hemophilia A (HA), caused by a deficiency in clotting Factor VIII (FVIII), leads to several hemostatic complications. Patients with HA have an increased risk of depression, anxiety, and attention deficit hyperactivity disorder (ADHD). The main treatment and research focus for HA is bleeding events, however despite poor neurological effects, these are rarely addressed. Previously, the Staber lab demonstrated significant differences between children with HA and healthy controls including executive dysfunction and smaller cerebellar volumes in children with HA when compared to controls. Here, we sought to uncover the mechanistic drivers of the observed neurocognitive and brain structure differences in patients with HA by leveraging the Staber lab's established FVIII deficient mouse model to further explore neuroinflammation and brain structure.

Purpose: To investigate the role of neuroinflammation by measuring gene expression and to analyze brain structure changes between HA and wild-type (WT). The long-term goal is to understand the effects of FVIII deficiency on brain structure and function.

Methods: Brains were harvested from 6-month-old HA and WT mice sectioned into brainstem, cerebellum cortex/hypothalamus/thalamus, and hippocampus, and subsequently RNA isolated from each of these regions separately (n=22/group). A panel of twenty-nine biomarkers linked to several pro-inflammatory and pro-repair pathways were analyzed via RT-qPCR to measure relative mRNA levels. Inflammatory marker expression was analyzed using the ΔΔCt method, followed by mixed effects analysis and a Šidák test for multiple comparisons using GraphPad Prism. Additional 5-6 month-old HA and WT mice (n=25 HA, n=20 WT) underwent quantitative structural magnetic resonance imaging (MRI). Following fast imaging employing steady-state acquisition (FIESTA) anatomical MRI scans, volumes from brain regions of interest (ROI) were calculated referencing the Dorr-Steadman-Ulman-Richards-Qiu-Egan (DSURQE) atlas. Volume data for 356 anatomical regions of interest and 294 sub-regions were normalized to intracranial volume. Resulting region volumes were expressed as a proportion of intracranial volume, and subsequently fit to a linear model with group (HA or WT) as the predictor variable and ROI as the dependent variable. Analysis of ROI volumes was preformed using RStudio version 2023.06.2+561 "Mountain Hydrangea".

Results: Pro-inflammatory and pro-repair markers differed in relative expression between HA and WT mice. Initial exploration pointed to a neuroinflammatory phenotype in HA mice. Markers such as GPX1, SOD-1, and Cx3cl1 all revealed trends for increased relative expression. Subsequently, ROI volume analysis resulted in differences primarily in sub-regions of the brainstem, cerebellum, cingulum, hippocampus, hypothalamus, and pons. A focused analysis on 16 gross anatomic regions demonstrated several regions to significantly differ in size. Mean cerebellar and hippocampal volumes are significantly larger in the HA group relative to WT while the hypothalamus and thalamus are significantly smaller in the HA group compared to WT.

Conclusions: Upregulation of pro-inflammatory and pro-repair markers provides insight to the potential dysregulated neuroinflammatory state in HA. Additionally, volumetric differences between HA and WT were found in several neuroanatomic ROIs. HA mice showed significant differences in volumes of the cerebellum, hippocampus, hypothalamus, and thalamus compared to controls. These data suggest differences at the macroscopic and microscopic level. Relative expression of neuroinflammatory biomarkers, in conjunction with volumetric analysis of brain ROIs exemplify the utility of the HA mouse model to investigate effects of FVIII deficiency on the brain.

Novel Pacing Modality for Cardiac Conditioning and Enhanced Cardioprotection

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Introduction: Exercise has been increasingly understood as the most effective non-clinical intervention to promote cardiac conditioning, enhance myocardial stress resistance, and mitigate adverse outcomes in systolic heart failure (HF). However, many individuals with HF experience varying degrees of exercise intolerance, alongside barriers to effective treatment, highlighting the importance of establishing novel approaches to recover cardiac functional capacity. Sinus node function has been empirically proven as an indicator of cardiac health. Sinus node recovery time (SNRT) and heart rate recovery (HRR) measure sinus node function and describe the time taken for normal heart rate (HR) and rhythm to recover after a period of atrial pacing or exercise, acting as markers of proper HR autoregulation, cardiovascular fitness, and stress resistance.

Hypothesis and Purpose: Our study investigates the role and mechanisms of the clinically translatable exercise HR envelope effects on cardiac stress resistance. Since the magnitude and duration of exercise HR acceleration are tightly correlated with beneficial cardiac outcomes, it is hypothesized that an exercise-similar HR envelope, delivered by atrial pacing in a maximally physiologic way that avoids toxic effects of chamber dyssynchrony, may be a significant trigger of cardiac conditioning and stress resistance. Specifically, we investigate if exercise-similar HR acceleration may initiate favorable cardiac remodeling, leading to shortened SNRT in mice and HRR in humans. Previous data from our group have shown that this HR pattern, even without actual exercise, promotes changes in cardiomyocyte calcium handling and gene expression supporting a conditioned cardiac phenotype that is associated with ischemic protection in mice, improved walking distance and a trend toward improved cardiac contractile function in human subjects, and was shown to be safe and well tolerated. This study further investigates if exercise similar HR acceleration can promote changes in cardiac myocytes and sinus node cells' calcium dynamics, leading to improved SNRT and HRR.

Methods: Mice were atrial-paced once/d (8 days over 2 week period) via a transesophageal electrode to deliver an exercise-similar HR pattern with preserved atrio- and inter-ventricular synchrony. Effects on cardiac calcium handling and sinus node function were investigated on isolated retrogradely perfused hearts. Ca^{2+} transients and SNRTs were recorded post 5, 10, and 20 Hz stimulation. Humans with chronic ischemic and non-ischemic HF, EF < 30%, class II-III symptoms, and QRS ≤ 120 ms had their existing implanted defibrillators programmed to gradually accelerate HR to 80% maximum predicted for age while maintaining atrio- and inter-ventricular synchrony, or pretended to be programmed (sham) with the subject blinded to their study arm. This HR was maintained for 30 min and then slowly decelerated to baseline. Subjects underwent a cardiopulmonary exercise test (CPET) at baseline and 4 weeks of pacing/sham intervention, in which HR deceleration was examined to evaluate HRR. CPET data of 4 human subjects, with 2 assigned to each condition, were analyzed for potential changes in HRR slopes.

Results and Discussion: The paced mice cohort displayed changes in Ca^{2+} handling, coupled with improved recovery of sinus node function after rapid stimulation. Human subject studies revealed that 4 weeks of pacing intervention were sufficient to significantly improve HRR after CPET (HRR slopes were significantly different between baseline and 4 weeks of intervention $n = 2$ $p < 0.05$ for paced groups, while showing no difference in sham subjects $n = 2$ $p > 0.25$). Therefore, our data suggest that exercise similar HR acceleration delivered by atrial pacing results in improved sinus node stress resistance.

Conclusion: Mice studies demonstrated more rapid SNRTs following exercise-similar HR envelope atrial pacing, which are associated with healthy myocardial remodeling and recovery of sinus node dysfunction. The paced, exercise-similar HR acceleration is well-tolerated in subjects with both ischemic and non-ischemic cardiomyopathy, and when applied over 1 month, results in improved HRR. If confirmed by larger and longer studies, this strategy could offer an inexpensive, safe, rapidly clinically translatable, high-impact adjunct to standard heart failure treatments for improvement of sinus node function.

The Effect of Systemic Immunosuppression and Nutrition on the Cutaneous Wound Environment

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Background: Wound healing is a dynamic process that requires appropriate signaling to progress through its four phases, hemostasis, inflammation, proliferation, and remodeling until properly healed. When wounds fail to complete this process, they enter a state of chronicity that is associated with increased morbidity, mortality, and economic burden. Although technically healed, scars themselves also hold a burden, including loss of function, restricted movement, growth limitations, aesthetic concerns, and psychological effects. Thus, we must explore the microenvironment of wound healing to determine effective treatments for chronic wounds and scars.

While much is known about the role of individual cytokines, chemokines, and growth factors present in the wound milieu, more must be discovered about how systemic changes such as immunosuppression and nutrition status can alter these factors. Both aims of this study utilized samples from patients undergoing Mohs Micrographic Surgery for skin cancer along with several indices of wound healing. In the first aim of this study, we determined how systemic immunosuppression influenced the cutaneous wound environment compared to non-immunosuppressed patients. In the second aim, we determined if nutritional status on the day of surgery influenced inflammation and wound healing.

Hypothesis: Systemic immunomodulatory therapies and nutritional status will each influence levels of inflammatory and wound healing factors in the cutaneous wound environment following skin cancer excision.

Methods: To assess immunomodulation in wound healing, the skin was collected from patients undergoing excision of non-melanoma skin cancer who were already on immunomodulatory anti-rejection medications post organ transplant, or healthy controls (10/group) (IRB#201905800). Skin samples were collected on the day of surgery and 14 days post-operation. RNA was extracted using New England Biolabs' Monarch Total RNA Miniprep Kit. RNA was then converted into complementary DNA using Applied Biosystems' High-Capacity cDNA Reverse Transcription Kit. Real-time quantitative polymerase chain reactions were run on a panel of cytokines, chemokines, and growth factors involved in wound healing. Data was analyzed using the delta-delta Ct method. Mann-Whitney and two-way ANOVA tests were run to determine significance.

To assess nutrition in wound healing, skin and peripheral blood samples were collected from patients undergoing Mohs Micrographic Surgery for skin cancer (n= 41) (IRB #202404302). Patients were given a Mini Nutritional Assessment and Food Frequency Questionnaire at the time of excision. Protein was extracted from the tissue using Thermo Scientific's T-PER buffer. Patient sera and tissue protein were run in ELISA and Multiplex arrays to assess for cytokines, chemokines, and growth factors.

Results: To compare the wound environment of healthy control (HC) vs immunosuppressed (IS) patients, a panel of 15 cytokines, chemokines, and growth factors was analyzed by RT-qPCR. On the day of excisional surgery, EGF, a growth factor important in reepithelization, was significantly decreased in the wound environment of immunosuppressed patients. PDGFA, TGFBR1, TGFB2, and TGFB3, which are all involved in ECM and collagen formation, were also decreased, though not significantly. When comparing Day 0 (n=1) samples with Day 14 (n=2-3) samples, levels of EGF, FGFR3, TGFB2, TNF, and VEGFA significantly increased in HC tissue post-op. When looking specifically at Day 14, all factors were statistically different between the HC and IS groups excluding IL1B, IL6, and TGFB3. Analysis of the nutrition-focused ELISA and Multiplex arrays are underway.

Conclusions: This study indicates that systemic immunosuppression modulates factors that influence wound healing in a way that may be beneficial to the healing of acute surgical wounds. The impact of patient nutritional status on factors involved in wound healing will be presented on the poster.

IL-17A Inflammation Correlates with Hyperglycemia in Cystic Fibrosis Patients Regardless of Vitamin D Deficiency

Presenter: Holly Hemann, MA[1] **Mentor:** Katie Larson Ode, MD, MS[1]

Other Collaborators: Catherina Pinnaro, MD[1], Andrew Norris, MD, PhD[1], Christine Chan, MD[2], Amir Moheet, MBBS[3]

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Background

Cystic fibrosis (CF) is a severe autosomal recessive disorder caused by mutations in the Cystic Fibrosis Conductance Regulator (CFTR) gene. As therapies for lung dysfunction in CF improve, patients are living longer, and the incidence of non-pulmonary complications is climbing. One common complication is glycemic dysregulation associated with decreased insulin secretion, which can progress into a distinct form of diabetes known as cystic fibrosis-related diabetes (CFRD). CFRD is associated with clinical decline due to dysglycemia even prior to the diagnosis of CFRD. However, the pathophysiology of glucose metabolic abnormalities in CFRD is poorly understood. Studies have hypothesized that CFRD pathogenesis may reflect the imbalance of pro-inflammatory cytokines, including T-helper 17 (Th17) lymphocytes that produce and secrete the pro-inflammatory cytokine IL-17A. This pathway is involved in both CF lung inflammation and β-cell destruction in type 1 diabetes, making it a probable link between dysglycemia and lung function decline in CFRD. An additional consideration in the Th17 inflammatory pathway is $1,25(OH)_2D_3$ (Vitamin D_3) which directly inhibits the production of IL-17A. Thus, underlying vitamin D deficiency – which is frequently observed in CF patients – may contribute to immune dysfunction.

Objective

This project aims to determine the possible association of IL-17A and Vitamin D and the development of CFRD. Investigating early pathophysiology can define areas of future research aimed at delaying onset of CFRD and halting clinical decline in CF patients.

Methods

120 age-and-sex-matched participants from the EnVision CF Multicenter Study of Glucose Tolerance in Cystic Fibrosis (NCT03650712) cohort were separated into three groups based on results of frequently sampled oral glucose tolerance testing (fsOGTT): Hyperglycemia, Hypoglycemia, and Euglycemia. *CFTR* genotype was abstracted from chart review. 0min serum samples were assessed for Vitamin D using enzyme-linked immunosorbent assay (ELISA). 0min and 120min serum samples were assessed for IL-17A using a customized human magnetic luminex assay. Statistical analyses were performed in RStudio utilizing Analysis of Variance (ANOVA) and Linear Regression models.

Results

IL-17A 0min, IL-17A 120min, or Vitamin D values did not differ by glycemic group (hyperglycemia/hypoglycemia/euglycemia) or *CFTR* genotype group (ΔF508 homozygous/heterozygous/other). There were no significant correlations between Vitamin D and IL-17A 120min or between Vitamin D and IL-17A 0min within the full dataset, any glycemic group, or any genotype group. Baseline 0min IL-17A inflammation correlated significantly with 120min glucose readings in an OGTT in the full dataset ($R = 0.19$, $p = 0.042$, beta = 0.48). This relationship did not remain significant on subgroup analysis by glycemia, however, the correlation was significant in those whose *CFTR* genotype was heterozygous for ΔF508 mutations ($R = 0.28$, $p = 0.033$, beta = 0.45) or with only non- ΔF508 mutations ($R = 0.68$, $p = 0.03$, beta = 15.09).

Conclusion

Though, inflammation associated with dysglycemia in CF is more complex than IL-17A alone, IL-17A may have a role in the development of hyperglycemia prior to CFRD onset that is potentially correlated with CFTR genotype. Vitamin D deficiency, though clinically important, at least in our hands does not seem to play a role in IL-17A inflammation in CF patients.

Establishing a Normative Database for the Iowa VR Headset Perimeter

Student: Joe Heyrman, M2
Mentors: Dr. Michael Wall MD; Dr. Edward Linton MD – University of Iowa Department of Ophthalmology and Visual Sciences

Background: Visual field (VF) testing, specifically standard automated perimetry (SAP), is an essential part of diagnosing and monitoring the progression of ocular diseases such as glaucoma. The gold standard devices, such as the Octopus 900 (O900), used for these tests are expensive, lack portability, and uncomfortable. Consequently, these tests have poor accessibility. Virtual reality (VR) headsets are being explored as a cheaper, more portable, and comfortable alternative. One such device is our own Iowa VR open-source head mounted display (HMD) which has previously shown great potential as an alternative to SAP. However, there are still limitations holding back our device and other VR devices from being used in clinical settings. Namely, few of these devices have gathered a large normative database for use in the diagnosis of ocular disease in new patients.

Purpose: The goal of this study is to collect a normative database of healthy controls with our HMD (for both luminance and size modulation) and the O900 (luminance only). We hypothesize that the Iowa HMD will produce a normative database with similar sensitivities and repeatability as the O900. We will also use this database to develop confidence limits for normals for each test location.

Methods: 59 healthy observers underwent visual field testing using the Open Perimetry Interface platform with size V stimuli, a custom test location grid spanning the central 26° of the VF, and a ZEST (Zippy Estimation by Sequential Testing) thresholding algorithm. Each patient was tested twice on each of the three modalities: HMD luminance, HMD size, and O900 luminance. Mean sensitivity and pointwise repeatability coefficients were calculated for each of the 3 modalities from the pointwise threshold values obtained from the VF tests. 95 percentile confidence limits were calculated for the HMD tests.

Results: Mean sensitivity and pointwise RCs were 1.20 and 3.20 for the O900 luminance, 1.44 and 3.20 for the HMD luminance, and 2.78 and 5.37 for the HMD size, respectively.

Conclusions: We found that the retest variability of the HMD luminance was acceptable and comparable to that of the Octopus 900 luminance. Our results also showed that retest variability for the HMD size modality was slightly higher than the other two modalities. These findings further demonstrate that the Iowa HMD has exciting potential to be an alternative perimetry test at a fraction of the cost of the traditional devices currently being used clinically. The normative healthy data collected here will allow for future studies that examine the diagnostic capabilities of the HMD for diseases such as glaucoma.

2024 Medical Student Research Conference Abstract

Researchers: Jared J. Hill, Evan Williams, Steven Long, Marcus Tatum, Donald D. Anderson, Geb Thomas, Heather Kowalski, Kyle Duchman , Matthew Karam

Title: Evaluating Assessment Methods for Measuring Resident Surgical Skills in the Operating Room

Introduction: The traditional apprenticeship model for surgical education (see one, do one, teach one) can expose patients to risks of suboptimal care[1]. The "July Phenomenon" reflects this diminished care, this refers to the start of surgical residency in July, and this month coincides with a higher rate of preventable complications ($p < 0.013$)[2]. The American Board of Orthopedic Surgeons has recently required that residents receive evaluations (OP Score) on their OR performance to combat this reduced care by tracking resident performance. However the OP scoring method is subjective, and could introduce bias.

Hypothesis: Subjective OP evaluations of resident operating room (OR) performance will correlate with objective surgical metrics such as pin spread and surgical time.

Methods: Intraoperative fluoroscopy from wire navigation procedures were saved for post-operative analysis to measure metrics such as OR time, tip apex distance, and pin spread. Diagnostic arthroscopy (knee and shoulder) videos were recorded to evaluate surgical time and shift between diagnostic regions. OP scores were also collected for correlation analysis.

Results: In wire navigation procedures, the pin spread ratio, which has been shown to correlate with surgical outcomes, has no correlation with P-scores for residents on the same case. Similar trends were observed when comparing P-scoring and procedure time. For diagnostic arthroscopy, significant differences were observed between attendings and residents with regards to time in the medial condyle and ACL/PCL, indicating room for targeted resident training.

Conclusions: Attending P-Scores have a very weak correlation with objective measurements in wire navigation procedures such as pin spread ratio and procedure time. The collection of diagnostic arthroscopy videos demonstrated areas for targeted resident training and provided a robust dataset for future analysis of objective resident performance.

The effect of an acute care-cardiothoracic joint team consultation protocol on rib fixation patient outcomes: A quality improvement project

University of Iowa Carver College of Medicine
Acute Care Surgery Division, Department of Surgery
Student: Max Holt
Mentors: Patrick McGonagill, MD, Annika Storey, DO; Colette Galet, PhD

Background and hypothesis. Traumatic rib fractures are serious injuries whose management can greatly influence patient outcomes. Traditional management approaches vary widely, leading to inconsistent results and prolonged recovery times. Surgical stabilization of rib fractures (SSRF) has emerged as a promising intervention for improving pain management and functional recovery in patients with severe rib fractures. Our institution recently developed a joint consultation protocol between the acute care and cardiothoracic teams to identify patients eligible for SSRF. This study was designed to assess the impact of the implementation of this protocol on patient outcomes. We hypothesized that protocol implementation would increase the number of evaluations for SSRF and subsequent rib fixation procedures due to an increase in consultation and provider awareness. We further hypothesized that implementation of this quality improvement (QI) project would improve patients' outcomes.

Methods. This is a retrospective cohort study of all trauma patients with >3 rib fractures admitted from February 1st, 2022, to January 31, 2024. Criteria from the Chest Wall Injury Society SSRF Guidelines were utilized to determine if patients qualified for SSRF. These criteria included > 3 rib fractures, two or more pulmonary derangements, and the presence of flail chest. The QI project was implemented on February 2023. Data were obtained from the University of Iowa trauma registry and medical record review. Demographics, comorbidities, injury, and hospital information including length of stay, rib fracture management, complications, mortality, and discharge disposition were collected in a REDCap database. Chi-square, Fisher's, and Mann-Whitney tests were used to compare the pre- and post-implementation groups. $P < 0.05$ was considered significant.

Results. Five hundred and two patients were included with 233 and 269 patients admitted pre- and post-implementation, respectively. Post-implementation, 32 (11.9%) cases were eligible for SSRF consultation, while 25 (10.7%) would have been pre-implementation. QI implementation was associated with a significant increase in SSRF consultation (13.8% vs. 2.6%, $p < 0.001$) and subsequent surgical stabilization of the ribs and/or sternum (6.3% vs. 2.2%, $p = 0.028$). Non-adherence to the protocol, defined as either over- or under-consulting based on protocol guidelines, was low post-implementation (13.5%). Post-implementation, of the 32 patients eligible for SSRF, only 8 underwent SSRF. Although not significant due to low numbers, ambulation improved in patients who underwent SSRF compared to those who did not (87.5% vs. 68.2%). Those who underwent SSRF were more likely to be discharged home (62.5% vs. 35%). No changes were observed in hospital and ICU length of stay, pain, ventilator days, and complication rates.

Conclusion. The implementation of a joint consultation protocol for SSRF at our institution was associated with a significant increase in the number of patients evaluated for SSRF. There was an increase in SSRF rates, reflecting improved provider awareness and adherence to the protocol. Although improvements in ambulation were noted, there were no significant impacts on length of stay, pain management, or complications. These findings underscore the necessity of targeted QI projects to optimize the management of severe rib fractures and suggests that protocol adherence can enhance surgical intervention rate. Further longitudinal research and multi-center studies are needed to fully understand the impact of the SSRF protocol on broader patient recovery metrics.

Examining Clinical Outcomes of Multiple Sclerosis Patients Who Utilized Diet as Part of Their Personal Treatment Plan: A Longitudinal Study

Jordan Hook BS; Landon Crippes, MD, Erika Dorff, MD; Bridget Easler, BS; Farnoosh Shemirani, PhD; Mary Ehlinger, BS; Patrick Ten Eyck, PhD; Linda Rubenstein, PhD; Linda Snetselaar, PhD, RDN; Tyler Titcomb, PhD, RDN; Terry Wahls, MD

Background
Emerging evidence suggests that diet may significantly influence the symptoms and severity of multiple sclerosis (MS). Ongoing clinical trials are evaluating the potential benefits of therapeutic dietary and lifestyle interventions. Currently, there are no established diet recommendations for patients with MS. Despite this, previous studies have demonstrated that a large proportion of people with MS are implementing special diets into their treatment plans.

Purpose
To compare clinical outcomes (relapse rate, severity of MS-related symptoms, number and size of enhancing lesions on MRI, and utilization of disease-modifying therapies [DMTs]) between patients with MS who reported utilizing diet as part of their treatment plan (dieters) to those who did not (non-dieters).

Methods
Electronic medical records (EMRs) of patients newly diagnosed with MS at the University of Iowa Health Care (UIHC) Department of Neurology from January 1, 2018, to May 1, 2024, were analyzed. Initially, EMRs were randomly selected and screened for eligibility, with inclusion criteria including ages 18-56 and ongoing MS care at UIHC. After the first 56 eligible participants were identified, 14 additional EMRs of patients who reported using a diet were selectively included to balance the groups. For each eligible participant, a comprehensive review was conducted of all MS-relevant progress notes, demographics, medications, laboratory results, and radiology studies to gather information on MS-related symptoms and disease course. The clinical course of MS was primarily assessed through relapse rate, determined by reviewing each MS-related progress note for documented MS-related symptom worsening and explicit statements of relapse occurrence. MRI analysis included brain, cervical spine, and thoracic spinal cord scans. Cox proportional hazards regression models with time-varying exposures, outcomes, and DMT covariates adjusted for baseline age, sex, race, and body mass index were utilized to compare the risk of outcomes between dieters and non-dieters, with p-value <0.05 to determine statistical significance.

Results
Seventy EMRs were abstracted (38 non-dieters and 32 dieters) with a mean follow-up of 3.54 (SD 1.3) years. No differences existed between groups for age, sex, race, BMI, or DMT use at baseline. Participants who adopted a diet did so at a mean of 1.38 (SD 1.5) years after diagnosis. During follow-up, dieters had a significantly reduced risk of new non-enhancing lesions (HR=0.74; 95% CI=0.55, 0.99). Additionally, dieters were more likely to have overall MS symptom improvements compared to non-dieters (HR=1.87; 95% CI=1.08, 3.25). Specifically, improvements in memory (HR=2.14; 95% CI 1.01, 4.35) and reduction in walking aid use (HR=6.49; 95% CI 1.32, 31.9) were more frequently observed for dieters. Furthermore, a significant reduction in worsening memory was observed among dieters (HR=0.33; 95% CI 0.12, 0.93).

Conclusion
In the present study, people with MS who adopted diets were more likely to have favorable clinical outcomes; however, due to the limited sample size, these results must be replicated in a larger and more diverse sample.

Intraoperative Severe Hyperglycemia During Hypothermic Circulatory Arrest in Cardiac Surgery Patients: A Retrospective Study

John Howell, BS, Aravin Sivamurugan, BS, Satoshi Hanada, MD

Purpose: Hypothermic circulatory arrest (HCA) is a technique used during aortic dissection and aneurysm repair procedures that has provided patients and care teams with a chance for more favorable outcomes. This advancement does not come without a cost. Adverse neurological outcomes remain a serious and relatively common concern. Blood glucose (BG) levels appear to reach profound levels during and after use of HCA. Although neurological outcomes following procedures using HCA have been well researched, the neurological effects of hyperglycemia remain under-studied. The purpose of this study was to identify the incidence of profound hyperglycemia (PHG) during procedures using HCA, as well as to investigate its relationship with adverse neurological outcomes.

Methods: Data was collected retrospectively from the electronic medical records of 277 patients who underwent cardiothoracic procedures that involved use of HCA techniques within the past 15 years. The reviewed cases were sorted into two groups based on peak intraoperative glucose levels: normal to severe hyperglycemia (BG < 300 mg/dL) and profound hyperglycemia (BG > 300 mg/dL). In addition to glucose measurements, factors regarding demographics, pre-existing comorbidities, intraoperative characteristics, and postoperative complications were also gathered and compared between groups.

Results: Among the patient demographics assessed, patient sex (45.1% female v. 30.0% female p=0.0216) and prevalence of hypertension (85.9% v. 74.3% p=0.0435) were significantly greater for PHG cases compared to non-PHG cases. All other demographics, comorbidities, and intraoperative characteristics did not differ significantly between groups. We identified the incidence of PHG during these procedures to be 25.63%, with an average intra-HCA BG of 340.1. Both pre-DHCA intraoperative peak BG (233.0 mg/dL v. 180.0 mg/dL) and post-DHCA intraoperative peak BG (339.5 mg/dL v. 277.9 mg/dL) measures were increased in cases involving PHG during HCA. PHG was also shown to be associated with increased intraoperative units of insulin dosage (94.9 units v. 52.1 units p=0.0001), time to extubation (28 hours v. 24 hours p=0.0001), rates of postoperative neurology consult (38% v. 20.9% p=0.0041), and rates of positive Brain MRI or CT findings (23.9% v. 12.6% p=0.0231) when compared to the normal to severe hyperglycemia group.

Conclusion: We found that PHG is not only a common consequence of HCA, but that it is also associated with adverse postoperative outcomes, such as extubation time, postoperative neurological consult, and positive brain imaging results. In addition, our findings highlight the importance of conducting further investigation in order to better understand both the causes and consequences of PHG in the context of HCA.

Title: Investigating the metabolic landscape of alopecia areata

Name: Jason Hristopoulos
Mentor: Ali Jabbari
Collaborators: Samuel Connell, Madison Lensing, Otgonzaya Ayush, Zhaowen Zhu, Cristina Dix, Ryan Reis, Idil Apak Evans, Reid Brown, Eric Taylor

Introduction: Alopecia areata (AA) is an autoimmune disease of the hair follicle that results in non-scarring hair loss. In a physiologic state, the hair follicle is an immune privileged site, characterized by low expression of MHC Class I in the inferior segment. In AA, however, there is increased MHC Class I expression throughout the follicle, indicating a loss of immune privilege, and subsequent lymphocytic infiltration. A key component of the immune response in AA are NKG2D+ CD8 T cells, which are hypothesized to be a pivotal pathogenic cell population and disease mediators. Currently, the only targeted FDA-approved treatments for AA are JAK inhibitors, which suppress cytokine signaling to prevent immune activation. However, concerns of worrisome side effects with long-term use of JAK inhibitors and incomplete efficacy underscore the need for safer and more effective therapies.

Purpose: One avenue for new therapeutic targets that is being investigated in other autoimmune diseases is to target metabolic vulnerabilities in critical, pathogenic cell populations. However, very little is known about metabolic alterations in AA. In this study, we aimed to explore the serum and intracellular metabolome of alopecic mice to identify novel metabolic therapeutic targets.

Methods: We made use of an inducible murine disease model, whereby AA was induced in female C3H/HeJ mice by skin-grafting alopecic skin. For serum metabolome studies, serum was collected from AA and unaffected (UA) mice and sent for targeted metabolomic analysis using the GC-MS broad metabolite panel. For intracellular metabolome studies, NKG2D+ and NKG2D- CD8 T cells were isolated from skin-draining lymph nodes of female AA mice via flow sorting. Isolated cell populations were sent for targeted metabolomic analysis using the LC-MS broad metabolite panel.

Results: Xanthine and hypoxanthine, intermediate metabolites in the purine degradation pathway, were among the most significantly decreased metabolites in the serum of AA mice. Publicly available RNAseq data from skin-draining lymph nodes in alopecic mice showed no significant differences between expression of hypoxanthine transporters in NKG2D+ and NKG2D- CD8 T cells. Data from the intracellular metabolome studies are forthcoming.

Discussion: Our study demonstrated decreased purine metabolites in the serum of alopecic mice, consistent with findings in other autoimmune diseases. There is an increasing number of studies implicating the purine metabolic pathway in autoimmunity and assessing its potential as a therapeutic target. However, this pathway has never been studied in AA and the specific roles of hypoxanthine and xanthine in autoimmunity are not well described. Therefore, further studies are needed to assess the role of this pathway in AA and its potential as a therapeutic target.

Peripheral calcitonin gene-related peptide induces brain-wide resting state functional connectivity changes in mice

Student: Michael Huebner
Mentor: Andrew Russo

One sentence summary: We find brain-wide functional connectivity changes in mice after peripheral CGRP injections.

Background

Migraine is associated with disabling sensory abnormalities, is one of the most common neurological disorders and remains undertreated in 50% of patients. One reason treatments fall short is our lack of understanding of the neuroanatomic contributors to migraine pathophysiology. Human functional imaging studies have identified neural networks associated with migraine, but which networks are relevant for migraine behavior remains unknown. Small-animal imaging studies can address this gap by probing functional networks linked to migraine; in particular, central brain regions critical for multisensory integration like the cerebellum, are novel targets for understanding migraine pathophysiology and to understand how they affect migraine-like behavior. We hypothesized that peripheral CGRP injection would induce functional changes in brain-wide blood oxygen level-dependent (BOLD) resting-state functional magnetic resonance imaging (rs-fMRI) response.

Methods

Male and female C57BL/6J mice underwent a baseline rs-fMRI sequence to collect anatomical images and 15 minutes of BOLD activity recording for a “baseline state” measurement. Mice were anesthetized with ~1.5% isoflurane during entire recording. Following baseline recordings, mice were injected with 0.1mg/kg CGRP and placed back into the MRI machine for the treatment resting state recordings 30 minutes post injection. This was followed by brain-wide hierarchical clustering analysis to determine changes in resting state connectivity between baseline and CGRP. Seed based approaches focused on brain areas associated with pain and sensory processing were used to determine connectivity changes between regions of interest. We also used awake behaving electrophysiological studies to confirm changes in activity in two regions identified by hierarchal clustering analysis.

Results

Preliminary results identified brain-wide changes in clustering of brain networks post-treatment. These include significant increases in connectivity between somatosensory and visual cortices and changes in other pain sensory networks including the deep cerebellar nuclei and insula. Preliminary electrophysiology data in the somatosensory and visual cortices confirm activity increases in awake behaving mice.

Conclusion

These data provide a possible mechanism for CGRP-induced migraine-like sensory hypersensitivity in mice including touch hypersensitivity and photophobia. Future studies will begin to understand how other clinically validated migraine triggers that cause similar phenotypes in mice contribute to functional connectivity in the brain.

Examining the link between spur cell anemia and dysregulation of iron metabolism in patients with cirrhosis

Raghuram Inturi
PI: Dr. Kyle Brown

Background

Spur cell anemia (SCA) is an uncommon form of acquired non-autoimmune hemolytic anemia occurring in patients with advanced liver disease. SCA is characterized by acanthocytes (spur cells) on peripheral blood smear. These cells have a markedly diminished lifespan, often leading to the need for blood transfusion. There is no effective treatment for this condition, but liver transplantation is curative. SCA classically presents as a severe hemolytic anemia in the setting of advanced alcohol-associated liver disease, but studies have shown that spur cells are not uncommon in hospitalized patients with cirrhosis due to various causes, and that their presence is a strong predictor of mortality. Other literature has suggested a link between SCA and iron overload, due to the combined effects of hemolysis and the frequent need for transfusion. It is unknown whether acanthocytes occur in patients with compensated liver disease, and if so, whether their presence is significant. Therefore, our project aims include 1) to determine whether acanthocytes can be found in patients with compensated cirrhosis seen for routine follow-up in Liver clinic, 2) to assess whether there is evidence of hemolysis in cirrhotics with spur cells, and 3) compare serum iron studies in compensated cirrhotics with or without spur cells.

Methods

We conducted a retrospective chart review of patients with cirrhosis followed in the Liver clinic at UIHC from 2015-2023. Patients met the criteria of the study if they a) had not demonstrated signs of decompensated liver disease (hepatocellular carcinoma, hepatic encephalopathy, ascites, jaundice, and/or variceal hemorrhage) AND b) had acanthocytes on peripheral blood smear.

Results

Of 900 Liver clinic patient charts reviewed for this project, 11 met the criteria of the study. This group comprised 8 males/3 females, mean age 63, and the cause of liver disease ranged from Hepatitis C, alcoholism, and metabolic-dysfunction associated steatohepatitis (MASH). In this group of patients, serum ferritin was markedly elevated (686.28 ng/mL) compared to patients with compensated cirrhosis without spur cells (344.92 ng/mL), despite the fact that none of the patients with acanthocytes required blood transfusions. Levels of hemolysis markers (lactate dehydrogenase, % indirect bilirubin, haptoglobin, reticulocyte count, and MCV) did not differ significantly between compensated liver cirrhotics with and without spur cells.

Conclusion

These findings demonstrate that acanthocytes are present in approximately 1% of compensated cirrhotics. Although we found no evidence that acanthocytes are associated with hemolysis in these stable patients, the presence of these abnormal red cells may contribute to abnormal iron studies in patients with chronic liver disease.

Functional Connectivity in Parkinson's Disease

Connor Johnson

Narayanan Lab

Introduction

Recent advances in the field of computational neuroscience, combined with existing signal processing methods, enable the application of new techniques in analyzing both the physical and connective structure of the brain. Specifically, the phenomena of functional connectivity has recently emerged as a way of describing non-causal interactions in the brain. In this exploratory study, we analyze fMRI scans collected from 82 patients with Parkinson's disease (PD), apply a host of computational and statistical tools, and compare to controls in an attempt to elucidate more information about the pathology of PD. We hypothesize that PD patients will show differential connectivity between brain regions as compared to those of controls. Further, we attempt to validate the findings of previous studies, especially with regard to impaired connectivity in the basal ganglia network, salience network, frontoparietal network, and the default mode network.

Methods

For this study, we utilized a combination of canonical fMRI analysis toolkits and bespoke computational pipelines, with the overall analysis pipeline drawn from previous studies and reviews (Seth, 2015; Hao, 2020). In short, these steps combine the standard analysis steps (head motion correction, slice timing correction, co-registration, standard space alignment, and anatomical segmentation and normalization) were performed by fmriprep (Esteban 2019). Further analysis, including confound regression, ROI definition, signal extraction, hemodynamic response function (HRF) deconvolution, and correlation analyses were performed with custom tools implemented using nilearn (Abraham, 2014) and nipype (Gorgolewski, 2016). In total, these steps take us from a brain volume captured on an fMRI machine to a set of signals, with confounds regressed out and other corrections made, which represent a set of brain regions. These signals also undergo HRF deconvolution to make the data more closely represent neural activity, rather than the blood-oxygen level dependent (BOLD) signal.

Findings

Unfortunately, our analysis did not reveal any significant differences between the control and PD population. However, this does not mean there is not more analysis to be done as this was just a first pass exploration of the data. Further, more advanced, analysis techniques may be used, specifically those that take into account time-lag between effects on brain regions, like weighted phase-lag indexing or Granger causality analysis. Further, clustering of the patients based on their connectivity profiles could reveal subtypes of PD or improve prognosis prediction for patients diagnosed with PD. Consensus hierarchical clustering of the brain regions in PD patients could also be compared to controls to investigate differential connectivity and network atrophy in PD. Finally, we also have access to EEG data from the patients, taken at the same visit, so any findings that emerge from this dataset can be easily validated using the same or similar methods in EEG.

B. burgdorferi alters synovial architecture in a human *ex vivo* model of Lyme Arthritis

Rachel Johnson[1], Christine A Petersen[2,3], Katherine Butler[4], Jacob M Elkins[5], KariAn Mulford[6], Cale Dobson[1], Karen Cyndari[6]

1: Carver College of Medicine; 2: Interdisciplinary Graduate Program in Immunology; 3: Ohio State University College of Veterinary Medicine; 4: Interdisciplinary Graduate Program in Immunology; 5: Department of Orthopedics and Rehabilitation; 6: Department of Emergency Medicine

Introduction: Lyme Disease (LD) is the most common vector borne disease in the U.S., with approximately 476,000 patients diagnosed and treated each year. LD occurs when an infected tick transmits *Borrelia burgdorferi* to a human. From the skin, the infection can spread through the circulation and reach other organs to cause long-term sequelae. The most common form of late disseminated LD in the U.S. is Lyme Arthritis (LA), in which *B. burgdorferi* enters the joint space and causes inflammation. The mechanism by which *B. burgdorferi* interacts with resident synovial macrophages (RSMs) to bypass the synovial membrane and enter the joint space is unknown. We hypothesized that *B. burgdorferi* damages RSM tight junction connections and subsequently facilitates the RSM phenotype from anti-inflammatory (M2) to pro-inflammatory (M1). To test this, we began by analyzing human synovium in an *ex vivo* model of LA.

Methods: Human synovium was obtained from patients 18-80 years of age receiving a scheduled, non-emergent, total knee replacement. We used 3 mm biopsy punches to create explants, then placed explants in the top well of our 0.4 μm Transwell system. The bottom well was inoculated with highly pathogenic *B. burgdorferi* at 250k, 500k, and 1000k (low, medium, and high dose, respectively) in 50% BSK-H and low glucose DMEM with FBS. Tissue was cultured for 3 days. For each day, outcomes were measured with histomorphology. We used two-way ANOVA to compare the inoculate of *B. burgdorferi* to synovial barrier integrity, cellularity, and depth. We also examined similar metrics for the sublining layer. Media was collected for sandwich ELISA.

Results: Our preliminary results found that when treated with low dose *B. burgdorferi*, the intimal and sublining layers were significantly thinner than controls at 24 hours. When treated with high *B. burgdorferi*, the layers were significantly thicker. Cellularity of the intimal layer decreased by 24 hours when treated with low dose *B. burgdorferi*, and cellularity of the sublining layer increased when treated with high dose *B. Burgdorferi*. The percent intact intimal lining decreased significantly compared to controls after 24 and 48 hours when treated with high dose *B. burgdorferi*. Analysis of different inoculate doses and later time points is in progress. ELISA analysis showed that the concentration of osteoprotegerin increased in both control and *B.burgdorferi*-treated samples over 72 hours.

Conclusions: We conclude that there is a dose-dependent response between *B. burgdorferi* and thickness and cellularity of the intimal lining and sublining. Additionally, there is a time- and dose-dependent response between *B. burgdorferi* exposure and percent intact intimal lining. This evidence supports the hypothesis that *B. Burgdorferi* damages the synovium to gain access to the joint space. This may explain the adverse symptoms of LA, but not its relapsing course. Using ELISA analysis, we found that OPG expression increased with time. However, RANKL expression must be measured to conclude whether *B. burgdorferi* leads to increased osteoclastogenesis.

Musculoskeletal pain is one of the most common complaints in the emergency department, and LA must be ruled out as a cause. However, there is little knowledge about how to adequately diagnose LA. To do so, the mechanism by which *B. burgdorferi* causes inflammation and/or damage in the joint space to cause LA must be investigated further.

Quantifying trends in hospital admissions of adults with intellectual disabilities based on demographic and hospital course variables

Student: Abby Jones, M2
Mentor: Meghan Connett, M.D., Department of Family Medicine

Background:
Patients with intellectual and developmental disabilities (IDD) were designated as a population experiencing health disparities by the NIH in September of 2023. Disparities between adult patients with and without IDD have been identified in outcomes of cancer treatment, kidney disease, heart disease, severity of disease at presentation, and hospital mortality. The aim of this quality improvement project was to create a database of comprehensive and population specific demographic and hospital admissions data. This database was made for two purposes. Firstly, to assess admission outcome trends within the population of adults with IDD. Secondly, as the foundational step to answer future research questions comparing adults with and without IDD.

Methods:
A retrospective chart review was done using the EMR (Epic) at Iowa Hospitals and Clinics (IHC). Patients met inclusion criteria who were age 18 or older as of 2023, had at least one non-elective admission between 1/1/2023-12/31/2023 at IHC, and had at least one of the ICD-10 codes for IDD in their chart. Demographic and hospital admission data was collected as a REDCap database. One-way ANOVA, Tukey Tests, and Chi-square were used when appropriate to analyze associations between demographic and outcome variables.

Results:
Repeated analysis of the database (n= 414) was done grouping the population by the four demographic variables below. Outcome variables analyzed were Total Hospital Days in 2023, Longest Length of Stay beginning in 2023, Number of Admissions in 2023, and Readmission within 30 Days (y/n) in 2023.
Disability Diagnosis: No outcome variables showed significant difference between groups.
Living Situation: Significant differences exist between the means for number of admissions ($p < 0.001$), total hospital days ($p = 0.019$), and longest length of stay ($p = 0.005$). Post-hoc Tukey tests were used to describe which groups showed significant differences in each outcome. Readmission within 30 days was also significantly different between groups ($p < 0.001$).
Guardianship Status: Significant differences exist between the means of total hospital days ($p = 0.003$) and longest lengths of stay ($p = 0.013$).
Communication Style: Longest length of stay showed significant differences ($p = 0.008$) between nonverbal patients who used sign and those who used gestures/vocalizations.

Conclusions:
The aim of this project was to create a framework from which to ask and answer further research questions. Trend analysis on the database uncovered demographic factors that may be influential in the disparities faced by patients with IDD. Due to the extremely limited research on adults with disabilities in the hospital, especially in the U.S., this database serves as the necessary starting point in the identification of disparities and associated risk factors. Addressing these risk factors will require closing the critical gap in knowledge on healthcare experiences of patients with IDD.

Title: Investigating Alternative Splicing of Mediator Complex Genes in Heart Disease

Author: Christopher Jun
Mentor: Chad Grueter, PhD

The Mediator complex and its associated proteins are integral in the regulation of eukaryotic gene transcription and subsequent gene expression. Previous literature has investigated the potential connections between aberrant Mediator complex function to neurological, cardiovascular, and developmental disease. Another well-understood mechanism regulating eukaryotic protein expression is alternative splicing of mRNA transcripts, generating protein diversity from a single gene. Alternative splicing is thought to contribute to cellular differentiation and developmental processes and is associated with human disease and cancer. Therefore, the discovery of alternative splicing events in critical genes, like the Mediator complex, may grant better understanding of human disease, and thus lead to better treatments and health outcomes. Here, we analyzed RNA-sequencing data for differences in alternative splicing of Mediator complex genes in ventricular cardiomyocytes between healthy mice and a mouse model simulating heart failure secondary to dilated cardiomyopathy. We then performed the same analysis on RNA-sequencing data collected from human ventricular cardiomyocytes, comparing healthy controls to decompensated heart failure patients secondary to pulmonary hypertension. Our findings show significant changes in alternative splicing of CDK8 transcripts in both the diseased mouse and human samples relative to controls.

AAV2.5T Transduction of Basal Cells in Ferret Airway Epithelium

Presenter: Joseph Karippaparambil
Mentor: Ziying Yan, PhD

Background: Cystic fibrosis (CF) is an autosomal-recessive disorder affecting over 80,000 people worldwide. It is caused by mutations in a single gene, the *cystic fibrosis transmembrane conductance regulator (CFTR)*, that are often lethal. In the respiratory tract, CFTR facilitates transepithelial chloride movement for regulating airway surface fluid volume, viscosity, and pH. The primary cause of morbidity and mortality in CF is therefore lung disease with thick viscous mucus and chronic bacterial infections. Until recently, treatment of CF has primarily relied on managing symptoms through mucoactive agents like hypertonic saline, rhDNase, and mannitol powder, which work by thinning mucus in order to clear the lung epithelium. Recently, a new class of drugs were approved for CF which target the underlying genetic cause itself by rescuing CFTR function. However, its effectiveness varies based on the particular CFTR mutation involved. Although CFTR modulating drugs are effective in ~90% of CF cases, patients who have drug-resistant missense mutations, misfolded CFTR proteins, or little to no baseline CFTR expression cannot benefit from this therapy and must continue to rely on symptomatic treatment. Therefore, there continues to be a critical need for developing reliable therapy for CF that is effective in all patients regardless of genotype. A promising strategy is gene therapy.

Purpose: AAV2.5T is an adeno-associated viral vector with well demonstrated tropism (specificity) for airway surface epithelial cells in both ferret lungs *in vivo* and polarized human airway epithelium in an air-liquid interface culture (HAE-ALI). The aim of this study is to demonstrate the ability of AAV2.5T to transduce basal cells in a polarized ferret airway epithelium culture, and profile the AAV2.5T transduction of major epithelial cell types in the polarized FAE-ALI culture. The results of this study will help ascertain whether AAV2.5T can potentially serve as an effective gene delivery tool for CF gene therapy.

Methods: FAE-ALI cultures of nasal and tracheal origin are first fully differentiated then apically inoculated with rAAV2.5T vectors carrying cDNA encoding enhanced green fluorescent protein (eGFP). The cells are digested off the supportive membrane, cytospun onto a slide, and immunostained with cell type markers for each of the different cell types. Images of the cells will be acquired using a Zeiss confocal microscope and analyzed using an image processing software (Fiji). Alternatively, the cells are sorted through fluorescence activated cell sorting (FACS) to isolate only eGFP-positive (transduced) cells. These cells can then be immunostained with the same cell type markers and imaged for further analysis.

Results: In nasal ferret airway epithelium differentiated in an Air-Liquid Interface, AAV2.5T transduced a mean of 10.3% of cells. Of the 10.3% cells infected, an average of 4.9% of cells were progenitor basal cells. In the tracheal ferret airway epithelium, AAV2.5T transduced a mean of 14.6% of cells.

Conclusions: AAV2.5T is a promising vector for gene delivery in CF with demonstrated success in targeting human respiratory airway cells in culture. For permanent CFTR gene correction, the progenitor basal cells that reside deep along the basement membrane must be targeted. Our studies demonstrate that AAV2.5T can successfully transduce basal cells of both the nasal and tracheal ferret airway. With the successful targeting of ferret basal progenitor cells *in vitro,* we are closer in concluding that the ferret airway epithelium is an adequate representation of the human airway epithelium with respect to AAV2.5T, so that ferret models can be utilized for testing CF gene therapies in the future in a safe and cost-effective manner.

Role of hyperthermia in GBM cell killing and PD-L1 expression

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Introduction: Glioblastoma (GBM) is the most common primary brain malignancy in the US with a 5-year overall survival <5% despite aggressive standard of care. Immune checkpoint inhibitors (ICIs) have seen great success in the treatment of many cancers, but due to the blood brain barrier, tumor microenvironment (TME), and immunosuppressive nature of GBM, ICI's have seen little success in improving patient outcomes. Laser Interstitial Thermal Therapy (LITT) is another approach to treating GBM that has gained traction. LITT is a modernized intraoperative approach to thermally ablate tumor tissue, heating the tumor bed to 43 °C for 10 minutes as an optimal dose. This therapy provides a safe option for reducing intracranial tumor burden but does not significantly increase progression-free survival when used alone. LITT is believed to potentially increase the efficacy of ICIs. Neither ICIs nor LITT are sufficient in treating GBM on their own as both are used clinically in combination with standard of care therapy (temozolomide and ionizing radiation). Recent research has documented how LITT addresses the key challenges faced by ICIs; by disrupting the BBB, altering the TME, and facilitating immune killing of tumor cells, LITT is poised to work well in combination with ICI's. However, the biochemical mechanisms underlying the modulation of immune checkpoints in GBM cells have been poorly characterized.

Purpose: The present study seeks to clarify the effects of thermal therapy on GBM immune modulation. We aimed to determine how expression of PD-L1 in GBM cells is affected by hyperthermia ± irradiation to discern if the environment created by thermal therapy may modulate the tumor immune checkpoint programmed death ligand -1 (PD-L1) to better contextualize the use of LITT for patients with inoperable GBM.

Methods: Colony formation assays were used on primary GBM cell lines U87 and its IDH mutant counterpart ($U87^{R132H}$), which was generated using a crispr-cas9 knock-in approach. Each cell line was treated on a heat block at 43 °C, 46 °C, and 50 °C for 3 minutes and 10 minutes, in addition to an untreated control group. Following heating, cells were then plated as single cells to allow colonies to form. Following colony formation, colonies were stained with Coomassie blue and counted. To assess how SOC radiation may affect cell survival, the same two cell lines were treated at 43 °C for 10 minutes and irradiated (2 Gy) immediately following thermal treatment. This treatment group was compared to an untreated control, a treatment group consisting of irradiation alone, and a treatment group consisting of thermal ablation. Following treatment, cells were plated according to the same clonogenic assay as above. Cells were harvested from these treatment groups immediately to analyze PD-L1 expression with respect to various iron metabolic parameters (mortalin (HSPA9), transferrin receptor, and ferritin heavy chain) using western blot.

Results: In both U87 and $U87^{R132H}$ cell lines, thermal therapy showed a temperature-dependent cell killing effect. The $U87^{R132H}$ IDH mutant cells were significantly more sensitive to thermal treatment as compared to the U87 wild type cell line. Moreover, thermal therapy only showed a mild enhancement of radiosensitivity in $U87^{R132H}$ cells. Treatment with thermal therapy downregulated PD-L1 expression in $U87^{R132H}$ cells, which was associated with increased expression of the mitochondrial iron metabolic regulator, HSPA9. HSPA9 is a heat shock protein that is a known negative regulator of PD-L1. Moreover, thermal therapy reversed the radiation-induced overexpression of PD-L1, transferrin receptor, and ferritin heavy chain in $U87^{R132H}$ cells. Again, this effect was not observed in the wild-type U87 cell line.

Conclusion: These results are suggestive that thermal therapy alone can downregulate the immune checkpoint PD-L1. This effect is more pronounced when thermal therapy is combined with radiation. Moreover, HSPA9 may coordinate an iron metabolic regulation of PD-L1 in the context of thermal therapy and ionizing radiation. These novel findings warrant further mechanistic investigations.

Choosing Immune Suppression in kidney Transplant by Efficacy and Morbidity (CISTEM) Model Enhancement | Defining and Validating Computable Phenotypes for the application of Machine Learning

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Mentor: Dr. David Axelrod, MD MBA – University of Iowa; Melissa Swee, MD, MS, MME – University of Iowa
Collaborators: Dr. Vikas Dharnidharka MD MPH & Dr. Raja Dandamudiz MD – University of Washington St. Louis

Introduction: Long-term immunosuppressant (IS) medications are essential for preventing allograft rejection in kidney transplant (KTx) recipients. However, prolonged IS use is associated with adverse outcomes such as infection, malignancy, cardiovascular disease, and nephrotoxicity. There is a crucial need for enhanced evidence based IS management to optimize long-term kidney function while minimizing IS complications.

Purpose: This study aims to define computable phenotypes for the CISTEM2 model which will be used to employ machine learning algorithms to provide dynamic, patient specific IS therapy recommendations over time. Unlike the previous CISTEM model, CISTEM2 model will enhance longitudinal IS management by integrating a novel, comprehensive clinical registry, healthcare claims, and transplant registry dataset within the Patient Centered Outcome Research Network Common Data Model (PCORnet CDM). The initial phase of the research involves developing and validating machine-readable computable phenotypes to identify key clinical events in the PCORnet CDM. These phenotypes, focusing on five adverse outcomes in KTx patients, will be critical for creating a longitudinal model to optimize IS management.

Methods: We conducted a retrospective IRB-approved chart review of 150 randomly selected KTx patients from the University of Iowa (January 2014 - December 2023). This sample was drawn from 926 KTx records shared in the PCORnet CDM. The patient electronic medical records (EMR) were reviewed for the instance of one of five predefined adverse outcome and data was collected on the methods of diagnosis and treatment for each outcome. The data collected from the chart review was compared against diagnostic codes captured in the PCORnet CDM dataset. Iterative computable phenotypes were developed and evaluated using performance metrics including positive predictive value (PPV), negative predictive value (NPV), sensitivity, and specificity to evaluate the accuracy of these phenotypes.

Results: Diagnosis codes (ICD9/10) alone were insufficient for identifying acute rejection episodes. 21 patients were identified within the EMR as having acute kidney rejection within 12 months post-transplant. Algorithms combining diagnostic codes with CPT biopsy codes and treatment data showed a notable improvement in predictive performance. The PPV increased to 84% and specificity to 95.9%, compared to a PPV of 51.2% and specificity of 79.7% with diagnostic codes alone.

Discussion: Our study demonstrates that robust computable phenotypes can be derived from PCORnet CDM data to identify adverse events in KTx patients. These computable phenotypes can be deployed across the entire PCORnet CDM providing access to larger and more comprehensive real-world evidence for the foundation of the CISTEM2 tool. The study also finds that the inclusion of multiple covariates, beyond diagnostic codes, is essential for enhancing predictive accuracy. Future work should address data limitations by incorporating additional clinical details such as procedural codes, medical prescriptions, and lab values to further refine the other computable phenotypes in this study.

Differentiative Capacity of Airway Basal Cells at Various Anatomical Levels in the Tracheobronchial Tree.

Sean Kim, Kyle Freischlag, Kusum Devi, Carolina Chu, Chen Chen, Caitlyn Gries, Kalpaj R. Parekh

Introduction: Lung transplantation remains an essential treatment option for patients facing end stage lung disease. However, the long-term survival of transplant recipients is limited by obliterative bronchiolitis (OB). OB is a terminal form of chronic lung allograft dysfunction (CLAD) characterized histologically by the irreversible fibrosis of the terminal bronchioles of the small airways. With no current treatment options, there is a critical need to investigate the mechanisms of pathogenesis to develop targeted therapies for OB. Distinct epithelial basal stem cell populations exist along the airway that are crucial for maintaining the surface airway epithelium. Parekh laboratory has shown that following lung transplantation there is a depletion of epithelial basal stem cells in large and small airways of the lung in allografts that develop OB. However, the proliferative and differentiative capacity of airway epithelial basal stem cells at various anatomic levels in the tracheobronchial tree remains unknown. We hypothesize that there are differences in the differentiation capacity of basal cells in various anatomical regions (large vs small airways) of the lung.

Methods: Wild-type adult sable ferrets were euthanized, and their airways were resected using a standard sterile surgical technique. The airways were divided into 6 anatomical regions – trachea, carina, main bronchus, primary pulmonary bronchus, secondary pulmonary bronchus, and tertiary pulmonary bronchiole. Surface Airways Basal Cells were enzymatically isolated and incubated in Pneumacult Ex+. The Air-Liquid Interface (ALI) Interface was employed by seeding basal cells onto 804G coated 12 well plates with around 200,000 cells per well. Basal cells at 80% confluency were incubated for 21 days in ALI Media. At 21 days, basal cells were fixed and stained for immunofluorescent markers of differentiated cells. These markers included Acetyl- αTubulin for ciliated cells, uteroglobin for secretory cells, Muc5AC for mucous cells, and nuclei.

Results: The preliminary findings suggest differences in basal cell differentiation capacity through the various regions of the lungs. The preliminary data demonstrates an increase in ciliated cells in the trachea as indicated by an increase in alpha tubulin expression and an increase in mucus cells in the secondary bronchioles as indicated by increase in Muc5AC expression. Furthermore, the data trends towards an increase in secretory cell expression after the carina as indicated by a significant increase in uteroglobin expression. More data sets will be added to demonstrate the potential significance of these results.

Conclusion: OB pathology has been shown to predominately affect the small distal airways, producing histological changes and irreversible fibrosis. Notably, The Parekh lab has previously demonstrated that in OB the proliferative capacity of basal cells is significantly decreased in the large and small airways including tertiary bronchioles. Our preliminary data supports the hypothesis that the differentiative capacity of airway basal cells differ based on the various anatomical regions of the airway suggesting a region-specific capacity to regenerate airway epithelium. The differences in progenitor capacity of these basal cell populations provide more insight into the pathogenesis of OB and the potential therapeutic role of targeted stem cell therapy in the distal airways.

Validating the Genetic Drivers Responsible for Driving Trametinib Resistance in Low Grade Serous Ovarian Cancer (LGSOC)

Kondaboina S, Peplinski R, Dupuy A

Low-Grade Serous Ovarian Cancer (LGSOC) is a rare subtype of epithelial ovarian cancer, accounting for approximately 5% of all ovarian cancers. Due to its low incidence, LGSOC has been designated as an orphan disease. Symptoms of LGSOC—including bloating, early satiety, fatigue, indigestion, menstrual irregularities, changes in bowel habits, and painful intercourse—are non-specific and often lead to a diagnosis at advanced stages. Treatment options for LGSOC are limited, as the disease is highly recurrent and resistant to chemotherapy. This underscores the need for a deeper understanding of LGSOC pathogenesis to develop targeted therapeutic strategies.

Preliminary genetic analyses of LGSOC have identified frequent mutations in KRAS, NRAS, and BRAF genes. Specifically, KRAS mutations are present in 32% of LGSOC samples, NRAS mutations in 11%, and BRAF mutations in 9%. The molecular profile of LGSOC includes mutations in the MAPK (mitogen-activated protein kinase) pathway, with MEK being a downstream target of trametinib, a drug used in the treatment of LGSOC. Although trametinib has been shown to delay disease progression compared to standard care, resistance invariably develops, leading to eventual progression and patient mortality. This highlights the critical need to investigate the mechanisms underlying trametinib resistance in LGSOC.

In this study, the Dupuy Lab employed a forward genetic screen using transposon mutagenesis in two ovarian cancer cell lines, ES2 and VOA7681, to identify candidate drivers of trametinib resistance. Resistant cell populations were generated through trametinib treatment, followed by genomic extractions and transposon-insertion site analysis, which identified 21 potential drug resistance drivers. Of these, six genes—RAF1, BRAF, AKTdd, ETV1, ETV4, and ETV5—were selected for validation based on their predicted significance.

To validate these candidate drivers, each gene was over-expressed in LGSOC cell lines using plasmid transfection, and stable populations were established. These populations were then challenged with trametinib, and cell growth was monitored over 10 days using a resazurin assay, with results normalized to baseline values. Western blotting was employed to confirm successful over-expression of the candidate genes.

Initial results indicate that, except for ETV4 in the ES2 cell line, all transfections were effective. Most candidate genes, with the exceptions of AKTdd in both cell lines and ETV4 in ES2, exhibited slight resistance to trametinib compared to controls. Prior literature suggests that the constitutive expression of ETV1 and ETV4, which are part of the PEA3 family of transcription factors along with ETV5, mimics oncogenic Ras/MAPK signaling in other cancers. A similar mechanism may contribute to trametinib resistance in LGSOC. Furthermore, ETV1 and ETV5 have been shown to be significantly down-regulated during early trametinib treatment, indicating that over-expression of these factors might enhance cell growth and viability, leading to resistance.

Further quantification of these results is necessary to draw definitive conclusions. Future work will involve additional in-vitro characterization of these candidate genes, validation of the remaining 15 potential drivers identified, and investigation of resistance mechanisms to newly approved drugs for LGSOC treatment, such as Avutometinib (a RAFi and MEKi) and Defactinib (a FAKi).

Short and Long-Term Outcomes of Laryngeal Cleft Injection in Pediatric Patients

Aditya Kotla, Emma Thayer, Eiman Habani, Matthew Hoffman

Introduction/Background

Laryngeal cleft is a fissure between the laryngotracheal and pharyngoesophageal systems caused by a lack of separation between the laryngotracheal axis and the esophagus (1). Benjamin and English described laryngeal cleft in a classification system based on severity or downward extension of the cleft (2). Type 1 laryngeal cleft is classified as a supraglottic interarytenoid cleft that doesn't extend below the level of the true vocal folds. Type 1 clefts, unfortunately, may not be recognized until patients are symptomatic, making the diagnosis very challenging. The presenting symptoms are usually non-specific; however, aspiration with thin liquids is the most common presenting symptom, seen in 90% of patients (3). Other symptoms include recurrent aspiration pneumonia, chronic cough, stridor, and hypoxia with cyanotic attacks. Initial management for type 1 is often conservative treatment (anti-reflux therapy, thickened feeds, and maneuvers during feeding to prevent aspiration), though 80% of patients fail conservative therapy and eventually require surgical repair (3). A less-invasive surgical treatment that is growing in popularity includes interarytenoid injection augmentation (IIA), otherwise known as injection laryngoplasty (IL). For this procedure, the cleft is managed on the initial endoscopic evaluation, which may obviate the need for repeat anesthesia at a later time point for repair (4). Additional studies are required to determine the long-term efficacy of IIA on dysphagia and pulmonary complications, as well as patient- and caregiver-related outcome measures (4). Current literature also consists primarily of reports on small series of patients (fewer than 15). This project addresses these shortcomings in the field of research.

Hypothesis

This study aims to identify and establish short- and long-term outcomes, such as the need for follow-up visits and CO2 laser-assisted surgical cleft repair, for children aged 0-10 undergoing laryngeal cleft injection from 2010 to the present.

Methods

A retrospective review of 27 patients aged 0-10 diagnosed with laryngeal cleft and undergoing laryngeal cleft injection from 2022 to the present was completed. Charts were reviewed for presenting symptoms, pre-operative videofluoroscopy impressions, and operative details. After each injection, post-operative videofluoroscopy results were then analyzed, as well as any changes in symptoms over the course of months. Subsequent follow-up was also noted.

Findings/Results

Presenting symptoms among the 27 patients with a laryngeal cleft mainly included dysphagia, cough, and stridor. Every patient, excluding one, had a pre-operative videofluoroscopic swallow study (VFSS) done to assess the presence of penetration or aspiration and swallowing function of various feeding consistencies. Each patient presented with varying levels of swallowing impairment, with the majority showing aspiration on thin liquids. For the operative treatment, each patient underwent a laryngeal cleft injection consisting of 0.1-0.3 cc of Juvederm Ultra XC, with the volume of the injection depending on the patient. No complications were found, except in one surgery where a portion of the true vocal cord traveled inferior to the subglottis and was removed. Twenty-three out of the 27 patients showed improved symptoms and swallowing function immediately upon analysis of post-operative VFSS. This included no wet cough and no aspiration or penetration of liquids upon swallowing. However, in 18 of those 23 patients, symptoms began to reappear between 3-5 months post-injection. Subsequent follow-up was noted for each patient to either proceed with observation or a CO2 laser-assisted endoscopic cleft repair.

Conclusion

The findings from this study suggest that laryngeal cleft injections are a less-invasive option that obviates the need for additional anesthetic procedures and provides temporary relief to many patients suffering from dysphagia. While this treatment approach may not be a long-term solution, further research is needed to evaluate the long-term efficacy of injection laryngoplasty and refine strategies for managing persistent or recurring symptoms.

Title: Exploring the impact of alpha-synuclein overexpression in the locus coeruleus
Student Presenter: Campbell Krusemark
Faculty Advisor: Georgina Aldridge
Introduction: Fluctuations, defined by uncontrolled and unpredictable changes in cognition, attention, and arousal, are a hallmark symptom of Lewy Body dementia (LBD). Despite the prevalence of LBD in the population, the neuronal mechanisms behind cognitive fluctuations have yet to be elucidated. Despite this, presence of α-syn pathology, specifically in the ascending arousal network (AAN), has been associated with a higher risk of cognitive fluctuations. Critically, the AAN is a system of cortical nuclei which work to regulate consciousness and our awareness of our cognitive state. The locus coeruleus (LC), a key nucleus within this network, has been shown to accumulate early and severe synuclein pathology in LBD. To explore the relationship between α-syn, fluctuations, and the ascending arousal network, we sought to investigate how arousal in mice is affected by alpha-synuclein overexpression in the locus coeruleus. To do this, we evaluated how arousal measures like movement and sleep change after exposure to novel stimuli.
Hypothesis/Purpose: These experiments have allowed us to better understand how novelty can promote an arousal response in mice and how synuclein pathology in the LC may affect this response. We hypothesized mice with LC alpha-synuclein overexpression will show decreased consolidation, with more frequent microsleeps during their active period and more frequent arousals during the rest period, beyond changes seen in normal aging. We also hypothesized that these mice will exhibit a delayed return to sleep following exposure to novelty.
Methods: Overexpression of the alpha-synuclein protein was mediated via intracranial injection of adeno-associated viral vectors into the mouse LC. For measures of novelty-evoked arousal in mice, latency-to-sleep and distance travelled following exposure to a novel object or environment was recorded. Following behavior testing, mice were perfused to localize the initial seed site, evaluate spread, and compare pathology with behavior.
Results: Mice with overexpression of alpha-synuclein in the LC were more reactive to the presentation of a novel environment than mice that received control injections. Additionally, overexpression mice displayed greater levels of arousal when stimulated with novel objects. Interestingly, both control and overexpression mice were less responsive to novel objects than to the novel environment. There was no significant difference between the latency to sleep or time spent asleep when comparing the control and overexpression mice.
Conclusion: Here, we demonstrate that novelty in mice can be used to evoke arousal. The increased movement of the overexpression mice in response to a novel object and environment suggests that accumulation of alpha-synuclein in the locus coeruleus drives arousal in mice. However, more work must be done to understand how sleep behavior is affected by alpha-synuclein overexpression in the LC. Future studies should employ larger cohorts of mice to more clearly visualize any differences in the data. Should future studies into the LC produce no changes in arousal, further investigation into other arousal-associated brain regions, such as the hippocampus or nucleus accumbens, should be conducted and compared with the LC model.

Characterizing Patients Presenting with Chronic Scrotal Content Pain

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Background: Men with chronic scrotal content pain (CSCP) commonly present to various providers within the healthcare system. Despite its prevalence, little research has been done to understand risk factors for the development of CSCP. In many cases, the cause of pain is unknown and there are no widely accepted protocols for evaluation or management.

Objective: To characterize associated symptoms and concomitant concerns of those presenting with CSCP.

Design and Methods: Retrospective review of validated questionnaires and a comprehensive intake form on men presenting to a single urologist's office with CSCP was performed. Analysis included linear regression between subjective chronic testicular pain rating and other numerical rating scales.

Results: Questionnaires from 94 male patients were reviewed. The average pain subscore on the chronic orchialgia symptom index (COSI) was 8.00 out of 17. When assessing the association between pain and other domains, more severe chronic scrotal pain was associated with worse pain in and around the genitourinary system ($p < 0.001$), worse urinary symptoms ($p = 0.001$), worse hip ($p = 0.001$) and back ($p < 0.001$) symptoms, worse sexual function ($p = 0.025$), and worse anxiety ($p = 0.019$) and depression ($p = 0.003$) symptoms. Patients were found to have a wide variety of presentations with differing aggravating and relieving factors, urological and surgical histories, and interventions.

Conclusions: Men presenting with CSCP are complex. More severe scrotal content pain may be associated with worse symptoms in multiple other domains. In order to create a personalized treatment plan, a more comprehensive understanding of these men is critical. Future studies should assess how directed interventions on associated symptoms may impact outcomes.

Patient Centered Outcomes: Identifying Drivers of Satisfaction and Anxiety in Mohs Micrographic Surgery

Christopher J. Langland, BS; Kirk Sidey, MD, MBA; and Jennifer G. Powers, MD

Introduction: Mohs Micrographic Surgery (MMS) is highly specialized skin cancer surgery that remains the gold standard for treatment for many cutaneous tumors. MMS has the highest cure rate for primary and recurrent basal cell carcinoma, squamous cell carcinoma, and early-stage melanoma as well as rare cutaneous tumors like atypical fibroxanthoma, dermatofibrosarcoma protuberans, sebaceous carcinoma, extramammary Paget disease, and adnexal carcinomas. While Mohs surgery offers a highly successful form of skin cancer control, the unpredictability of the surgical day may influence patients' anxiety and satisfaction. Patients' anxiety levels can impact their overall experience, potentially leading to increased stress and longer recovery times. Conversely, high levels of patient satisfaction may enhance cooperation and adherence to postoperative care, ultimately improving recovery outcomes. In today's healthcare environment, multimedia (or video) approaches may be a convenient tool in setting appropriate patient expectations for the surgical day and managing the associated stressors.

Purpose: Patient reported outcomes provide a patient centered approach to quantify quality of care and identify factors that influence the patient experience. This project aimed to identify perioperative and postoperative drivers of anxiety, satisfaction, and quality of life for patients undergoing MMS and to determine the effectiveness of preoperative education videos in improving these outcomes.

Methods: IRB approval was obtained for recruitment of patients undergoing Mohs Micrographic Surgery at the IRL Mohs Surgery Clinic from three Mohs surgeons. Half the patients received the normal pre-operative procedural workflow while a second set of patients halfway through the study were sent two educational YouTube videos made by the American College of Mohs Surgery (ACMS) via MyChart. Informed consent was obtained, and a survey was administered following the first stage of Mohs surgery and before any additional stages or reconstruction. The survey contained two anxiety questionnaires (VAS-A, STAI form Y-1 and Y-2), general satisfaction questionnaire (PSQ-18), and four non-validated questions assessing preparedness, understanding of MMS, preoperative education satisfaction, and post-operative wound care education satisfaction. Additional chart review collected patient demographics, biopsy data, MMS data, and other factors that may influence anxiety, satisfaction, or quality of life (e.g. comorbidities, time to surgery, MyChart use, anticoagulation). Future datapoints (e.g. satisfaction, QOL) will be collected at 3-months post-surgery to assess longitudinal associations. Statistical significance was set at $p<0.05$.

Results: 66 subjects were enrolled consisting of 36 males (55%) and 30 females (45%) with an average age of 69 (range 32-88). The average number of days from biopsy to surgery was 46 days. 48 subjects (73%) used the patient portal MyChart. 39 subjects (59%) had family/friends accompany them during surgery. 31 subjects (47%) had their initial biopsy at a clinic outside of the UIHC. The average distance traveled for surgery was 47 miles. 20 subjects (30%) used anti-depressant and/or anti-anxiety medications. 13 subjects (20%) have a diagnoses of diabetes type 1 or type 2. 19 subjects (29%) are diagnosed with other non-cutaneous forms of cancer. 8 out of the 22 subjects who received the ACMS education videos viewed them. Subjects sited prior Mohs surgery, time constraints, and trouble finding the link as reasons why they did not view the video. Further recruitment is needed for analysis of the education video outcomes.

Prior MMS was found to be significantly associated with decreased state anxiety ($p=0.0055$) with no difference in trait anxiety and general satisfaction. Patients accompanied by family and friends were associated with significantly higher self-reported anxiety ($p=0.0287$). No association was found in anxiety or general satisfaction for distance travelled or number of days from biopsy to surgery. Anxiety or satisfaction was unaffected by location of waiting between stages (waiting room v. surgical room) as well as initial biopsy site location (UIHC vs Other). MyChart use was significantly associated with higher general satisfaction ($p=0.0316$) with no difference in anxiety. MyChart use was also significantly associated with increased preparedness ($p=0.0356$), understanding of MMS ($p=0.0189$), preoperative education satisfaction ($p=0.0061$), and post-operative wound care education satisfaction ($p=0.0037$).

Conclusions: This study identified several drivers that may influence satisfaction, anxiety, and other patient-reported outcomes, including prior MMS, lack of accompaniment by family or friends, and MyChart use. Identification of these drivers may improve quality of care by changing how healthcare systems approach individual patients. The current preoperative education protocol is a phone call and a corresponding message in MyChart. Further analysis will reveal if the education videos should be incorporated into the standard protocol. Patients referred from an outside clinic met the Mohs surgeon for the first time on the surgical day and over half this population did not use MyChart. This study identified MyChart use as an actionable factor that is associated with significantly improved patient reported outcomes. Encouraging patients to enroll in MyChart may be a straightforward approach to potentially improve education and communication leading to improved patient outcomes. Future analysis will investigate longitudinal factors that may further influence the patient experience.

Accuracy of Administrative Codes for the Diagnosis of Autoinflammatory Syndromes

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Introduction: Autoinflammatory syndromes (AIS) are innate immune system disorders that manifest with symptoms such as recurrent fever, abdominal pain, and rash. Low disease prevalence of AIS has long been an obstacle for AIS research. Administrative claims codes such as the 10th edition of the *International Classification of Diseases* (*ICD-10*) codes have been utilized in research to collect clinical data; however, research regarding their accuracy in identifying AIS has been limited.

Hypothesis: *ICD-10* codes can accurately diagnose AIS.

Method: We identified potential AIS patients from the electronic medical records at the University of Iowa Hospital and Clinics and the Stead Family Children's Hospital using a screening filter composed of AIS-related *ICD-10* codes and interleukin-1 antagonists. Diagnostic criteria for adult-onset Still disease (AOSD), systemic juvenile idiopathic arthritis (SJIA), Behçet disease (BD), familial Mediterranean fever (FMF), cryopyrin-associated periodic syndrome (CAPS), and synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome and chronic nonbacterial osteomyelitis (SAPHO-CNO) were reviewed for each patient. We calculated the sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV), and area under the receiver operating characteristic curve (AUC) to assess accuracy of the ICD codes in diagnosing AIS.

Results: 338 out of the 502 patients with potential AIS (67%) had accurate AIS diagnosis. Sensitivity ranged from 80% (SAPHO-CNO) to 100% (BD and FMF) and PPV ranged from 15% (FMF) to 80% (SAPHO-CNO). Specificity ranged from 81% (FMF) to 99% (CAPS and SAPHO-CNO) while NPV ranged from 98% (AOSD) to 100% (SJIA, BD, FMF and CAPS). All ICD codes or code combinations for the diagnosis of specific AIS subtypes showed high accuracy with AUCs ≥0.89.

Conclusion: *ICD-10* codes may be used to accurately diagnose AIS and build AIS cohorts for clinical research.

Title: Outcomes of Transjugular Intrahepatic Portosystemic shunt (TIPS) for the treatment of refractory ascites (RA)

Student: Htut Myat Linn
Mentor: Kyle Brown

Abstract

Background

Ascites is defined as accumulation of more than 25 ml of fluid in the peritoneal cavity with the most common cause of ascites being portal hypertension resulting from cirrhosis. Treatments for ascites include sodium intake restriction, diuretics, and large volume paracentesis (LVP). Patients who fail to respond to these treatments are considered to have refractory ascites (RA). For patients with RA, transjugular intrahepatic portosystemic shunt (TIPS) is another treatment option. TIPS is a procedure that creates an anastomosis within the liver by linking a branch of the portal vein with a branch of an hepatic vein using a stent-graft that reduces portal hypertension. Although some patients with RA have dramatic responses to TIPS, others continue to require LVP, and some do not respond to it at all. To investigate the question of which RA patients are most likely to benefit from TIPS, we performed a retrospective chart review to investigate whether there are clinical or laboratory features that can predict the outcome of TIPS for RA.

Methods

Medical records of 239 patients who underwent TIPS at UIHC between January 2010 and January 2023 were reviewed. Of these, 121 patients had TIPS for an indication other than RA. These patients were excluded, leaving a study group of 118 patients. Of these 118 patients, a further 25 were excluded due to death or liver transplantation occurring within 3 months post TIPS. For the remaining 93 patients, pre-TIPS data such as basic demographics, age at TIPS, MELD score, ultrasound of right upper quadrant and liver doppler, frequency of paracentesis, echo results, amount of fluid removed in the last paracentesis prior to TIPS, and other laboratory data such as sodium, potassium, etc were collected. For the following variables, pre- and post-TIPS data were collected: hepatic hemodynamic measurements and alcohol usage. The cohort was then separated into 2 groups: complete responders (N= 66) or not complete responders (N=27). We defined complete responders as patients who did not require a paracentesis beyond the first 3 months after TIPS. Not complete responders continued to require paracentesis beyond the 3 months post-TIPS. The data for the two groups were then analyzed via a two tailed unequal variance T test. Chi square tests were performed for the following variables: gender and alcohol usage pre- and post-TIPS.

Results

Velocity of the portal venous flow pre-TIPS was 18.87±7.19 (cm/sec) and 24.31±7.18 (cm/sec) for complete responders and not complete responders, respectively (p=0.013). Frequency of paracentesis prior to TIPS was 12.33±12.56 and 20.8±15.49 for complete responders and not complete responders, respectively (p=0.021). E/A ratio pre-TIPS was 1.1±0.36 and 0.93±0.19 for complete responders and not complete responders, respectively (p=0.037). CO2 level pre-TIPS was 24.37 ±3.29 (mEq/L) and 21.57±3.10 (mEq/L) for complete responders and not complete responders, respectively (p=0.0003). BUN level pre-TIPS was 19.98±10.43 (mg/dL) and 26±13.19 (mg/dL) for complete responders and not complete responders, respectively (p=0.043).

Conclusion

Our data suggests that more severe portal hypertension (as reflected by lower portal vein flow) and better cardiac function (higher E/A), along with less established RA (fewer paracentesis) prior to TIPS were predictive of complete response. Our next steps include creating a regression model to determine whether we can predict the outcome of TIPS to aid in decision-making for RA patients.

Longitudinal Inflammatory Biomarker Profiling in Intrauterine Growth Restricted Preterm Infants

Laura E Lorenger, Timothy J Boly, Jennifer R Bermick

Introduction:

Infection and sepsis are significant clinical problems among preterm infants. Preterm infants demonstrate decreased immune responses to pathogens or vaccine antigens compared to full-term infants. The diagnosis of sepsis or infection in preterm neonates traditionally relies on blood counts and bacterial cultures which can be nonspecific. Infection leads to an increase in proinflammatory cytokines, acute-phase proteins, and results in leukocyte activation. These markers of inflammation are attractive biomarkers for a more precise diagnosis of infection or sepsis. Intrauterine growth restricted (IUGR) infants are a high-risk population cared for by many NICUs, with IUGR preterm infants exhibiting an increased risk of infection compared to appropriate for gestational age (AGA) infants. A few studies have evaluated inflammatory biomarker profiles in term and near-term IUGR infants, demonstrating altered inflammatory profiles at birth. In this project, we investigated a panel of pro-inflammatory cytokines and chemokines to further understand differences in IUGR preterm infants. We hypothesized that preterm IUGR infants would have increased serum levels of pro-inflammatory cytokines and chemokines in the first month of life compared to preterm AGA infants, but that these differences would resolve before NICU discharge.

Methods:

The Bermick laboratory has a well-established biorepository of preterm infant samples, collecting all residual serum from clinically-indicated laboratory draws throughout a subject's entire NICU admission (IRB 202012208). The bank includes 31 IUGR preterm infants. Infants were included in the IUGR group if they had a prenatal diagnosis of IUGR, were SGA based on the Fenton growth chart (<10%ile) and had a Ponderal Index of less than 10%ile ((weight in grams x 100)/ (length in cm)). The IUGR subjects were sex and gestational-age (±1 week) matched 1:1 to preterm AGA infants based on the Fenton growth chart (10-90%ile) and a Ponderal Index of greater than 10%ile. The Bio-Plex Pro Human Cytokine Assay system was used to measure levels of an array of pro- and anti-inflammatory cytokines and chemokines (IL-1β, IL-6, IL-8, IL-10, TNFα, IP-10, MCP-1, MIP-1α, IL2-Rα) in serum samples collected from the matched subjects throughout their entire stay in the NICU. Data points were binned for analysis. These groups were analyzed using generalized estimating equations in SPSS, allowing for the longitudinal analysis of paired samples with missing data points in some of the bins.

Results:

Most significant differences between IUGR and AGA infants were observed during the first few days after birth. IL8 was significantly greater in IUGR infants at days 0, 1 and 2. IL10, MCP1 and TNFα were significantly greater in IUGR infants at day 1 of life, day 2 of life and day 3 of life, respectively. There was also a significant difference in AGA and IUGR in a couple biomarkers in later weeks. AGA infants had significantly greater IL1β at 71-77 days of life and IUGR infants had significantly greater MCP1 at 64-70 days of life.

Conclusion/significance:

IUGR infants had increased levels of systemic inflammation during their first few days after birth, including IL8. IL-6 was not found to be elevated in IUGR infants, in contrast to previous studies, and requires further investigation. These findings are an important first step in being able to utilize these biomarkers to care for these high-risk patients.

Workplace Violence in Healthcare: A Retrospective Review of Hospital Incident Report Data at a 189 Bed Midwestern Hospital

AUTHORS: Scott Lorimor, BA; Hayden Smith, PhD; Alexis Roberts, BSN, RN; Mark DeRee

AFFILIATIONS: University of Iowa Carver College of Medicine, Des Moines Area Medical Education Consortium

Abstract

Introduction: Since 2011, intentional injury rates among healthcare workers have nearly doubled, with psychiatric and substance abuse hospitals experiencing the highest rates. The prevention and treatment of in-hospital violence cost the U.S. approximately $1.5 billion in 2016. Despite this, peer-reviewed research on the topic remains sparse, highlighting the need for further investigation into the factors contributing to this increase.

Objectives: To examine trends in violence rates and types across different roles within a hospital setting.

Methods: Incident reports from a 189-bed hospital specializing in emergency, inpatient mental health care, and substance abuse treatment were analyzed. Reports from 2016-2023 categorized under "agitated/combative" patients or visitors were included. Violence rates were calculated using payroll hours and expressed as events per 10,000 full-time equivalents (FTE). Security role rates were estimated based on discussions with security leadership.

Results: A total of 572 records were analyzed, showing a particular increase in violent incident counts from 2020-2023, with a significant rise in 2022. Nursing and clinical support roles had the highest counts of violent events. Mental Health & Counseling and Security, followed by Clinical Support roles had the highest violence rates of violence per 10,000 FTE, with significant increases in 2021. Security personnel experienced the highest overall rates of violence, with some years approaching or surpassing one assault per FTE per year.

Six incidents required time away from work (range from 1 day to 71 days, median of 1.0 day), and 45 required work restrictions (range of 1 day to 109 days, median of 11.0 days).

Upper extremity injuries made up the largest percentage of all injuries experienced at 45% for males and 41% for females. Head & Neck, lower Extremity, Back, Chest and Abdominal injuries made up 26%, 12%, 5%, 3% and 3% of injuries in males, and 29%, 6%, 4%, 4% and 2% of injuries in females, respectively.

Conclusions: Discerned increases in violence across all roles aligns with national trends, highlighting the need for more research into contributing factors. National reporting may underestimate the true occurrence of injuries. Improved reporting mechanisms could provide better insights into the nature of these incidents.

Expedited Mood Tracking with the ASERT Digital Survey

Presenter: Isaac Lynch; Mentor: Dr. Vincent Magnotta; Other Collaborators: Dr. Gail Harmata, Dr. John Wemmie, Dr. Jess Fiedorowicz, Dr. Aislinn Williams, Dr. Jeffrey Long, Sarah Smith, Jenny Gringer Richards, Spencer Smith, John Barsotti, Cari Linkenmeyer.

Introduction

Bipolar disorder (BD) is characterized by chronic, alternating episodes of depression and mania or hypomania. An ongoing challenge in BD research is accurately tracking subjects' moods over longitudinal studies. Historically, mood state tracking was done using standard clinician-administered assessments, which are difficult to obtain on a regular basis. However, frequent mood assessments are necessary to capture the rapid mood changes typical of BD. Therefore, a simpler method of objectively capturing patients' mood states is necessary. The ASERT questionnaire is a ten-question, unassisted, smartphone-based mood survey. We sought to examine the feasibility of administering the ASERT survey weekly and its correlation to standard clinical assessments over the first six months of a two-year study. We hypothesized that we would achieve 80% adherence from participants with BD in filling out weekly ASERT surveys. We also hypothesized that depression and mania sub-scores derived from ASERT responses would exhibit statistically significant correlation to clinical mood assessments.

Methods

42 patients enrolled in the study over the first six months were sent weekly text messages with links to complete ASERT surveys. Patients were compensated with five dollars per survey if they completed two or more in a given month. If patients exhibited at least a five-point change on the manic or depressive sub-score of their weekly ASERT surveys, they were called and given the YMRS or MADRS surveys, respectively. Correlation between the ASERT sub-scores and standard clinical assessment scores was assessed twice using Pearson's correlation and robust regression in two scenarios: 1) when both assessments were obtained on the same day during their baseline visit and 2) when the two surveys were taken within 3 days of each other throughout the study course. The internal validity of the manic and depressive ASERT portions were assessed using Cronbach's alpha.

Results

Patients' median time to complete their weekly ASERT surveys was 73 seconds. The median patient's adherence to completing weekly ASERT surveys was 96%. Patients' ASERT depressive sub-scores exhibited significant correlation to their MADRS total score when measured at baseline ($p<0.001$) and throughout the study course ($p< 0.001$). Patients' ASERT mania sub-scores exhibited significant correlation to their YMRS total score when measured at baseline ($p<0.001$) and throughout the study course ($p< 0.001$). Depressive (0.90) and manic (0.79) components of the survey demonstrated strong internal validity.

Conclusions

Our preliminary results suggest that the ASERT survey can feasibly be administered weekly. They also suggest that the ASERT survey provides a reasonable estimation of what patient would score on a standard clinical mood assessment, especially regarding depression symptoms. Therefore, the ASERT survey may be an ideal tool to track BD patient's moods over longitudinal research studies.

Title: Natural History of C3CAb Activity and Prevalence in Healthy Populations

Name: Zack Lynch[1]
Mentor: Carla Nester[2,3], MD, MSA, FASN
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[1]University of Iowa Roy J. and Lucille A. Carver College of Medicine, [2]Stead Family Department of Pediatrics, [3]Molecular Otolaryngology and Renal Research Laboratories

Introduction: C3 Glomerulopathy (C3G) refers to a group rare kidney disorders characterized by glomerular accumulation of complement-associated proteins, resulting in hematuria, proteinuria, and glomerulonephritis. A key component of C3G is hyperactivation of the alternative complement pathway, either from mutations in complement-related genes or the presence of pathogenic autoantibodies known as Nephritic Factors (Nefs). Nefs have been shown to stabilize and prolong the activity of the C3bBb (C3) convertase facilitating the deposition of complement intermediates in the renal glomeruli. While the origins of Nefs remain unknown, recent work has revealed benign C3 convertase autoantibodies (C3CAb) in the healthy population. C3CAb can bind to and stabilize the C3 convertase similarly to Nefs but do not cause disease. This study aims to gather valuable insight into the development of Nefs by investigating the activity of benign C3CAbs across various age ranges in a healthy population.

Hypothesis: We hypothesize that C3CAbs first emerge during adolescence, reach a peak in prevalence during young adulthood and are then lost during aging. Furthermore, we hypothesize that the stabilizing activity of C3CAb antibodies continuously increases with age.

Methods: Blood plasma was collected from 144 patients across 15 age cohorts. Patients had no diagnosis or evidence of current infection, autoimmune/inflammatory disorders, or glomerular disease. Of the 144 plasma samples, IgG was isolated from 141 samples using the Melon Gel IgG purification protocol and its effects on the C3 convertase were assessed using surface plasmon resonance (SPR). Briefly, C3b was bound to a chip surface and Factors B and D were introduced as a fluid-phase analyte in the presence or absence of IgG. Formation of the full C3 convertase results in an increase in resonance units. C3 convertase stabilization and antibody binding affinity were subsequently assessed by measuring half-life and the dissociation constant, K_D, in 129 and 118 samples, respectively.

Results: Formation of the C3 convertase was highest in the presence of IgG isolated from 1 year olds and steadily declined with IgG from 2-15 year olds. Formation of the C3 convertase with IgG from adults remained similar regardless of age. Kinetic studies showed that the half-life of the C3 convertase was highest with IgG from patients in early childhood and early adulthood (30-40 years old), but across all ages the half-life never reached levels seen in C3G patients. Binding affinity of C3CAb for the C3 convertase showed little variation across all age groups. When compared with Nefs from patients with C3G, C3CAb from healthy patients have lower binding affinity for the C3 convertase.

Conclusions: C3CAb autoantibodies are more prevalent within the first year of life and taper off in the following years. When compared to Nefs, they show less binding affinity and stabilizing effects, which might contribute to their benign nature. However, further sample analysis and studies are needed to fully assess the function of C3CAb.

12 August 2024

Associations between histologic classifications, molecular profiles, and clinical outcomes in patients with clear cell renal cell carcinoma: a laboratory and clinical retrospective study

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Background: Clear cell renal cell carcinoma (ccRCC) is the 7th most common cancer in men, the 9th most common cancer in women, and the most common subtype of kidney cancer, accounting for approximately 70-80% of all renal cell carcinomas in the United States. For decades, the standard of care for localized disease involved nephrectomy alone; in more recent years, however, we have started to use adjuvant or neoadjuvant systemic therapy along with nephrectomy in high-risk patients. It is important to identify specific risk groups that would most likely benefit from systemic therapy to minimize unnecessary and unwanted side effects.

Objective: In this retrospective study, we aim to identify differences in tumor biomarker expression among ccRCC tumors with and without sarcomatoid histology, which often has a poorer prognosis. Additionally, we aim to identify differences in clinical outcomes between patients with ccRCC treated with nephrectomy alone versus those who received adjuvant or neoadjuvant therapy.

Methods: We conducted the initial investigation using de-identified EHR data from 50 patients with a diagnosis of ccRCC being treated at the University of Iowa. We collected the following data: patient age, sex, BSA, and baseline IMDC risk score (range 0-3); date of diagnosis; nephrectomy date; nephrectomy type (partial or radical); additional therapies; and clinical response at various time points, as determined by the RECIST criteria. We then retrieved expression levels of the TGF-β, PD-L1, and VEGF biomarkers in each patient's tumor from the GUMER repository. Finally, we conducted a detailed survival analysis of these 50 patients, stratified by IMDC risk score, along with a crude survival analysis of a larger sample of patients from the TriNetX database, stratified by tumor histologic subtype, to investigate outcomes in patients who received nephrectomy alone versus nephrectomy with systemic therapy.

Results: Of our 50 patients, 47 were diagnosed with ccRCC; four tumors had sarcomatoid histology and 43 did not. We identified higher levels of TGF-β and lower levels of PD-L1 in tumors with sarcomatoid histology with no difference in VEGF levels. The addition of systemic therapy led to improved outcomes after 66 months ($p = 0.04$), with the difference more pronounced in patients with higher IMDC scores. The larger, crude analysis from TriNetX included 8,220 patients and revealed improved survival in patients with non-sarcomatoid ccRCC who underwent nephrectomy alone compared to patients with sarcomatoid ccRCC (HR 3.83, 95% CI: 1.44 - 10.22). Regardless of therapy, patients with non-sarcomatoid ccRCC had better overall survival compared to sarcomatoid ccRCC (HR 3.23, 95% CI: 2.05 – 5.09). There was not enough data to compare outcomes in patients who received nephrectomy ± systemic therapy.

Discussion: Our data suggests that the response of patients to treatment depends on their tumor's histologic subtype, corresponding biomarker expression, and associated known physiology. Performing histologic characterization thus gives us insight into a tumor's microenvironment and helps us risk-stratify, which then allows us to select more targeted therapies. Furthermore, the addition of systemic therapy was more beneficial in patients with a higher baseline IMDC risk score.

Assessing Income Inequality as a Predictor of Head and Neck Cancer Outcomes

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Mentor: Dr. Nitin Pagedar, MD, MPH, Associate Professor of Otolaryngology, CCOM
Other Collaborators: Jason Semprini, PhD, MPP, Des Moines University, College of Health Sciences, Department of Public Health

Introduction with background/rationale: It is widely accepted that significant socioeconomic disparities exist in head and neck cancer (HNC) outcomes among various patient populations, with those from more economically affluent backgrounds experiencing higher quality outcomes. However, studies differentially cite education level, income status, poverty, or other factors as the driving socioeconomic (SES) markers predicting HNC outcomes. Thus, although socioeconomic correlations to patient outcomes exist, it is unclear how this relationship is defined, or which SES variables should be prioritized. Furthermore, there is an increasing need to assess outcome disparities from a population perspective rather than identify. Although traditional SES markers can be useful for assessing an individual's risk profile, they may not capture the social and economic diversity within particular geographically-defined areas that may influence HNC outcomes.

We propose that income inequality is a population SES factor that captures variations in economic conditions within counties that can create pockets of disadvantage and amplify health disparities. Although few studies have correlated the Gini Index, a standardized measure of income inequality, with breast cancer outcomes, no other study has explored the relationship between income inequality and HNC outcomes.

Hypothesis/Purpose: We hypothesize that income inequality is a better predictor of HNC patient population outcomes compared to standard indicators of socioeconomic status – household income, poverty level, and education level. This study will also examine the effect of the interaction between income and income inequality on HNC survival rates.

Methods: De-identified patient cancer outcome data is publicly available in the SEER database. All population data available in the US since 2018 will be used, approximately 10,000 adult cases. This database includes information about the stage at presentation, survivorship, household income, education level, and poverty level. Survivorship is reported as an age-adjusted percentage after 60 months. The traditional SES markers are reported per-county as median household income, percent of population below a high school education, percent of population below the 150% poverty line, respectively. Income inequality is measured through Gini Index data from the Census Database in all counties where patient data is collected. To compare predictivity of the traditional SES markers with income inequality, the authors conducted four multivariate regressions. The first three included each SES marker as separate independent variable, while the fourth included GINI index as the independent. For all models, survivorship was the outcome variable, stage at presentation was adjusted for, and all independent variables were reported as quintiles. Model predictivity was assessed through regression results. Additionally, a separate regression including the interaction effect between income and income inequality was conducted to assess if certain combinations of income and income inequality levels were correlated with different HNC outcomes.

Finding/results: Results indicate that income inequality is associated with HNC survival. Specifically, the association between survival and living in higher GINI index areas (relative to lower GINI index areas) is stronger than the association between survival and living in lower SES quintiles (relative to higher SES quintiles) across all three SES indicators. Additionally, interaction effect results indicate that for those living in areas with low income inequality, increased median household income is associated with higher survival rates. However, after the third GINI quintile, increased household income no longer has the same positive impact on survivorship.

Summary and significance of the research: Income inequality shows a stronger predictive association with HNC survivorship compared to traditional SES markers like education level, poverty level, and median household income. Additionally, high income inequality can reduce the positive effect of increased household income on survival, while lower income inequality amplifies these benefits. By incorporating income inequality as a key factor in identifying higher-risk communities, public health experts can more accurately pinpoint populations that are disproportionately vulnerable to poor HNC outcomes. Proactively focusing on these areas with targeted interventions and resources could help mitigate disparities and improve overall outcomes.

Rotational Femoral Osteotomy to Treat Abnormal Femoral Version

Steele McCulley, BS, Robert W. Westermann, MD, Courtney Seffker, PA-C, Ashley Kochuyt, BS, Joshua Hockman, Jenna Jensen, RN, Michael C. Willey, MD

Objective: The impact of femoral version (also referred to as femoral torsion) on gait and hip mechanics is the topic of recent investigation. Femoral version is the primary driver of hip range of motion and can cause femoroacetabular impingement (femoral retroversion) and instability (femoral anteversion). Abnormal femoral version is a common cause of persistent hip pain after arthroscopic treatment. The aim of this study was to report clinical outcomes of rotational femoral osteotomy to treat abnormal femoral version.

Methods: Patients indicated for diaphyseal femoral osteotomy to treat either excessive femoral anteversion or retroversion prospectively completed the International Hip Outcome Tool-11 (iHOT) survey pre-operatively and 6 months and 1 year post-operatively to measure hip pain and dysfunction. Femoral osteotomy was performed with an open approach and repaired with a 4.5mm plate. Additionally, patient demographics, femoral version measured with CT scan, laterality, previous hip arthroscopy surgery, concomitant hip preservation surgery, and non-union requiring revision surgery was recorded.

Preoperative to 6-month and 12-month iHOT scores were compared. The incidence of achieving Minimal Clinically Important Differences (MCID) was recorded (Δ iHOT >15). Differences between groups were evaluated using t-tests.

Results: 42 patients underwent rotational diaphyseal femoral osteotomy and completed pre-operative, 6 month, and 1-year post-operative iHOT surveys. Average age was 22.7±7.2 years and 90.5% were female, with an average BMI of 26.87±6.24. Femoral osteotomy was performed for excessive anteversion in 57% retroversion in 43%. Previous hip arthroscopy was performed in 40% of patients (2 had previous periacetabular osteotomy and 1 had undergone previous PAO with hip arthroscopy). 38 patients underwent hip arthroscopy (one labral reconstruction) and 5 underwent PAO during the same surgical procedure as the femoral osteotomy.

One patient experienced non-union that underwent revision fixation with an intramedullary nail. Mean (SD) preoperative iHOT scores was 32.5±17.4 and increased to 60.4±26.7. At 6-months post-operatively, the mean iHOT score increased 34.0±24.2 points ($p<0.001$) with 66.6% meeting MCID. Mean 1-year post-operative iHOT scores were 63.2±25.4, an increase of 34.8±25.4 ($p<0.001$) with 71.4% meeting MCID.

Conclusions: Diaphyseal rotational femoral osteotomy repaired with a plate has a high union rate and improved patient-reported hip pain and dysfunction. Nearly half of these surgeries were performed for patients with previous hip preservation surgery, with 40% having undergone previous hip arthroscopy, possibly contributing to the lower rate of meeting MCID compared to other hip preservation surgeries.

Targeting PRC2-Dependent Metastatic Phenotypes in Malignant Peripheral Nerve Sheath Tumors

Student: Megan McGovern[1]

Mentor: Rebecca Dodd, PhD[2]

Collaborators: Alexa Sheehan[2,3], Akshaya Warrier[1,2,4], Gavin McGivney[2,4,5]

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Introduction: Malignant peripheral nerve sheath tumors (MPNSTs) are a highly aggressive and metastatic sarcoma, with up to 50% of the cancers metastasizing. Approximately 60% of MPNSTs have a loss of function mutation of the polycomb repressive complex 2 (PRC2). PRC2 loss leads to an upregulation of lysyl oxidase (LOX) activity, resulting in extracellular matrix remodeling and collagen synthesis, and therefore a metastatic phenotype.

Hypothesis: Due to the role LOX activity plays in the metastasis of MPNSTs, inhibiting the activity of LOX using next-generation LOX inhibitors presents a promising therapeutic target.

Methods: A fluorescence-based LOX activity assay was utilized to investigate the effectiveness of LOX inhibitors on recombinant LOXL2 as well as MPNST cell conditioned media (CM) with and without loss of PRC2. MPNST cells were derived from mouse primary tumors, and CRISPR was used to generate PRC2-null MPNST cells.

Results: The activity of recombinant LOXL2 decreased when treated with the previously investigated LOX inhibitor BAPN (β-Aminopropionitrile). Additionally, the next generation inhibitors PXS-5505 and PXS-5382 decreased the activity of recombinant LOXL2 in a dose dependent manner. Contrastingly, MPNST CM, both wildtype and PRC2-null, did not respond to treatment with BAPN.

Conclusions: Next-generation LOX inhibitors appear to successfully inhibit LOX activity in recombinant LOXL2, suggesting they may also be effective in CM as well as in vivo. However, the results of BAPN treated CM suggest that further optimization of the LOX activity assay protocol is needed to accurately determine the inhibitors' efficacy in MPNST cell lines. Ultimately, further studies will determine if next-generation LOX inhibitors can decrease metastasis in vivo without toxicities and off-target effects associated with BAPN.

Oncogenic functions of SETDB1 in endometrial cancer

Ryan McLerran, Kiarash Salari, Shujie Yang

Introduction

Endometrial cancer is the most common gynecologic cancer, and the number of deaths has been on the rise for the past several decades. Epigenetic regulation has a strong influence in the development and proliferation of many types of cancer has been a subject of much research. However, many questions remain, particularly regarding endometrial cancer.

Purpose

Oncogene SETDB1 (SET Domain Bifurcated Histone Lysine Methyltransferase) has been reported overexpressed in many cancer types and predicts worse survival. The molecular mechanisms are SETDB1 promotes tumorigenesis and facilitates immune escape. However, SETDB1 was not well-studied in endometrial cancer; the exact molecular mechanism remains unknown. Our group focuses on EC, the only cancer that has decreased survival in the past 40 years. There is a critical and unmet clinical need to explore efficient treatment strategy. Our preliminary data has shown that knock out SETDB1 greatly decreases endometrial cancer (EC) proliferation using *in vitro* and *in vivo* assay and prolongs mice survival by over 100 days. We also found that knockout SETDB1 promotes macrophage infiltration into tumors potentially via upregulation of cytokine CCL5. We hypothesize that targeting the oncogene SETDB1 will be a plausible regimen to treat this disease. Our previous results have shown that knocking out SETDB1 in endometrial cancer cell lines ISH and ECC-1 decreased tumor growth. To compare these results in human endometrial cancer, we performed SETDB1 KOs in patient derived cell lines (PDC).

Method

a) PDCs were maintained until proper confluency was reached. RNA Sequencing and ChIP sequencing were performed and data analyzed. PDC8 KOs sg2-1 and sg3, as well as control NT1 were injected into mice (n=25) and their mass was measured for several weeks.
b) We evaluated the expression levels of genes involved in lipid regulation in normal type and SETDB1 KOs. Primers were designed using PrimerBank to test for expression in cell samples. RT-PCR was used to measure the expression levels of selected genes, and western blotting was used to confirm protein levels. ChIP and RNA Sequencing were performed and data analyzed.

Results

-ChIP data showed SETDB1 binding at pericentromeric regions, particularly on chromosomes 3 and 4.

-qPCR data of SETDB1 KOs revealed an upregulation of many human genes involved in fat production such as FABP4, FABP5, and PPARb. The opposite was found to be true in mouse samples.

-Mice injected with SETDB1 KO were shown to develop greater mass and were less likely to develop tumors.

Conclusion

Our results revealed a relationship between SETDB1 and many lipid regulating genes. However, this relationship appeared to be different between human and mouse species. Further research into this could be done, perhaps using larger samples of qPCR data. As expected, we also found that the mice injected with SETDB1 KOs had better health outcomes, including decreased tumor growth. Centromeric mapping and studying is a relatively novel area of study and further innovation in primer production will prove invaluable for future discoveries.

The Effect of Hyperglycemia on Mitochondrial Respiration in Corneal Endothelial Cells

Monson, Eli; Shevalye, Hanna; Eggleston, Tim; Skeie, Jess; Greiner, Mark

Introduction

Diabetes mellitus (DM) represents a global issue for modern medicine. Apart from disease burden for patients, DM has resounding impacts in the field of transplantation. As donor tissue from diabetic individuals increases, the impact that DM exerts in each tissue type has become of interest. Negative impacts of diabetes on corneal health and surgery have been documented, including donor tissue preparation failure and post-procedure graft failure.

Corneal endothelial cells (CECs) compose the innermost layer of the cornea and are responsible for corneal health and clarity. DM has been shown to decrease CEC density and function, and these changes also correspond with significant alterations in mitochondrial structure and respiration. Voltage gated anion channel 1 (VDAC1) is a mitochondrial protein fundamental to cellular respiration. Previous studies have demonstrated that VDAC1 is essential for cell viability and may exhibit changes in conjunction with DM.

Hypothesis/Purpose

We hypothesize that DM exerts its detrimental effects on CEC health via alterations in the structure/function of VDAC1 mitochondrial protein. Our studies aim to explore this connection as a method of combatting DM-related cornea transplantation complications.

Methods

Immortalized human CECs were cultured under four different hyperglycemic concentrations. Cells from each condition were harvested at one, two, and four weeks and analyzed via western blotting for structural changes. Hyperglycemic CECs were also fixed for immunohistochemistry at two weeks of hyperglycemia and stained for VDAC1 protein in combination with markers for apoptosis and mitophagy. Mitochondrial function assays were planned for hyperglycemic CECs at two-weeks of hyperglycemia to analyze for changes in respiration and for the effect of silencing VDAC1 protein expression.

Results

Western blot analysis demonstrated uniformity in VDAC1 protein structure at up to four weeks under hyperglycemic conditions. Antibodies for additional VDAC isomers were utilized, but optimization is still underway. Immunohistochemistry identified a correlation between hyperglycemia and a global increase in VDAC1 expression, the collection of VDAC1 protein on the plasma membrane, as well as colocalization with the mitophagy marker, LC3a. Mitochondrial plate assays indicated significant changes in respiration capacity, spare respiratory capacity, and ATP production. Mitochondrial plate assays with VDAC1 silencing are still underway.

Conclusions

While VDAC1 does not appear to exhibit structural changes at four weeks of hyperglycemic exposure, changes occur in VDAC1 expression and localization in CECs at as early as two weeks. While mitochondrial structure and function were known to be affected by DM, our initial plate assays established a quantitative relationship between hyperglycemia and extent of mitochondrial damage. These findings support our hypothesis that VDAC1 function is altered under hyperglycemic conditions, contributing to DM-related CEC mitochondrial changes. Our preliminary data and ongoing studies are promising steps in establishing the biochemical cause of DM-induced corneal dysfunction, improving cornea transplant prognosis, and widening transplant availability.

Effect of catheter ablation with vein of Marshall ethanol infusion vs catheter ablation alone on persistent atrial fibrillation.

Student: Sarah Nacos
Mentor: Paari Dominic, MD

Background: Atrial fibrillation (AF) is when there is rapid and irregular beating of the atria due to abnormal electrical impulses (Brundel), and it poses a major health risk as it has been shown to be a strong risk factor for other health complications such as stroke, heart failure, and myocardial infarctions. Ablations of the myocardium are employed for patients that continue to have AF despite other medical interventions and is usually done around the ostia of the pulmonary veins. However, a significant proportion of patients that undergo an ablation will still have recurrent AF, thus other forms of treatment such as ethanol infusions into the Vein of Marshall (VOM) are being pursued. The VOM is an embryological remnant located on the posterior left atrium, and several studies have provided evidence that is the trigger of ectopic beats leading to AF.

Hypothesis: We hypothesize that there will be a decrease in atrial fibrillation reoccurrence when de novo catheter ablation is accompanied by infusion of ethanol into the vein of Marshall.

Methods: 51 patients between the ages of 18 and 85 from February 2023 until August 2024 at the University of Iowa were included in the study. Qualitative information was collected at three-time intervals from patient records in EPIC and documented in a REDCAP database. First, Patient's demographic information, comorbidities, and other medical information prior to their respective procedure were collected and compared. Next, ablation procedure information and VOM attempts and success rates were collected. Patients that had a failed VOM infusion were used as the controls for the study. Other data such as discharge disposition was also collected. Lastly, a three-month post-procedure follow up information was collected for each patient to document AF recurrence and post-procedural complications, if any.

Mid-Term Outcomes Following 1st tarsometatarsal bone block arthrodesis (Lapicotton) in the Treatment of Medial Column Instability

Student: Kenan Najdawi, M2
PI: Dr. Bopha Chrea

Background

Medial column instability is associated with many conditions including progressive collapsing flatfoot deformity (PCFD), hallux valgus (HV), and midfoot osteoarthritis (MA). The LapiCotton procedure, introduced by De Cesar-Netto C et al. (2020), is a hybrid surgical technique combining the mechanical advantages of a Cotton osteotomy and a modified Lapidus procedure to treat medial column instability. Initial pilot data has shown promising results. The aim of this study was to assess medium-term outcomes following the LapiCotton procedure regarding complication profile, radiographic correction, and patient reported outcomes (PROs).

Methods

A retrospective chart review was conducted that included PCFD, HV, and MA patients who underwent a LapiCotton procedure between June 2020 and March 2023 from a single institution. Demographics, comorbidities, and Current Procedural Terminology (CPT) codes were recorded from the charts. Radiographic correction was assessed using pre-operative, 12-week follow-up, and latest follow-up X-rays or weight-bearing computed tomography (WBCTs). Patient reported outcomes were collected prospectively and postoperatively. Complications were stratified into minor and major.

Results

A total of 59 patients (49 females, 10 males, 61 feet) were included in this study. Mean age and BMI were 54.5 years (16-77) and 31.1 kg/m^2 (18.5-58.4), respectively. Diagnoses included 19 PCFD, 22 HV, 9 MA, 7 PCFD+HV, and 4 “other” patients. The mean follow-up was 22.5 months (6-49), and the median allograft wedge size was 9 mm (5-14). At least one minor complication was noted in the charts of 18 patients (29.5%), with the most common being sinus tarsi impingement. Regarding major complications, 24 patients (36.9%) went on to develop nonunion after their index procedure and 22 patients (33.8%) required a return to the operating room. Of the 22 patients that returned to the OR, 12 (19.7%) required a revision LapiCotton procedure which was on average 16.5 (3-36) months after the index procedure. Radiographic correction and PROs are yet to be assessed.

Conclusion

The results of this retrospective review of 59 patients (61 feet) who underwent the LapiCotton procedure demonstrate that the rate of both minor and major complications is substantial and should be considered before electing to proceed with this surgical technique. Moreover, the high rate of nonunion and number of patients that required a revision LapiCotton highlight the potential pitfalls in this novel technique. Future studies are needed to determine the long-term success and complication profile associated with this technique.

Does antibiotic prophylaxis reduce rate of urinary tract infection following urodynamic studies?

Student: Natalie Nguyen, M4
Mentors: Ilana Bergelson, MD, Gina Lockwood, MD

Introduction:

Per best practice guidelines, administering prophylactic antibiotics before urodynamic studies is not indicated unless patients have conditions associated with higher urinary tract infection risk. However, inconsistent practices among providers have raised concerns about balancing patient protection and antibiotic stewardship. This study evaluated whether prophylaxis is associated with decreased rates of post-procedural infection and if the infection rate is associated with comorbidities considered to increase infection risk.

Methods:

A retrospective review of urodynamic studies over a five-year period in adult patients was conducted using Epic software. Post-procedural infection was defined as urinary tract infection or sepsis noted on Epic diagnosis list, nitrite positive urinalysis, or urine culture of at least 10,000 CFU/ml within 14 days of urodynamic studies. Patient comorbidities such as immunodeficiency and anatomic anomalies were also evaluated.

Results:

2799 urodynamic studies were performed with overall rate of antibiotic administration of 53%. 65 patients (2.3%) developed a post-procedural infection. The rate of infection in those who received antibiotics was 1.3% (20/1486), while in those who did not, the rate was 3.4% (45/1313). Antibiotic use was significantly associated with 62% decreased odds of post-procedural infection ($p<0.01$). Patients with anatomical anomalies had a 5.48-times increased post-procedural infection risk despite antibiotic prophylaxis. No cases of sepsis were identified.

Conclusion:

Although there was a higher rate of post-procedural infection in patients who did not receive antibiotic prophylaxis, the overall rate in this large retrospective study was low. Antibiotics should be used judiciously and prospective studies are needed to optimize antibiotic stewardship and provide rigorous criteria on comorbidities that could increase infection risk.

Title: System-level Stakeholders' Perspectives on Food Insecurity in Pregnancy

Student: Alexandria Nicolaus
Mentor: Michael Haugsdal MD, Department of Obstetrics and Gynecology
Collaborators: Heather Reisinger PhD, Deshauna Jones PhD, Morolake Adeagbo PhD

Introduction: Food insecurity (FI) significantly affects health disparities and poor health outcomes, particularly in obstetric patients. At the UIHC Women's Health Clinic (WHC), 22% of high-risk pregnancies are affected by FI, especially among Medicaid recipients, single women, Black or Hispanic women, and rural patients. The Upstream Initiative screens and refers FI pregnant women to community-based food resources, though gaps remain in immediate support and awareness. Effective intervention requires understanding patients' barriers and references to improve access and reduce FI's health impact. Addressing structural and individual barriers, including stigma, is essential for equitable access to nutritious food.

Purpose: The objective of the study was to address FI disparities in pregnant women at the UIHC WHC by designing and implementing strategies to 1) identify and immediately address FI, and 2) increase the use of community-based food resources for better, sustained access to healthier foods. This segment of the study collected and analyzed the qualitative perspectives of clinical and community stakeholders on their task of identifying and addressing FI among persons in the Iowa City area and UIHC, High-Risk Obstetrics Clinic.

Methods: The study employed a qualitative narrative approach to understand system-level stakeholders' perspectives on identifying and addressing FI among patients in the Iowa City area and UIHC's High-Risk Obstetrics Clinic. Stakeholders, selected from UIHC, Department of Public Health, and Iowa City Community Organizations, were chosen for their roles in addressing FI and serving High-Risk Obstetric patients. Semi-structured interviews were conducted via Zoom with 8 stakeholders, focusing on their experiences with FI among pregnant community members. The interviews were transcribed Rev.com and analyzed using MaxQDA, with themes identified both deductively and inductively. The analysis process included developing and refining a codebook, coding for reliability and validity, and keeping reflexive notes to capture nuances in the data.

Results: This study identified several key themes that highlight the barriers faced by individuals in accessing necessary resources and support. *Theme 1: Stigma and Shame as Barriers to Self-Reporting FI.* Many patients experience embarrassment in acknowledging FI due to cultural norms that value independence, leading to underreporting and difficulty in accessing help. This stigma is often perpetuated by societal attitudes, organizational leadership, and the perception that FI is a personal failure rather than a social issue. *Theme 2: Social Determinants of Health (SDoH) and Access to Food Assistance Programs.* SDoH were identified as significant factors limiting access to food assistance programs. Non-citizens and individuals with language barriers often struggle to enroll in these programs, while lack of transportation and childcare further complicate participation. *Theme 3: SDoH and Access to Nutritious Foods.* SDoH can limit access to nutritious foods, worsening medical conditions. Geographic isolation and financial constraints contribute to this cycle. *Theme 4: Competing Resources and Food Procurement.* Financial pressures from rent, medical bills, and childcare often take precedence over food procurement, exacerbating FI. Many organizations lack efficient systems to connect patients with resources, leaving healthcare providers to fill the gap.

Conclusion: This study identified social stigma, SDoH, and competing demands worsens FI in high-risk pregnancies, particularly among marginalized groups. To improve outcomes, community resources should focus on reducing stigma, improving connections, and increasing access to food resources. This comprehensive approach is essential for ensuring equitable access to nutritious food for vulnerable obstetric patients.

Title: Metastatic Cancer and Extracellular Vesicles

Authors: Jacquelyn Nielson, Marion Dykstra, Amanda Pope, Guy Hudson, and Michael Henry

Introduction: Cancer remains a leading cause of mortality in the United States despite continuous advancement in surgery, radiation, and chemotherapies. Cancer metastasis is largely the driver of this phenomenon as treatments are significantly limited compared to primary tumors. Recent investigation has identified extracellular vesicle release from primary tumors and tissue cultured cancer cell lines as a key driver in preparing the metastatic niche for secondary tumor development. This includes extracellular matrix remodeling, angiogenesis, and neutrophil-mediated inflammation. Having previously observed an increase in extracellular vesicle release from cancer cells exposed to fluid shear stress similar to that experienced in the bloodstream, we investigated if these extracellular vesicles also enhanced secondary tumor formation.

Purpose: To investigate the role of extracellular vesicles released by cancer cells exposed to fluid shear stress in cancer metastasis.

Methods: We modeled circulating tumor cells by exposing cells from the murine breast cancer cell line EO771 to shear stress and isolated extracellular vesicles from the resulting supernatant. To determine their effect on neutrophil activation, we exposed the extracellular vesicles to murine bone marrow derived neutrophils. Additionally, we used the extracellular vesicles and EO771 cells in an isogenic immunocompetent murine model of cancer metastasis.

Results: Western blot analysis confirmed an increase in extracellular vesicle release by EO771 cells exposed to fluid shear stress compared to starved and static conditions. However, these extracellular vesicles did not increase neutrophil extracellular trap (NET) release compared to control. Extracellular vesicles similarly did not enhance tumor formation in vivo in the first 44 days of disease.

Discussion: Based on these results, extracellular vesicles from EO771 cells exposed to fluid shear stress were not shown to induce neutrophil activation in vitro or enhance tumor formation in vivo. However, it should be noted that there was no significant difference in neutrophil activation between our positive and negative controls, suggesting that further optimization may be necessary to obtain statistically significant results using this assay. There was also no difference in tumor formation in vivo between EO771 cells that had been exposed to fluid shear stress vs those in static conditions, an unexpected finding based on previous in vivo work using the prostate cancer cell line PC-3. Further work is necessary to better understand the effect of extracellular vesicles released from cancer cells exposed to fluid shear stress on cancer metastasis. The experiments presented here should be repeated using the prostate cancer cell line PC-3, a cell line which has been better characterized by the lab both in vitro and in vivo.

Evaluation of regulatory T cells in the skin of Bullous pemphigoid patients

Authors: Jennifer H. Ong, Tyler P. Crowe, Samantha C. Aust, Janet A. Fairley, Kelly N. Messingham

Introduction:
Bullous pemphigoid (BP) is the most common autoimmune blistering disease and is characterized by autoantibodies targeting collagen XVII/BP180 and BP230, components of the hemidesmosomal adhesion complex. The autoimmune reaction is localized to the skin, although BP180 is expressed in a variety of tissues, including the uterus, GI tract, eye, and brain. This observation suggests that skin-specific changes in immunity play a role in the pathogenesis of BP. While autoantibody-mediated mechanisms are critical for pathogenesis, regulatory T cells (Tregs) have also been implicated.

Tregs are characterized by nuclear expression of transcription factor forkhead box P3 (FOXP3), a key factor in their development and function. Peripheral Tregs maintain tolerance by limiting activation and expansion of autoreactive T cells that escaped clonal deletion in the thymus. One way Tregs exert their suppressive activities is through the release of the inhibitory cytokines IL-10 and TGF-β.

This study investigates whether the number or function of cutaneous Tregs is altered in the lesional skin of BP patients. This approach may uncover tissue-specific changes in cutaneous immunity that play a role in BP so they can be tested as specific therapeutic targets. Uncovering more specific therapies would represent a vast improvement over standard therapies that employ strong systemic immunosuppression and are associated with significant morbidity and mortality.

Hypothesis:
BP patients will exhibit skin-specific changes in immune cell subsets. Specifically, BP lesions will be characterized by changes in the number or function of Tregs.

Methods:
Skin biopsies (4mm) were obtained from BP patients and age- and sex-matched controls, embedded in optimal cutting temperature medium, and 5-7 μM cryosections were placed on charged glass slides. Immunostaining involved fixation in 4% PFA, permeabilization with Triton X-100, and blocking. Commercially available primary antibodies (CD3, CD4, FOXP3, IL-10, TGF-β) and fluorescently labeled secondary antibodies, and mounting medium containing DAPI nuclear stain were used. NIH ImageJ was used for quantification and colocalization analysis, and graphs were generated using GraphPad Prism.

Results:
There was a significant reduction in FOXP3+ cells, particularly CD4+FOXP3+ Tregs, in skin from BP patients compared to healthy controls. The frequencies of FOXP3+ and IL-10+ cells were markedly lower in BP lesional skin, underscoring the potential role of Treg reduction in the pathogenesis of BP. In contrast, no significant difference was found in the number of TGF-β+ cells between BP patients and controls. These results suggest that Tregs, especially those expressing FOXP3 and IL-10, may be crucial in maintaining immune tolerance to BP antigens, and their reduction could contribute to disease development.

Conclusion:
The reduction in FOXP3+ Tregs and IL-10+ cells in BP lesional skin suggests that impaired Treg numbers and function may contribute to the pathogenesis of BP by disrupting immune tolerance to skin antigens. These findings highlight the potential of targeting Treg pathways as a therapeutic strategy in BP, potentially reducing the need for broad systemic immunosuppression and its associated risks.

Exploring Drivers of Progression of Cutaneous Melanoma

Student: Stepan Orlovskiy
Mentor: Adam Dupuy, PhD
Other collaborators: Alisha Babu

Introduction: Melanoma is the deadliest form of skin cancer, accounting for around 80% of skin cancer deaths. Melanoma is treatable if found at an early stage, but survival of metastatic melanoma is generally around 30% of lower. This is because melanomas can quickly become invasive and rapidly metastasize. Some of the genetic events that can lead to the initiation and progression of melanoma are well known, such as the *BRAF* mutation found in roughly 50% of all melanomas, but these mutations are not the only players in the progression of melanoma. Benign nevi, or "moles", that are commonly found on human skin contain some of these well studied mutations, such as *BRAF*, *NRAS*, and loss of *CDKN2A*, but they do not progress to invasive melanoma through these mutations alone. This suggests that there are other unknown genetic alterations that contribute to the progression of invasive melanoma. This study looks to explore the role of *NEDD4L* in the progression of cutaneous melanoma.

Purpose: We hypothesize that overexpression of the gene *NEDD4L* will drive the progression of cutaneous melanoma.

Method: We will transfect CBT cells, which express similar mutations to benign nevi found on human skin, and several other derivatives of this cell line. Once stable transfection has occurred and the cells overexpress *NEDD4L*, we will engraft these cells into mice to create xenograft models. Growth of these xenografts will be monitored, and tumor volumes will be recorded to determine the effect of NEDD4L on in vivo progression of cutaneous melanoma.

Findings: I have transfected the cells, but we are still waiting for stable transfection. Mice have not yet been engrafted with tumors as the cells are still being prepared. However, our lab carried out a sleeping beauty transposon mutagenesis screen on A375 melanoma cells that showed that overexpression of *NEDD4L* could be driving the engraftment/growth of A375 cells in vivo.

Overall significance/broader perspective: Though the study has not been completed, there is good evidence suggesting that *NEDD4L* could be driving melanoma progression. A study by a group in Japan found that *NEDD4L* was found in 43% of primary melanomas, that cells expressing NEDD4L grew worse in vitro when *NEDD4L* was knocked out, and that cells that did not express NEDD4L grew better in vivo when transfected to express NEDD4L. One of our previous studies showed that NEDD4L could be aiding A375 melanoma cell engraftment/growth in vivo. If NEDD4L overexpression helps our mouse xenografts grow, we will explore the biology of the NEDD4L protein, an E3 ubiquitin ligase, and discover the substrates that it targets as well as the result of those modifications. These results can then potentially be used to create new therapies and strategies to treat/prevent melanoma.

Title: Long-term Outcomes of Surgical Management for Submandibular Sialolithiasis: Gland Resection vs. Preservation

Authors: Claire Orth, BS[1], Edward Tannenbaum, BA[1], Piper Wenzel, BS[1], Benjamin Fick, MD[2], Kailey Henkle, MS[3], Henry Hoffman, MD MS[4] (*1- University of Iowa Carver College of Medicine, 2- University of Iowa Hospitals and Clinics, Department of Radiology, 3- University of Iowa College of Public Health, Department of Biostatistics, 4- University of Iowa Hospitals and Clinics, Department of Otolaryngology Head and Neck Surgery)*

Introduction: Surgical management for submandibular sialolithiasis generally involves either a gland-preserving endoscopic procedure or gland resection. Xerostomia is a frequent post-operative complaint, raising the question of whether one approach poses a higher risk of this condition than the other.

Purpose: To evaluate the long-term outcomes following treatment of submandibular sialolithiasis, with a particular emphasis on xerostomia, by comparing patients who underwent a gland-preserving procedure versus those who underwent gland resection.

Methods: Thirty-six patients were evaluated with follow-up (phone, email, postal mail) five to ten years after surgery for submandibular sialolithiasis to compare sialendoscopy-assisted gland-preserving surgery with submandibular gland resection. These patients were identified through review of a single surgeon's log at an academic institution, encompassing procedures conducted between 2013 and 2018. Clinical parameters at the time of initial surgery were evaluated to include radiographic imaging and procedural details. Follow-up focused on the initial salivary symptoms of pain and swelling that prompted treatment. 'Success' was defined as the resolution of these symptoms without new salivary symptoms or the need for additional treatment on the same submandibular gland after the most recent procedure. Xerostomia was evaluated separately employing the validated XQ (Xerostomia Questionnaire) survey. Additional follow-up inquired about stone recurrence, the need for further treatments, and the presence of facial numbness, tongue numbness or weakness, or bothersome scar.

Results: Review identified 82 patients receiving 89 procedures directed to sialolithiasis. Efforts to contact all 82 patients resulted in 36 responding to a questionnaire addressing outcomes with a median duration of follow-up of 97.4 months. Among these 36 patients, 11 (30.6%) were initially treated with gland resection, while another 3 (8.3%) were treated with gland resection after failing a gland-preserving procedure (persistence of pain and swelling). Gland removal was avoided in 22 patients (61.1%), with one requiring a second gland-preserving procedure. Full resolution of pain and swelling symptoms after the first procedure was reported in 18 of the 25 patients (72%) who underwent gland-preserving procedures initially and in all 11 patients who underwent gland resection. Of the 22 patients who had their gland preserved, 6 (27.3%) experienced dry mouth, averaging a score of 8.0 on the Xerostomia Questionnaire (XQ), while 4 (28.6%) of those with gland removal reported dry mouth, averaging a score of 3.4. Two patients (14.3%) who had their gland removed reported symptoms of facial numbness, tongue numbness/weakness, or bothersome scar, while none of the patients with gland preservation reported these symptoms. Overall, 20 out of 22 patients (90.9%) who had gland preservation reported resolution of their initial pain and swelling symptoms without experiencing new salivary symptoms or requiring additional treatments since then. These patients were therefore considered 'successful' by our criteria. All 14 patients (100%) who underwent gland removal were deemed successful.

Conclusion: Preserving the gland during surgical management of submandibular sialolithiasis is considered less invasive and is often expected to result in fewer long-term undesirable outcomes. However, patients who elect to undergo this approach may face a higher likelihood of persistent salivary symptoms and require additional treatments, including potential gland resection, compared to those who have their gland removed initially. Additionally, long-term outcomes, such as the presence of xerostomia, show no significant differences between the two approaches.

Early Cranioplasty Promotes Functional Recovery in Rodent TBI Model

Osborn, Steffen G; Bartelt, Daniel C; Yin, Terry C; Andrews, Brian T

Traumatic brain injury (TBI) is a leading cause of death and disability in the United States. It is a complex condition with ranging severity making it difficult to study. Hemicraniectomy is often the treatment of choice for severe traumatic brain injury because it prevents compressive damage to the brain that otherwise results from elevated intracranial pressures. There is debate in the literature over the timing of cranioplasty — the restoration of the cranial vault post hemicraniectomy. This is due to the need to balance various surgical risks and the need to wait for neural inflammation to subside. The purpose of this study was to test the impact of earlier restoration of the cranial vault architecture on functional recovery following a TBI.

Long Evans rats were randomly assigned to one of two major experimental groups, an early cranioplasty group or a late cranioplasty group performed following a TBI with subsequent hemicraniectomy. In this study, early cranioplasty was defined as occurring within two days of the initial injury. Late cranioplasty occurred greater than two days after the initial injury. Control groups included a sham surgery cohort, a hemicraniectomy only cohort, and a hemicraniectomy post-TBI cohort.

Rats were trained until proficient in a one-meter beam walk. Baseline data was collected prior to surgery, and then weekly thereafter. Motor function was assessed by total foot slips. An open field test was also conducted in the week following surgery to assess anxiety-like behavior. Early cranioplasty resulted in significantly reduced motor deficits when compared to injury controls. Late cranioplasty did not produce the same effect. When assessing anxiety-like behaviors, no differences were observed.

This study adds further support to the notion that an intact cranial vault plays a critical role in the recovery of the brain in response to injury. While this rodent model is limited by the fact that these rats did not experience a comparable level of neural inflammation in response to TBI as a human would, the human syndrome of the trephined provides further motivation to restore the cranial vault as soon as possible following hemicraniectomy. Further studies should examine mechanisms of accelerating the reduction of neural inflammation in the human brain following traumatic brain injury.

Hospital Discharge Communication - Caregiver Perspectives

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Introduction: Previous studies have examined how discharge instructions are communicated and their impact on pediatric patients, such as readmission rates, to assess their effectiveness. Other research has focused on what providers consider essential in discharge communication. Additionally, studies have shown parental rating of discharge communication was significantly lower than those of providers and nurses, suggesting that parents and providers do not value the same components of discharge communication. To our knowledge, no study has investigated the preferences of caregivers for discharge planning and communication throughout the duration of pediatric hospital admission.

Purpose: The purpose of this qualitative study is to determine how caregivers perceive discharge communication throughout hospitalization, from admission to discharge. Additionally, this study aims to elicit factors, including timing, identified by caregivers as important during discharge communication.

Methods: Individual interviews of 20 caregivers of pediatric patients were conducted on the pediatric inpatient floors at The University of Iowa Stead Family Children's Hospital from March 2024 to April 2024. Inclusion criteria included pediatric patients ages 0 to 17 years old who were admitted to the general medicine units under the care of the pediatric hospital medicine service. Patients on hospice or airborne precautions and those with preferred languages other than English were excluded from the study. Interviews were audio-recorded and transcribed. Transcriptions were then reviewed by all three study authors with quotations selected for qualitative analysis. Common keywords were selected by consensus, followed by identification of codes and themes forming a conceptual model of discharge. A retrospective chart review was performed for all patients enrolled in the study, and the following data was recorded: demographics, need for assisted medical technology, enrollment in Continuity of Care program, presence of chronic medical conditions, and number of home medications.

Results: Interviews were conducted between day 0 and 6 of hospitalization, with 14 interviews (70%) occurring between hospital day 1 and 3. At the time of interview, 15/20 (75%) caregivers reported that discharge communication occurred. The following themes were identified as important factors by caregivers for discharge communication: family-centered communication, caregiver confidence, home medical transition, and medical discharge readiness. Ten of 20 (50%) caregivers conceptually identified preference of timing of discharge communication, stating diagnostic certainty and prognosis as determining factors for timing of discussion. The other half of caregivers expressed discharge timing preferences in terms of day of hospitalization, particularly on day of admission (n=8) and day of discharge (n=2).

Discussion and Conclusions: Overall, caregivers were generally satisfied with discharge communication in our study. We found that caregivers value diagnostic certainty prior to engaging in individualized discharge communication with familial involvement. Our findings suggest that preference for timing of discharge communication is reflective of caregivers' goals of care. Thus, it is recommended to reframe the discussion to assess and incorporate goals of care to prevent overwhelming caregivers and portraying a rushed discharge.

Non-Retinal Influences of Dietary Nicotinamide Relevant to the Search for Glaucoma Neuroprotective Therapies

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INTRODUCTION: Glaucoma affects millions of people and causes irreversible blindness. It is associated with loss of retinal ganglion cells and high intraocular pressures. Nicotinamide (Vitamin B3) is believed to be neuroprotective in glaucoma models. This study aims to test whether a diet high in nicotinamide (NAM^{HI}) can influence IOP in a mouse model of ocular hypertension and to test its effect on the microbiome.

METHODS: A sample size of 90 C57BL/6J mice were used in this study with even males and females. This cohort was further subdivided into 6 groups based on intervention and diet. Interventions include bilateral eye injections: naïve, ad5-empty, and ad5-ATF4. Ad5-ATF4 was used to induce ocular hypertension. Half of each group received either NAM^{HI} or control diet. IOP measurements were taken by masked researcher at weeks 1, 3, 5, and 7 post-injections. Slit lamp images were taken at weeks 1, 3, and 7 post-injections. Fecal samples were collected 6 weeks after introduction of the experimental NAM^{HI} diet for microbiome analysis. A mixed effects model with repeated measures was conducted to compare IOP measurements between each treatment group using Tukey's multiple comparison's test. The mixed effects model was repeated to compare weight between diet and sex groups throughout the course of the study. Within each injection group, Welch's t-tests were used to compare IOP in the presence of diet at each time point.

RESULTS: Statistical analysis provides significant differences in Ad5-empty virus on NAM^{HI} diet compared to control at weeks 3, 5, and 7 post-injections ($p= 0.0186$, $p= 0.0143$, $p=0.0491$), respectively. NAM^{HI} diet did not rescue ocular hypertension in the presence of Ad5-ATF4, indicating that ATF4 blocks the effect of nicotinamide on IOP. NAM^{HI} diet significantly decreases weight gain in the presence of high fat diet when comparing sex at each time point ($p<0.0001$). Gut microbiomes are influenced by NAM^{HI} diet as evidenced by Transnetyx taxa plot.

DISCUSSION: Nicotinamide rescues ocular hypertension in Ad5-empty. However, ATF4 blocks this effect. Microbiome sampling provides clear evidence that NAM^{HI} diet alters proportions of gut bacteria compared to control diet. Further analysis will aim to determine whether changes in microbiome correlate to influences in IOP. A future direction for this study entails tissue collection of optic nerves and retinas to determine if eyes with increased IOP exhibit glaucomatous damage, and if so, whether nicotinamide ameliorates this damage.

Impact of Neuraxial Block on Immediate Post-Extubation Respiratory Function in Fast-Track Pediatric Cardiac Surgery

Student: Spencer Pham
Collaborator: Aravinthasamy Sivamurugan
Mentor: Satoshi Hanada, MD

Introduction: Cardiac surgery induces significant stress and inflammatory responses, which can adversely affect clinical outcomes, particularly in pediatric patients. Traditionally, high doses of systemic opioids have been used to mitigate this stress, but this approach often leads to prolonged recovery after surgery. Neuraxial block techniques, such as caudal anesthesia and high spinal anesthesia (HSA), have been explored as alternatives to reduce opioid use and improve recovery times. In pediatric cardiac surgery patients, especially those with single-ventricle physiology, early extubation is desirable because spontaneous breathing improves pulmonary blood flow by eliminating the positive pressure associated with mechanical ventilation post-extubation. However, while neuraxial block techniques could facilitate early extubation, the impact of HSA on immediate post-extubation respiratory function, specifically PaCO2 levels as an indicator, has not been extensively studied.

Purpose: This study aims to compare PaCO2 levels between fast-track pediatric cardiac patients who receive a neuraxial block and those who do not. We hypothesize that a neuraxial block combined with general anesthesia (GA) will result in lower PaCO2 levels in the first arterial blood gas after extubation compared to GA alone.

Method: This study enrolled fast-track pediatric cardiac patients under 5 years old who were extubated in the operating room immediately after surgery. Patients who were transported intubated to the ICU were excluded. Based on the results of the first arterial blood gas taken immediately after extubation, enrolled patients were divided into two groups: one with PaCO2 levels of 45 mmHg or less (Normocapnia group) and the other with PaCO2 levels greater than 45 mmHg (Hypercapnia group). The primary outcome will be the use of a neuraxial block, either caudal anesthesia or HSA.

Results: The study enrolled approximately 209 patients, with 117 in the Normocapnia group and 92 in the Hypercapnia group. There were no significant differences between the groups in terms of the use of caudal anesthesia or HSA, intraoperative opioid usage, postoperative pain scores, length of stay in the ICU, or 30-day and one-year mortalities.

Conclusion: While adding a neuraxial block, such as caudal anesthesia or HSA, to general anesthesia can facilitate early extubation in pediatric cardiac surgery, it does not significantly impact postoperative respiratory function, as indicated by PaCO2 levels.

Correlation of 2020 presidential election results with state HCAHPS scores during COVID-19: Challenges in identifying associations

Isabella T. Phillips, Nicholas J. Fustino, Hayden L. Smith

Introduction: The Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey provides measures of patient experience. Reported data have shown a decline in HCAHPS scores since the onset of the SARS-CoV-2 pandemic. Understanding factors associated with changes in patient perception of care may be beneficial due to correlations with quality of care and clinical outcomes.

Aim Statement: To investigate whether an association may be discernible between voting trends in the U.S. 2020 presidential election and respective declines in patient satisfaction during the pandemic, as measured by statewide HCAHPS scores.

Methods: Aggregated HCAHPS scores from the 50 U.S. states for calendar years 2019-2022, adult 2020 Census data, and 2020 presidential election results were collected from publicly accessible sources. Analyses were conducted to explore changes in HCAHPS hospital rating scores versus voter margin of victory (i.e., Democrat vs. Republican) in the 2020 presidential election. These data were used to determine HCAHPS completion rates by state population and assess generalizability of results to the state and voter populations.

Results: An initial macro-trend between voter margins and relative declines in HCAHPS hospital ratings were observed in unweighted state level data. Hospital ratings by state were then plotted against time, with fitted lines weighted by state census and color coded by voter margin. States tended to have similar decreases in scores over time, however some Democratic states appeared to have lower initial scores, contributing to the relative change. The percentage of HCAHPS surveys completed per state census was calculated alongside voter turnout percentages for 2020 presidential election.
In Minnesota and Arkansas, the number of completed HCAHPS surveys represented approximately 0.7% and 1.0% of the state populations and each state had 74.3% and 51.9% voter turnouts, respectively.

Conclusions: The use of aggregate data without knowledge of unit-level descriptive characteristics can result in misleading assumptions and ecological fallacies. Surveyed hospitalized patients are not randomly representative of the voting electorate and there can be selection bias risks when attempting to make generalizations. In addition, the comparison of two macro trends can also be hindered by possible confounder or information biases. Novel approaches are available to identify state-level relationships (i.e., inverse weighting, data raking, and data fusion). However, without unit-level data or sufficient data on sampling distributions – overlaps in data samples cannot be fully known or recovered via statistical approaches. Consequently, establishing a robust association between state-level voting trends and changes in HCAHPS scores proved challenging when using accessible data composed of fluctuating cross-sectional data series. In addition, less than 1% of state populations filled out a survey, further limiting the ability to generalize or extrapolate results.

Title: Human Pegivirus Reduces low level HIV Replication and viral blips in people living with HIV infection

Tyler Pollock, M1

Jack Stapleton, M.D., Department of Internal Medicine; Jinhua Xiang, M.D., Al Klingelhutz, Ph.D., Michael Bates

Introduction and Hypothesis

Human Pegivirus (HPgV) was identified in the 1990s as a flavivirus, sharing features with Hepatitis C Virus without causing disease. Pegivirus interferes with T Cell surface receptors, activation, and proliferation, providing a survival advantage for patients co-infected with HIV. The detection of low-level HIV RNA (viral blips) is common in people living with HIV (PLWH), even when on ART treatments. The cause of these blips is not entirely understood but indicate a transient increase in HIV release from infected T-Cells. Because HPgV reduces T-Cell activation and HIV proliferation, we hypothesized that HPgV-positive HIV patients would have fewer incidence of viral blips than their HPgV-negative counterparts. In addition, in vitro Pegivirus culture remains difficult. A recent mouse model suggests adipocytes may be the target of Pegivirus replication. We also assess if human Pegivirus will replicate in human adipocytes.

Methods

549 serum samples were obtained from the University of Iowa Virology Clinic from HIV-positive donors and tested for Human Pegivirus using RT-PCR. Serum from the 47 samples with the highest viral concentration were pooled for adipocyte infection. Additionally, fresh serum was obtained from one patient selected for their chronic pegivirus infection. Pegivirus binding and entry experiments in subcutaneous and visceral adipocyte cell cultures were conducted by cooling the serum and cells to 4°C, adding the virus and incubating for 2 hours at 4°C, collecting and/or washing samples, then finishing with 1 hour incubation at 37°C. Cells were then washed and samples collected. In addition, cells warned to 37°C were treated with 0.25% trypsin/DMEM. Adipocytes RNA was then extracted and tested for HPgV concentration using RT-PCR.

Relevant clinical and demographic data were collated. Viral blips were defined as a HIV Viral Load >20 copies/mL, preceded by and subsequently followed by an undetectable viral load (<20). Similarity between pegivirus positive and negative sample groups were tested for all clinical variables using unpaired T-Tests, with P values < 0.05 indicating statistical significance.

Findings and Results

Pegivirus was shown to bind adipocytes after 2 hours at 4°C, and a portion of bound virus entered cells when warmed to 37°. Trypsin treatment reduced but did not abrogate viral entry. The highest production of Pegivirus RNA was subcutaneous adherent adipocytes infected with pooled serum. Longitudinal analyses showed a general downward trend of viral load over time.

The clinical comparison by pegivirus status revealed significant differences for three factors: Patients with HPgV were younger ($p<0.001$), had a lower CD4 percentage ($p=0.0119$), and had fewer viral blips ($p=0.0053$) compared to those without Pegivirus infection.

Conclusions

Human Pegivirus confers a survival advantage to those living with HIV/AIDS. Patients with HPgV have decreased CD4 percentage and activation, limiting the environment for HIV replication. We found that Pegivirus was associated with fewer viral blips throughout the latent infection period, which is known to be associated with lower rates of virologic failure and negative outcomes.

The presence of Human Pegivirus binding and entry suggests that adipocytes may be a target of infection, although sustained and efficient replication was not observed. Further research is required to fully understand HPgV replication.

Surgical Resection Does Not Confer a Survival Benefit to Elderly Hepatocellular Carcinoma Patients

Mary Powers, BA, Hassan Aziz, MD

Abstract

Introduction

As the population ages, there has been an increase in elderly patients seeking care for hepatocellular carcinoma (HCC). Recent work has suggested that age is a poor metric to determine surgical candidacy, but in some cases, is used to disqualify individuals from gold-standard surgical care. This study investigated the effectiveness of various therapeutic options in octogenarians (aged 80-90 years) diagnosed with HCC.

Methods

The National Cancer Database was used to identify patients (aged 80-90) diagnosed with hepatocellular carcinoma (HCC) from 2004 and 2019. The study evaluated median overall survival (mOS) using Kaplan-Meier curves among four treatment strata: ablation, resection, transplantation, and no treatment.

Results

From 2004 to 2019, 27,626 patients aged 80-90 were identified as having been diagnosed with HCC. There were no demographic differences between patients who underwent treatment and those who did not. Although most patients did not undergo treatment, survival analysis suggested there was no benefit to those who did. Of available treatments, resection, the gold standard, was the most common and conferred similar survival benefits to no treatment. Ablation and transplantation resulted in decreased survival.

Conclusion

Surgical resection, the current gold standard treatment for HCC, does not confer a survival benefit to elderly HCC patients over no treatment, suggesting an age at which patients cease to benefit from invasive surgical treatment. Care needs to be taken to ensure treatment plans maximize benefit to the individual patient without relying on surgical recommendations alone.

Faith Prochaska

Title: Traumatic Brain Injury Induced IFN-I Response Across the Lifespan
Mentor: Dr. Elizabeth Newell
Collaborators: Brittany Todd, Zili Luo, Noah Gilkes

Abstract:
Traumatic brain injury (TBI) is a leading cause of death and disability which lacks targeted therapies. Successful translation of promising neuroprotective therapies will likely require more precise identification of target populations through greater study of crucial biological factors. A growing body of work supports the impact of aging on the neuroimmune profile, as well as on the response to and recovery from TBI. Accumulating evidence additionally suggests that type I interferon (IFN-I) signaling is a key contributor to immune cell-mediated neuropathology in neurodegenerative diseases. Previous work in this lab has demonstrated a robust upregulation of type I interferon-stimulated genes in microglia and astrocytes following experimental traumatic brain injury (TBI). However, the effects and interplay of age and IFN-I are understudied in TBI. Our aims were to better understand glial reactivity and the IFN-I response to TBI, and to evaluate how these outcomes vary in response to age at injury. We accomplished this by first performing fluid percussion injury (a well-established model of TBI) in juvenile, adult, and aged cohorts. Samples from these different age groups were analyzed via qPCR, IHC, and RNAscope to characterize molecular and histological outcomes. Overall, we found robust upregulation of interferon stimulated genes following TBI in all age groups. Our findings in TBI replicate prior work demonstrating anoveractive neuroimmune system in aged populations. While our studies revealed slight differences in IFN-I gene expression between juvenile and adult TBI cohorts, IFN-I gene expression was greatly amplified in the aged TBIcohorts. These differences were consistent across tissue regions of interest. The age-dependent differences we discovered after FPI support the necessity of further exploring age as a biological variable in future TBI studies. Understanding mechanisms underlying age-dependent differences in the neuroimmune response to TBI will help to better choose therapeutic targets for patients with TBI.

UGDH Variants Cause Congenital Muscular Dystrophy with Hypoglycosylation of α-Dystroglycan

Anna M. Reelfs, Carrie M. Stephan, Theresa M. Czech, Mary O.Cox, Soumya Joseph, Benjamin W. Darbro, Steven A. Moore, Kevin P. Campbell, Katherine D. Mathews

INTRODUCTION
Biallelic variants in *UGDH* have been associated with hypotonia, developmental delay, and epilepsy. The *UGDH* protein product generates substrates for synthesis of matriglycan on α-dystroglycan (α-DG). Here, we report the first pathologic evidence of congenital muscular dystrophy (CMD) due to hypoglycosylation of α-DG in siblings with *UGDH* variants.

METHODS
We reviewed electronic medical records of two siblings followed for CMD. Clinical whole exome sequencing from both siblings and parents was independently analyzed with VarSeq v2.5.0 (including annotation, segregation, and minor allele frequency filtering) and PhoRank gene ranking. A diagnostic muscle biopsy from patient 1 was evaluated with immunofluorescence and western blotting.

RESULTS
Both brothers (current ages 10 and 5 years) presented at approximately 6 months with developmental delay and elevated creatine kinase (771-2108 U/L). They walked at 2 and 4 years, respectively, and have acquired minimal language. Patient 1 developed seizures at age 9; his brain MRI was normal. They shared two *UGDH* variants in trans. In silico analysis predicted that c.305G>A (p.R102Q) alters UGDH function and c.265-6C>G causes nonsense-mediated decay secondary to a splicing defect. The muscle biopsy showed necrotizing myopathy with reduced glycospecific α-DG immunostaining; α-DG hypoglycosylation was confirmed with western blot.

CONCLUSIONS
While studies of protein function imply *UGDH* variants could cause dystroglycanopathy, this is the first evidence of dystroglycanopathy pathology in muscle. We hypothesize that our reported *UGDH* variants alter synthesis of UDP-glucuronate and downstream UDP-xylose (substrates for α-DG glycosylation) and suggest that *UGDH* is a new dystroglycanopathy gene. Our CMD cases best fit a muscle-eye-brain phenotype.

Phenobarbital for Treatment of Alcohol Withdrawal Syndrome in Emergency Medicine

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INTRODUCTION: Alcohol is the most heavily used substance in the United States and nearly one-third of patients presenting to the emergency department (ED) with alcohol use disorder will develop moderate to severe alcohol withdrawal syndrome during their stay in the ED. Alcohol causes an increase in the inhibitory neurotransmitter γ-aminobutyric acid (GABA) and inhibits binding of the excitatory neurotransmitter glutamate to *N*-methyl-D-aspartate (NMDA) receptors in the brain. In chronic alcohol abuse, GABA receptors are upregulated, and NMDA receptors are downregulated. In the absence of alcohol there is an imbalance of neurotransmitters that causes the clinical symptoms of alcohol withdrawal. This can be potentially life threatening and cause delirium tremens or seizures which often necessitate admission. The current standard of care is benzodiazepines (such as lorazepam) in conjunction with the alcohol withdrawal scale (AWS). Previous studies have shown that phenobarbital may be beneficial in treating severe alcohol withdrawal to reduce mechanical ventilation, time in the ICU, and overall hospital length of stay. However, there is a need for further evidence of phenobarbital use and possible beneficial outcomes.

PURPOSE: The purpose of this study is to determine if the use of phenobarbital in the emergency department leads to improved outcomes such as reduced ICU admissions, shorter ICU length of stay and overall shorter hospital length of stay for patients compared to those who received benzodiazepines alone.

METHODS: This is a retrospective cohort study that used data from the electronic health record at the University of Iowa Hospitals and Clinics. An administrative data pull using EPIC obtained the MRN and order date of patients ≥18 years old who received the alcohol withdrawal scale order-set in the ED from 2/1/2020 to 4/30/2024. Phenobarbital was not included in the AWS order-set until 2/2/2022 so an additional EPIC pull was done that captured all Phenobarbital ordered from 2/1/2020 to 2/29/2024. Encounters with the same MRN and order date were combined, and a final list of 1484 encounters were imported into REDCap. From this list a manual chart review was done by two reviewers. Patient demographics, comorbidities, outcomes, and medications were recorded. Exclusion criteria included duplicate orders (another order during the same hospital stay), pregnant patients, prisoners, non-alcohol withdrawal phenobarbital use, documented allergy to anti-epileptics, and documented history of acute intermittent porphyria. The phenobarbital order list was also reviewed, and phenobarbital therapy that was not initiated in the ED was removed. At this time 922 records were reviewed and after exclusion criteria was applied there were 8 patients missing comorbidity information and 22 were missing AWS scores which were also excluded resulting in 293 individuals for analysis. All statistical analysis was performed in R version 4.3.1 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS: 293 records were included in this analysis. 53 records did not receive any treatment, 216 received benzodiazepines only (BZ), 2 received phenobarbital only (PB) and 22 received phenobarbital and benzodiazepines (PB+BZ). In the no treatment, BZ, PB, and BZ+PB groups respectively, 3.8%, 7.9%, 0%, and 18.2% of the records were identified as moderate to severe initial AWS score (≥8). In comparison to the BZ group, the adjusted odds ratio for ICU admission is 27.58 (95% CI 3.75-198.35) for PB, 20.84 (5.03-86.37) for PB+BZ, and 0.52 (0.06-4.39) for no treatment. PB, BZ+PB, and no treatment all had a reduced incident rate ratios for hospital length of stay when compared to BZ group 0.54 (0.15-1.98), 0.86 (0.57-1.30) 0.50 (0.37-0.66) respectively. However, only the no treatment group was statistically significant. For ICU length of stay there was a reduction as well 0.40 (0.11-1.51) 0.31 (0.11-0.82), 0.85 (0.29-2.47) respectively, and PB+BZ is the only group that is statistically significant.

CONCLUSION: The phenobarbital plus benzodiazepine group had a larger percentage of moderate to severe initial AWS score. This is not statistically significant but likely due to the small sample size in the phenobarbital and benzodiazepine group. Phenobarbital in addition to benzodiazepines showed an increased odds ratio of ICU admission but also a statistically significant reduction in ICU length of stay. This preliminary data analysis is encouraging that phenobarbital may shorten ICU length of stays. Further analysis is still needed and controlling for higher AWS scores in the phenobarbital treatment groups may be necessary. Additionally, more outcomes such as incidence of intubations, seizures, or delirium tremens may also be included in the final analysis.

Caffeine and SS-31 Effects on BBS-associated Mitochondrial Elongation and Dysfunction

Younes Rouabhi, Deng-Fu Guo, Kamal Rahmouni

Introduction: Bardet-Biedl Syndrome (BBS) is a genetic condition that is characterized by multiple comorbidities including obesity, hyperglycemia, and hypertension due to its underlying metabolic impairment. Recently, our group has identified a role of the BBSome, a protein complex of eight BBS proteins, in the regulation of mitochondrial dynamics. Specifically, BBSome deficiency was found to cause mitochondrial defects including elongation due to a decrease in the activity of key mitochondrial fission protein, dynamin-related protein 1 (DRP1). Moreover, we showed that this decrease in DRP1 activity and its related defects in mitochondria morphology can be rescued via the loss of a DRP1 inhibitor. Interestingly, this was associated with improvement in some of the phenotypes caused by BBSome deficiency such as obesity and insulin resistance. In addition, prior reports have demonstrated that caffeine promotes mitochondrial fission due to activation of DRP1. This leads to shortening of the mitochondria and a subsequent improvement in mitochondria quality. In a similar regard, Elamipretide (SS-31) is a synthetic peptide that has been primarily used to target a variety of mitochondrial disorders such as heart failure, ischemia, and acute kidney disorder. Because of their shown involvement in maintaining healthy mitochondria function, caffeine and SS-31 are intriguing potential modalities to mitigate obesity and diabetes in BBS.

Hypothesis: We hypothesized that caffeine and SS-31 treatment will lead to improved mitochondria function in BBS cells by increasing the activity of DRP1. Subsequently, we postulated that caffeine and SS-31 treatment will lead to improved body weight gain and glucose homeostasis in BBS mice.

Methods: To test our hypothesis, mouse hypothalamic N39 cells lacking the *Bbs1* gene (Bbs1KO) were treated with 50 μM caffeine, 50 nM SS-31, or vehicle. Wildtype cells were used as controls. Following treatment, these cells were subjected to transmission electron microscopy to evaluate differences in mitochondria morphology. Proteins from these cells were also extracted and processed via Western blotting to assess levels of phosphorylated and unphosphorylated DRP1.

Findings: We found that treatment of Bbs1KO cells with both caffeine and SS-31 resulted in a significant decrease in mitochondria length, area, and form factor. Furthermore, Bbs1KO cells treated with caffeine and SS-31 showed heightened levels of phosphorylated DRP1 compared to vehicle controls. Increased phosphorylated DRP1 was due to increased total DRP1 protein expression. Additionally, we also observed that caffeine and SS-31 treated Bbs1KO cells significantly reduced mitochondrial reactive oxygen species compared to untreated cells. Preliminary findings of caffeine treatment in BBS mice have also shown improved glucose handling, although more data is required to verify this.

Conclusions and Perspectives: Our data demonstrates that caffeine and SS-31 successfully rescue impaired mitochondria morphology and function in Bbs1KO cells and suggests that this improvement works by increasing total DRP1 activity. Additionally, rescue of mitochondrial dynamics through caffeine treatment improves the associated weight gain and hyperglycemia seen in BBS mice. Taken together, these findings suggest caffeine and SS-31 as potentially effective therapies to manage BBS-associated pathologies.

The Road to Failure: A Retrospective Analysis of Past Ophthalmic and Medical History Associations with Corneal Transplant Failure

Simran Sarin BA (Presenter), Anuradha Trivedi BS, Mohana Sunkara, Gregory Schmidt MBA CEBT, Mark A Greiner MD, Christopher S Sales MD MPH (Mentor)

Introduction: Cornea transplantation, or keratoplasty, is the most frequent organ transplant procedure performed in the United States. Penetrating keratoplasty (PKP), Descemet stripping endothelial keratoplasty (DSEK), and Descemet membrane endothelial keratoplasty (DMEK) are keratoplasty approaches that differ in corneal tissue thickness, surgical invasiveness, and complexity. PKP was the exclusive standard of care from about 1945-2006; DSEK emerged as a new standard for corneal endothelial disease in 2006, and in 2014, DMEK came to the fore as a superior endothelial keratoplasty approach to DSEK. As of 2022, a comparable number of PKPs, DSEKs, and DMEKs are performed annually in the United States. Repeat corneal transplants due to allograft failure are the 3rd leading indication for keratoplasty, comprising of 6,457 allografts per year. The University of Iowa and Iowa Lions Eye Bank were early adopters of PKP, DSEK, and DMEK, providing a unique longitudinal dataset of PK, DSEK, and DMEK graft outcomes. This study aimed to identify ocular and medical risk factors associated with allograft failure.

Methods: We conducted a 1:1 retrospective case control study of allografts over 15 years. Inclusion criteria were all patients who received a PK, DSEK, or DMEK at the University of Iowa between March 1, 2009 and January 1, 2024. Exclusion criteria were patients under age 18 at the time of data collection. Charts were reviewed for demographics, ocular and medical comorbidities, and graft outcomes. Graft failure was defined according to the Cornea Donor Study parameters, a landmark corneal transplant clinical trial.

Results: Data were collected from 415 corneal transplants; 209 failed transplants and 206 successful procedures were identified. The most common indications for keratoplasty were Fuchs' endothelial corneal dystrophy (33%) and repeat corneal transplants (24%). Failure was not associated with age, sex, or intraocular lens status. Cases that resulted in graft failure had significantly worse visual acuity compared to controls at baseline, 6 months, 12 months, and 24 months following keratoplasty (all $p \leq 0.001$). Past ocular history of immunologic rejection was associated with an increased risk of failure (odds ratio (OR) = 5.7; $p<0.001$) in addition to ocular herpes simplex virus (HSV) history (OR = 2.9; $p<0.001$). There was no significant association between diabetes or ocular trauma with graft failure. Glaucoma history was associated with graft failure (OR=2.9; $p<0.001$), but there was no relationship between failure and whether glaucoma was managed surgically or medically ($p=0.69$). When stratified by keratoplasty type, glaucoma history was a significant predictor of failure in PKP (OR=2.8, $p=0.02$) and DSEK (OR=3.2, $p=0.006$), but not DMEK (OR=2.3, $p=0.07$). Among failed corneal allografts, those with a history of prior immunologic rejection (2.8 vs 7.8 years; $p<0.001$), HSV (2.7 vs 7.7 years; $p<0.001$), and glaucoma failed faster (2.3 vs 9.8 years; $p<0.001$). Cases with a past medical history of diabetes trended towards faster allograft failure, albeit not significantly (4.9 vs 7.5 years; $p=0.06$). The mean number of repeat allografts needed per patient was associated with a past ocular history of prior immunologic rejection, but this trend was not significant (0.91 vs 0.50; $p=0.051$) except in cases with a history of HSV (0.88 vs 0.48; $p<0.001$) and glaucoma (0.74 vs 0.44; $p=0.003$). Multivariate Cox regression analysis revealed glaucoma as a significant contributing factor to graft failure compared to immunologic rejection history, HSV, and keratoplasty type (HR 1.4; 95% CI 1.03-1.90; $p=0.03$).

Conclusion: This is the first study to analyze predictive factors of allograft failure across all corneal transplant indications for PK, DSEK, and DMEK. Past ocular history of immunologic allograft rejection, HSV, and glaucoma were all significant predictors of failure. Additionally, all of these factors were associated with accelerated time to graft failure and an increased number of repeat grafts following the first keratoplasty. When these risk factors were analyzed in multivariate analysis, glaucoma was found to be an independent risk factor for failure, increasing allograft failure risk by 1.4 times. Glaucoma was also found to be predictive of failure in PKP and DSEK but not DMEK, the least invasive of the 3 keratoplasty approaches. These findings may inform therapeutic approaches and prognostic discussions with patients in high-risk transplant candidates. Confirmatory prospective studies are needed to further analyze associations between past medical history, ophthalmic history, and long-term allograft outcomes.

Healthcare Professional Perspectives on Oral Feeding Preterm Infants in the NICU: A Survey

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Introduction: One in every three premature infants will struggle to develop typical feeding milestones, such as sucking, swallowing, appropriate breathing, and esophageal bolus transport, which can delay oral feeding initiation and progression. The approach to feeding preterm infants requires a multidisciplinary effort, including the family, nurses, dieticians, occupational therapists, speech-language pathologists, social workers, and physicians. Interventions to improve the oral feeding rates and to decrease the length of hospital stay have been studied, however, there is a general lack of understanding surrounding the perceptions of healthcare professionals about oral feeding in the Neonatal Intensive Care Unit (NICU).

Purpose: The aim of this study is to elucidate the perceptions, knowledge, and opinions regarding the initiation, evaluation, and progression of oral feeds from healthcare professionals in the Neonatal Intensive Care Unit of the Stead Family Children's Hospital (SFCH).

Methods: As the first phase in an IRB approved mixed-method study, a survey regarding current oral feeding approaches was designed based on current literature and collaborator recommendations, uploaded to RedCap, piloted and subsequently distributed to healthcare providers in the SFCH NICU electronically. Informed consent was obtained prior to survey initiation. The survey was composed of 19 questions, including multiple choice, "select all that apply", and free response formats, and took approximately 10 minutes to complete. Questions addressed predicted sources of variability in the current approach to oral feeds, such as appropriate postmenstrual age and respiratory support at initiation of oral feeds, what educational resources are necessary, the utility of swallow studies, and satisfaction with parent participation in oral feedings. The survey was open for 6 weeks with reminder emails sent out to roles with the lowest response rates. The results were analyzed utilizing SPSS software for descriptive statistics and stratified based on healthcare professional role and years of experience.

Results: There were 83 responses to the survey at closure representing several roles: Nurses (57.8% of survey population), Neonatologists (14.5%), Advanced Practice Providers (12%), Fellows (3.6%), Dietitians (3.6%), Speech Language Pathologists (2.4%), Lactation Consultants (3.6%), and Occupational Therapists (2.4%). Survey results indicated: 1) There is variability in agreement with the current approach to oral feeding in healthcare professionals overall as well as between roles, 2) Certain roles feel more hesitancy with initiating oral feeding both prior to 34 weeks postmenstrual age and while infants require respiratory support, 3) Instrumental swallow studies are viewed with variable efficacy in determining both swallow function as well as safety based on role in the NICU, 4) Areas in need of educational resources include discussions of different interventions for improvement of oral feeding, determining safety of oral feeding while infants are utilizing non-invasive respiratory support, and determining infant readiness for oral feeding, 5) The NICU team reports that the most important factors for determining oral feeding success are cardiorespiratory instability, presence of respiratory support, and postmenstrual age at initiation of oral feeds. Overall, there are divides between individual healthcare professionals as well as between roles on important topics, such as: when preterm infants are old enough to begin oral feeding, what levels of respiratory support are appropriate and safe for initiation of oral feeding, how well we are listening to preterm infant cues for hunger and stress, how consistently protocols are applied and whether they should be viewed rigidly or fluidly depending on clinical picture, etc.

Conclusions: This survey uncovered major topics of importance and variability between healthcare professionals, and this data was used to inform an interview guide for the second phase of a mixed-method study evaluating healthcare professional perspectives on oral feeding in the NICU. Interview guide questions expand on those covered in the survey, particularly where high variability was discovered. The combined survey and interview data from the mixed-method study will be used as a measure of the NICU's current state to inform quality improvement efforts targeted at improving oral feeding rates and reducing length of hospital stay for preterm infants.

The Impact of Obesity and Lymphedema on Peri-Incisional Perfusion and Post-Operative Outcomes After Primary Total Knee Arthroplasty

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Disclosures:

INTRODUCTION: Rates of class III obesity (BMI ≥40kg/m^2) continue to rise in the United States, leading to an increased prevalence of patients undergoing total knee arthroplasty (TKA). Obese patients face higher risks of post-operative complications such as wound healing issues and periprosthetic infections. Obesity, however, isn't the only contributor to increased risk of post-operative complications. It is estimated that patients with lymphedema carry a 30-37% complication rate post-total joint arthroplasty despite being extremely underdiagnosed in medical records. As increased adipose tissue is known to impact angiogenesis, it is a plausible theory that complications associated with wound healing and obesity could also be related to decreased perfusion at the surgical incision site. SPY Portable Handheld Imaging (SPY-PHI) fluorescent imaging systems are used heavily in plastic and general surgery and have been validated for use after TKA and other orthopedic procedures, but no current literature has investigated the technology's utility in obese and lymphadenopathic patients with increased risk of wound healing complications. Our study aims to investigate the relationship between differences in incisional perfusion gradients at the time of TKA incision closure, lymphedema, body composition metrics, and 3-month post-operative wound healing complications in obese patients with a BMI >30kg/m^2. We hypothesize there is a significant negative relationship between lymphedema, BMI, and peri-incisional perfusion. Additionally, we anticipate lower peri-incisional perfusion will be associated with wound healing complications at 3-month post-operative follow up.

METHODS: This study was approved by our institution's IRB. Informed consent was obtained from all research subjects prior to study procedures. Our study aims to investigate 46 patients (23 male and 23 female) undergoing primary TKA. All subjects will undergo standard of care pre-operative assessments of knee function using KOOS-JR and PROMIS Global Health patient reported outcomes (PROs), and body composition metrics using InBody Scan to assess characteristics including BMI and lymphedema. Intraoperatively, peri-incisional blood flow is measured using the SPY-PHI fluorescence imaging system immediately following TKA closure. Patients then return for a routine 3-month follow up for reassessment of post-operative knee function. A thorough chart review is conducted on subjects after 3-month follow up to assess evidence of wound healing complications via surgical team documentation and assessment notes. Upon completion of data collection, Kendall's Tau correlation will be used to investigate the relationship between BMI, lymphedema, and peri-incisional perfusion. Regression analysis will be completed to explore the relationship between BMI and PROs, BMI and wound healing complications, lymphedema and PROs, lymphedema and wound healing complications, peri-incisional perfusion and PROs, and peri-incisional perfusion and wound healing complications.

RESULTS: At the time of submission, 13 subjects have been enrolled into this study. 8 TKA surgeries have been performed with perfusion values obtained, and 2 patients have completed their standard 3-month follow-up visits. Descriptive statistics of 8 subjects to this point show an average pre-operative BMI of 37.1, systemic lymphedema level of 0.403, with operative side leg lymphedema measurements of 0.410 and non-operative side leg lymphedema measurements of 0.408 (**Table 1).** 8 perfusion values obtained at this point show highest median perfusion medial to the surgical incision (110%), with the lowest median perfusion measurements occurring at the center of the surgical incision (26.0%) and at the lateral to the incision (28.0%) (**Table 2).**

DISCUSSION: Ongoing data collection negates the use of advanced statistical analysis for preliminary findings. If completion of advanced statistical analysis supports the stated hypotheses, there will be significant impacts on intra-operative care. We anticipate the results will support implementation of a new standard of care where obese lymphadenopathic patients are scanned intraoperatively to indicate their level of risk for wound healing complications secondary to perfusion gradient measurements using the SPY-PHI system. While there are numerous methods of how to improve blood perfusion, such as the use of silver nitrate or hyperbaric chambers, future research should expand on the anticipated results of this study to assess and determine which method is most effective in treating obese lymphadenopathic TKA patients who are at a greater risk for post-operative wound complications.

SIGNIFICANCE/CLINICAL RELEVANCE: Our prospective study is the first documented utilization of the SPY-PHI fluorescent imaging system to investigate the role of perfusion in the development of wound complications in an obese and lymphadenopathic patient population, specifically in TKA. This study also demonstrates the importance of properly evaluating patients for lymphedema, a major risk factor for post-operative complications that is extremely underdiagnosed, due to its importance for risk stratifying patients for post-operative complications such as impaired wound healing.

ACKNOWLEDGEMENTS: We thank the Fraternal Order of the Eagles for supporting our research.

IMAGES AND TABLES:

Table 1. Demographic and Pre-operative InBody Metrics (n= 8)

Variable*	Median (Q1- Q3) or Count (%)
Age at Scan (year)	67.6 (65.3 - 71.3)
Sex	
Female	3 (37.5%)
Male	5 (62.5%)
Pre-operative BMI (kg/m^2)	37.1 (32.9 – 39.8)
Body Fat (%)	41.1 (38.8 – 43.2)
Water Retention Rate (ECW/TBW)	0.403 (0.397- 0.407)
Operative Leg ECW/TBW	0.410 (0.403- 0.412)
Non-operative Leg ECW/TBW	0.408 (0.399- 0.411)

*Data are presented as median (Q1- Q3) for continuous variables

Table 2. Post-operative Incisional Perfusion Gradients (n= 8)

Variable	Median (Q1- Q3)
Center of Incision (%)	26.0 (9.5 – 29.8)
Superior Incision (%)	44.0 (31.3 – 66.0)
Inferior Incision (%)	21.0 (13.8 – 48.5)
Medial to Incision (%)	110.0 (75.0 – 124.8)
Lateral to Incision (%)	28.0 (16.5 - 31.0)

Massive Transfusion Protocol at a Level 1 Trauma Center: A Quality Improvement Project

Jacob Sharafuddin, BA, Harnoor Singh Bhardwaj, MD, Colette Galet, PhD, Charles Knudson, MD/PhD, and Dionne Skeete, MD

Introduction. Hemorrhage is a leading cause of death after trauma, secondary only to nervous system injury. Clinicians must therefore act rapidly to restore homeostasis in hemorrhaging patients. Patients with significant blood loss often require massive transfusion (MT), traditionally defined as the transfusion of 10 or more packed red blood cells (pRBCs) within 24 hours. To ensure rapid and organized delivery of blood to hemorrhaging patients, hospitals have implemented massive transfusion protocols (MTPs) that define predetermined numbers of pRBCs, platelets, and plasma, as well as cryoprecipitate.

Purpose. Before April 2023, our institution's Blood Bank MTP contained 4 pRBCs and 3 plasma in each set with 1 platelet or a 5-pooled cryoprecipitate in alternating sets starting at set 2. In April of 2023, the MTP protocol was changed to have each set contain 6 pRBCs : 5 plasma : 1 platelet with cryoprecipitate no longer automatically included in each set. Our study's main purpose was to assess the impact of this quality improvement (QI) project. We hypothesized that although the newer shipments took longer to prepare, there would be fewer returned blood products, particularly cryoprecipitate. Additionally, we assessed whether patients with severe hemorrhage could be better defined using newer MT definitions such as the modern MT definition (10 or more pRBCs within 6 hours) and the substantial bleeding definition (1 pRBC within 2 hours and 5 pRBCs or death within 4 hours). We hypothesized that newer definitions would be better at identifying the need for activation of the MTP protocol.

Methods. This was a QI project. All MTs from March 2022 to March 2024 were reviewed. Changes in the MTP were implemented on April 1st, 2023. We queried the UIHC Blood Bank Database and medical records to collect data from each instance of an MTP ordered at our institution. Set preparation time and usage as well as return of cryoprecipitate, plasma, pRBCs, and platelets were collected to assess the impact of the QI on preparation time and blood product return. pRBC usage at 2, 4, 6, and 24 hours and mortality within 4 hours due to hemorrhage were collected to determine whether other MT definitions would be useful. We assessed trauma MTs separately from non-trauma MTs. Univariate analysis was performed to compare the pre- and post-implementation periods. Concordance and Fleiss Kappa tests were used to assess agreement between MT definitions. Receiver operating characteristic curve (ROC) was used to determine whether the modern MT definition and/or substantial bleeding definition was better at identifying MTs compared to the traditional MT definition. $P < 0.05$ was considered significant.

Results. For our trauma population, cryoprecipitate usage and return decreased (0.5 units before and 0 after, per set, $p < 0.05$ and 0.001, respectively). However, returned plasma products increased (3 units before to 7.5 after, per MTP episode, $p < 0.05$). Notably, there was no significant change in set preparation time ($p = 0.98$). Using the traditional MT definition, only 24 (25.8%) MTs were considered true positives. Similarly, only 21 (22.8%) and 37 (41.6%) MTs were considered true positives using the modern and substantial bleeding definitions, respectively. There was a high concordance (77.6%) and interrater agreement between the 3 definitions (Fleiss Kappa = 0.648, $p < 0.001$). ROC curve analysis showed that compared to the traditional MT definition, the modern MT definition was better at identifying MTP activation than the substantial bleeding definition (AUC = 0.938 [0.858-1] $p < 0.001$ and 0.814 [0.715 -0.914] $p < 0.001$, respectively).

Conclusion. Changes to our MTP did not significantly lengthen shipment preparation time but significantly reduced use and return of cryoprecipitate. However, plasma was returned more often which could represent wastage. Additionally, for future audits, the modern MT definition may be more accurate to use than the traditional one, as it is more sensitive. Finally, we found that clinical gestalt may not be the best way to call MTP cases, seeing as how less than 50% were true positives. It would be worthwhile to assess how clinical gestalt compares to established MTP scoring systems, as this may help lower the false positive rate. Analysis of the data for the non-trauma MTPs is underway.

Denervation of Lungs affects Airway Basal Cell phenotype and Function

Student: Kareem Shoukih
Mentor: Kalpaj Parekh, MBBS, Cardiothoracic Surgery

Lung transplantation, an effective treatment for patients with end stage lung diseases, is hampered by poor long-term survival compared to other organ transplants. This is due to the development of chronic lung allograft dysfunction (CLAD) in 50% of recipients by 5 years. CLAD is progressively fatal and there are no definitive diagnostic modalities or treatment options for this condition due to unclear mechanisms of pathogenesis. Therefore, there is a vital need to investigate mechanisms leading to development of CLAD. Our laboratory has shown that in CLAD there is depletion of airway basal cells and submucosal glands in allografts. During the lung transplant procedure, the lung is denervated, severing its connection to the nervous system. This study focused on understanding the regulatory role played by the nervous system in airway basal stem cell and submucosal gland proliferation and regulation which are important airway stem cell niches. We developed a ferret model of left lower lobe denervation by dividing the left lower lobe bronchus and reimplanting the lobe resulting in denervation like lung transplantation. Their lower right lobes served as innervated controls. To study the effect of denervation, these ferrets were injured with polidocanol (in the lower right and left lobes) to compare the basal cell regeneration following injury in innervated and denervated lobes. Quantitative analysis was done by immunofluorescence on structural and proliferative protein markers in the basal cells and submucosal glands to assess basal cell and submucosal gland health: Ki67, Axin2, P63, Keratin 5, Keratin 15, Keratin 14. Analysis thus far has suggested that the expression of markers such as P63 and Keratin 14 show a significant difference 14 days post injury between the denervated and innervated lobes. Further analysis will develop an early understanding of how basal stem cell phenotype in the lung airway is regulated by the nervous system. The data suggests that innervation may play a role in basal cell phenotype and function which may contribute to development of CLAD in the allografts. Future studies will investigate mechanistic insights into how the nervous system plays a role in regulating basal cell phenotype and health in lung airways.

Examining the Relationship Between Patellar Tendon Thickness and Tendinopathy with ACL Graft Success Rates

Student: Chirayu Shukla
Mentor: Robert Westermann

Abstract:

Introduction:

Graft failure after ACL reconstruction surgery is a devastating complication often requiring revision surgery to restore knee function and stability. Graft thickness and tendinopathy have been identified as potential risk factors; however, their relationship to graft failure has not yet been fully evaluated in bone-patellar tendon-bone (BPTB) autografts. This study aims to identify if decreased patellar tendon thickness and increased tendinopathy are associated with higher graft failure rates.

Methods:

We retrospectively reviewed a prospectively collected ACL reconstruction registry and identified patients with BPTB autografts who had a pre-operative MRI. Patellar tendon thickness was measured on sagittal view, and tendinopathy was graded as none, mild, moderate, or severe. We then performed a chart review to determine graft failure incidence and return to normal activity after revision surgery. Fischer's exact test and Wilcoxon sum rank test assessed significance.

Results:

We identified 147 patients, of which 6 (4.1%) had graft failure. Failed grafts had a mean thickness of 4.36 mm (SD = 0.29) compared to 4.77 mm (SD = 0.79) in the non-failure group. There was no significant difference in graft thickness between groups ($p=0.18$). Out of the 6 failures, 3 had proximal tendinopathy ($p=0.31$), and 1 had distal tendinopathy ($p=1$), but no significant difference was found.

Conclusions:

In this small sample size, we found no significant association between patellar tendon thickness or tendinopathy and graft failure following ACL reconstruction with BPTPB autograft. However, failed grafts trended towards decreased thickness and increased tendinopathy. Future studies are warranted.

The Effect of Spinal Analgesia on Peri-operative Outcomes after Lung Transplant

Aravin Sivamurugan BS, Satoshi Hanada MD

Introduction: Lung transplant is the definitive treatment option for patients with end-stage lung diseases. In the post-operative setting, pain control is crucial for overall success. In cardiothoracic surgeries, the use of intrathecal morphine has been reported to reduce postoperative pain for up to 48 hours. However, there is currently limited evidence to support its use in lung transplant surgeries. Following thoracic surgery, the management of acute pain is critical to facilitate respiratory weaning as early extubation is associated with better outcomes. It is a common practice to place a thoracic epidural postoperatively for pain control either before or after endotracheal extubation in the ICU. However, intrathecal morphine may offer better pain control during the immediate postoperative period and ease the transition to epidural analgesia. Understanding the importance of pain control in the post-op setting in these cases, the University of Iowa Hospitals and Clinics (UIHC) has utilized preoperative administration of intrathecal morphine in lung transplant surgery, although its adoption varied among practitioners.

Aims: In this study, we examined the impact of intrathecal morphine in lung transplant by comparing the outcomes between patients who received intrathecal morphine and those who did not. We hypothesized that preoperative administration of intrathecal morphine provides similar pain control during the immediate postoperative period while decreasing systemic opioid dosage.

Methods: We retrospectively reviewed 131 lung transplant cases were performed between November 1, 2010, and February 28, 2020. Intrathecal morphine was administered preoperatively in 32 cases (ITM group) and was not administered in 99 cases (Control group). The primary outcome measures were the average pain score within 24 hours postoperatively and at the time of endotracheal extubation. Secondary outcomes included the length of ICU and hospital stays, as well as Opioid use measured in milligram morphine equivalent (MME). Normality of the primary and secondary outcome variables was assessed by the Shapiro-Wilk test. Statistical tests of significance were used to assess differences between the two groups. No significant differences were observed in characteristics such as age, gender, or indications for surgery between the two groups.

Results: From our analysis, there was not a significant difference in the average pain score during the first 24 hours after ICU admission or at the time of extubation between the ITM and Control groups (6.6 vs 6.0, $p = 0.120$). Patients in the ITM group did, however, require fewer opioids intraoperatively (75 vs 90, $p = 0.03$). Opioid use in the postoperative period was lower, but not significant in the ITM group (128 vs 143, $p = 0.397$). There was also no difference between the groups regarding the length of ICU stay and total length of hospital stay.

Conclusion: Our findings indicate no difference in pain scores with the use of intrathecal morphine in lung transplant surgeries and a significant reduction in the use of systemic opioids intraoperatively period. Though our sample size is small and there are confounding factors that could potentially affect the subjective evaluation for the effect of ITM, further studies with larger sample sizes could fully elucidate the effects of ITM.

Drosophila models of *TMEM43*-associated Emery-Dreifuss muscular dystrophy reveal disease mechanisms

Jessica F. Smith
Mentor: Dr. Lori L. Wallrath
Department of Biochemistry and Molecular Biology

Mutations in the *TMEM43* gene encoding Transmembrane Protein 43 (TMEM43) cause Emery-Dreifuss muscular dystrophy (EDMD), a genetic, degenerative disease primarily affecting specific skeletal muscles. EDMD presents with muscle atrophy in the shoulders, upper arms, and calves as well as joint contractures. Frequently, cardiac conduction defects and arrhythmias co-occur with the loss of skeletal muscle function. While EDMD has been associated with mutations in several genes encoding nuclear envelope (NE) proteins, including *TMEM43*, the molecular mechanism underlying the disease is not well understood. Two point mutations in *TMEM43* that cause single amino acid substitutions (p.E85K and p.R268W) were identified in EDMD patients. To determine how these substitutions affect skeletal muscle, the equivalent substitutions were generated in the orthologous Drosophila *CG8111* gene using CRISPR genome editing and larval body wall muscles were analyzed. These substitutions cause chromatin protrusions from the nucleus and cytoplasmic DNA that are recognized by the DNA binding protein Barrier to Autointegration Factor (BAF). The nuclei of *TMEM43* mutants show elevated levels of phospho-histone H3, indicating a lack of chromatin decondensation. Taken together, these findings suggest that mutations in *TMEM43* alter the integrity of the nuclear envelope leading to nuclear rupture and a loss of chromatin decondensation suggestive of genome-wide changes in gene expression.

Title: Comparing the effects of netarsudil and ripasudil, two rho-kinase inhibitors, in the treatment of Fuchs endothelial corneal dystrophy

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Background: Fuchs Endothelial Corneal Dystrophy (FECD) involves a progressive deterioration in corneal endothelial cell (CEC) health, resulting in corneal edema and vision loss. Affecting approximately 300 million people worldwide, FECD is the leading cause of corneal transplant (keratoplasty) in the US. Currently, keratoplasties are the primary treatment for FECD. With declining access to corneal donor tissue and high failure rate of keratoplasties, recent research has focused on using topical rho-kinase inhibitor therapies. These treatments focus on stimulating the growth and migration of functional CECs in patients undergoing Descemet stripping only (DSO) surgery and in preventing disease progression to the point of requiring transplantation. RKIs, such as netarsudil (FDA-approved) and ripasudil (approved in Japan), have demonstrated potential in enhancing CEC density, improving intercellular adhesion, promoting cell migration, and reducing apoptosis.

Purpose: To conduct a comparative study of netarsudil and ripasudil, two rho-kinase inhibitors, in the treatment of FECD. The goal is to provide critical insights into the feasibility and noninferiority of netarsudil as a potential treatment for FECD in the US.

Hypothesis: Netarsudil is as effective and safe (noninferior) as ripasudil in the treatment of FECD making it a feasible alternative for FECD treatment in the US and reducing the burden caused by the lack of corneal donor tissue.

Methods: The efficacy of netarsudil and ripasudil was assessed through gap closure assays using FECD phenotype cell cultures. Corneal endothelial cells (CECs) were cultured to confluency in gap assay chambers. Once confluent, the chambers were removed to create a defined gap. At time=0, the CECs were treated with either control saline, netarsudil or ripasudil and imaged every 8 hours over a 72-hour period. Gap closure and CEC proliferation were measured using ImageJ software.

Results: **Netarsudil was noninferior to ripasudil in promoting CECs to reach full confluency at lower concentrations.** At concentrations of 0.01 μM and 0.10 μM, netarsudil outperformed both the control and ripasudil, particularly early in the healing phase, as observed in gap closure assays. However, at higher concentrations, specifically 1.00 μM, the effectiveness of netarsudil decreased and became inferior to both the control and ripasudil in gap closure assays. However, regarding cell counts, netarsudil underperformed at all three concentrations. We are in the process of finalizing the collection of morphometric data, essential for evaluating the cellular impacts of these treatments. This analysis will assess whether netarsudil is noninferior to ripasudil in preventing FECD-like phenotypes, which include increased CEC area, reduced CEC density, decreased hexagonality, and higher multinucleation. These metrics are critical indicators of cellular health and function in FECD, and their assessment will offer a thorough comparison of the efficacy of netarsudil versus ripasudil.

Conclusions: While netarsudil demonstrated noninferiority to ripasudil in the initial gap closure assays, ongoing collection of morphometric data is crucial for a thorough evaluation. A detailed understanding of netarsudil's potential in preventing FECD progression may uncover new therapeutic options.

Main Title: Predictive value of preoperative CT assessment in submandibular sialolithiasis surgical treatment

Authors: Edward Tannenbaum BA[1], Claire Orth BS[1], Piper Wenzel, BS,[1] Ben Fick MD,[2] Kailey Henkle MS[3], and Henry Hoffman, MD MS[4]

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Introduction:
Density and composition of renal calculi have been reported to be factors affecting the surgical outcomes of nephrolithiasis treatment. There has been limited research evaluating the role of these factors in the management of salivary stones.

Purpose:
Investigate the relationship between preoperative CT density assessment and clinical outcomes of submandibular sialolithiasis surgical management.

Methods:
A retrospective review was conducted of a consecutive series of patients who underwent surgical treatment for submandibular sialolithiasis between 2013 and 2018 at an academic institution by a single surgeon with follow-up by chart review. A focus on initial surgical treatment at our institution provided review of three categories: (a) 49 gland preserving procedures without the use of laser lithotripsy, (b) 7 gland preserving procedures with the use of laser lithotripsy, and (c) 26 gland resections. Data collected for analysis included patient age, sex, density of stone in Hounsfield Units (HU), stone volume, HU density (defined as stone density divided by volume), stone length, number of stones, location of stones, procedure information, persistent symptoms, and subsequent treatment. Additional radiomic parameters were obtained for each stone to further assess correlation to clinical outcomes. Successful outcome was defined as relief of pain and swelling after the initial surgical treatment without need for subsequent treatment identified during the follow-up period defined.

Results:
Median follow up durations for gland preserving procedures without laser, gland preserving procedures with laser, and gland resections were 20 days, 76 days, and 8 days, respectively. Successful outcome was identified in 83.7% (41/49) of the gland preserving procedures performed without laser, 57.1% (4/7) of the gland preserving procedures performed with laser, and 100% (26/26) of the gland resections. Proximal stone location was noted on CT in 33% (16/49) of the gland preserving surgeries without laser, 100% (7/7) of the gland preserving procedures with laser, and 81% (21/26) of the gland resections ($p<0.001$). Of the patients treated with gland resection, presence of a large, proximal stone was identified as the primary indication for gland removal in 69.2% (18/26) of cases. Among the 8 other gland resection cases, 75% (6/8) had small to moderate size (5 mm or less), proximally located stones as well as abnormal ductal anatomy as the primary reason for gland removal. For each of the three procedures performed, there were no significant differences in stone density, volume, HU density, and length when comparing successful and unsuccessful outcomes. In gland preserving procedures without laser, the number and location of stones differed significantly when comparing successful and unsuccessful outcomes. Patients with multiple stones ($p=0.028$) and stones in the middle third of the submandibular duct ($p=0.033$) had a higher proportion of unsuccessful outcomes.

Conclusions:
The location of calculi may affect the outcome of submandibular stone treatment and is an important variable to consider in preoperative evaluation of surgical management options.

COPD Subtypes and Risk of Cognitive Dysfunction

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Background: Chronic Obstructive Pulmonary Disease (COPD) is a leading cause of death worldwide. Between 30 and 60% of patients diagnosed with COPD experience cognitive impairment. The definition of COPD is evolving beyond a historical focus on spirometry alone and its heterogeneity is increasingly recognized. Phenotyping work within the multi-site longitudinal COPDGene study has identified subgroups of patients with differential risks for poor clinical outcomes. Factor analysis of COPDGene lung CT and spirometry data has identified 4 factors/subtypes: airway predominant disease (APD), emphysema predominant disease (EPD), gas trapping (GT), and hyperinflation (HI). APD and EPD have been associated with mortality and APD with systemic inflammation and cardiovascular comorbidities. The current analysis leveraged COPDGene data regarding COPD subtypes together with objective cognitive assessment data obtained approximately 5 years later.

Aims/Hypothesis: We hypothesized that APD would be associated with a higher prevalence of cognitive impairment as assessed using the Mini-Cog in the complete COPDGene cohort, and that patients with high risk APD would also have increased risk of cognitive impairment on comprehensive neuropsychological testing, specifically in the executive function and processing speed domains.

Methods: COPDGene is a 21-site cohort project that originally enrolled individuals with >=10 pack-years of cigarette smoking exposure and has completed three phases to date. The four subtypes were identified by combining 21 spirometric and chest CT measures from Phase 2 using factor analysis and the Mini-Cog was administered during Phase 3 with probable cognitive impairment (PCI) defined as a score <=3. Phase 3 occurred an average of 5.22 years after Phase 2. A subset of participants with no prior cognitive/neurological conditions completed comprehensive neuropsychological testing an average of 4.15 years after their Phase 2 visit as a part of a single site study. Normatively adjusted cognitive domain t-scores were derived for 6 domains (executive function, language, memory, attention, visuospatial, and processing speed). We used logistic regression to examine the association between the four COPD factors and PCI on the Mini-Cog and linear regression with the factors and continuous cognitive domain t-scores as the outcome. All models included the following covariates selected based on prior research: age, gender, BMI, education, and symptoms of anxiety. Significance was set at $p = 0.05$ for each model.

Results: 2646 COPDGene participants with complete Phase 2 and Mini-Cog data were included (mean 64.5±8.3 years old, 48.7% male). 593 (22.4%) met criteria for PCI. Logistic regression demonstrated that greater APD (beta = 0.26; $p< 0.001$) and lower hyperinflation (beta = -0.15; $p = 0.003$) were associated with PCI after covariate adjustment. 119 participants (mean 71.5±7.2 years, 50.4% male) with Phase 2 factor data and comprehensive neuropsychological testing were included in the domain-specific analysis. APD was significantly associated with worse performance in the executive function (-1.90; $p = 0.007$) and language (-2.16; $p = 0.034$) domains in the adjusted models.

Conclusions: We observed that APD was associated with cognitive dysfunction among individuals with cigarette smoking history. This association held among both an unselected sample assessed using a dementia screening tool and a subset of individuals with no known history of cognitive disorder diagnosis assessed by reduced performance on comprehensive executive function and language measures. These findings raise the possibility that APD may place individuals with a smoking history at greater risk for cognitive dysfunction, potentially via inflammation and cardiovascular comorbidities, even early in disease before cognitive impairment reaches threshold for diagnosis.

Optimizing Non-opioid Analgesia Timing after Cesarean Section

Student: Anna Townsley, BS, Carver College of Medicine
Mentor: Stephanie Radke, MD, MPH, Department of Obstetrics and Gynecology

Background: Cesarean sections are associated with moderate-to-severe postoperative pain, which can often be under-treated or underestimated. The American College of Obstetricians & Gynecologists (ACOG) recommends a stepwise, multimodal analgesic approach including nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen with oral opioids reserved for breakthrough pain. Scheduled NSAIDs and acetaminophen have been shown to be most effective for pain reduction. However, the optimal timing of this scheduled non-opioid analgesia following cesarean section has not been determined.

Purpose: In this study, our institution implemented a quality improvement intervention to compare staggered verses combined dosing of acetaminophen and NSAIDs following cesarean section in an effort to decrease postpartum pain scores and opioid utilization. As a proxy for nursing convenience, we also analyzed the timeliness of the administration. We hypothesized that the combined dosing regimen would result in decreased pain scores, reduced opioid utilization, and improved timeliness of administration. The invention did not change the total amount of NSAIDs and acetaminophen scheduled for each patient, but rather focused on the scheduling patterns of these medications to determine the optimal timing for our institution.

Methods: This quality improvement planned experiment evaluated all patients who delivered a newborn by cesarean section at University of Iowa Health Care in Iowa City postpartum units from May 13st, 2024 to August 26th, 2024. Patients were excluded for having NSAID, acetaminophen, or opioid allergies, receiving general anesthesia, receiving medication for opioid use disorder, and having a hysterectomy at time of cesarean section.

The historical orders for cesarean delivery postoperative analgesics included 650 mg acetaminophen every 4 hours and NSAIDs consisting of 30 mg ketorolac every 6 hours for 24 hours followed by 600 mg oral ibuprofen every 6 hours. These were started based on time of order signing. With historical orders, administration was overall staggered with every third dose of acetaminophen and second dose of NSAIDs being administered together. 5 to 10 mg oxycodone was available every 4 hours as needed for breakthrough pain. Feedback from nursing staff suggested this was an inconvenient pattern of medication administration. The decision was made to increase acetaminophen dose to 975 mg every 6 hours, however the medical literature was inconsistent on whether to administer this combined or staggered with NSAIDs. Two versions of an updated medication schedule were tested during this study for 5 weeks each to compare staggered verses combined timing of the existing multimodal analgesia of ibuprofen and acetaminophen, both administered every 6 hours.

Baseline demographic, pregnancy, and delivery characteristics were obtained for each patient who underwent cesarean section. The primary outcome of interest was average perceived pain on a numeric pain scale from 0-10 along with the patient's perception of whether the pain is acceptable or unacceptable. Secondary outcomes include average postoperative opioid usage per day (milligram morphine equivalents/day), length of stay (hours), average postoperative acetaminophen and NSAID usage per day (mg/day), and timeliness of dose administration.

Results: Data collection is still ongoing until all patients who delivered by cesarean section before 8 am on August 26th are discharged from the hospital. No results can be determined as of yet.

Conclusion: Overall, this study will be able to add more insight into optimal pain management following cesarean section.

Functional Characterization of a Novel Brugada Syndrome Gene

Student: Linh Tran

Mentor: Barry London, MD, PhD

Collaborator: Jin-Young Yoon, PhD

Introduction: Brugada syndrome (BrS) is an inherited arrhythmia syndrome that is responsible for up to 1 in 3 sudden cardiac death (SCD) cases in patients with seemingly normal hearts. Initially, autosomal dominant loss-of-function mutations in the *SCN5A* gene—responsible for encoding the main cardiac sodium channel $Na_V1.5$—comprised the sole known genetic etiology of BrS. However, the advancement of massively parallel sequencing technology has led to the discovery of BrS-associated variants in over 20 other genes. Because a majority of patients with diagnosed BrS lack a clear genetic diagnosis, it is difficult to perform comprehensive genetic risk assessments for first-degree relatives and in turn work to prevent BrS-caused SCD.

The London Lab previously identified via segregation analysis of a large multigenerational family a putative BrS-causing variant of the *DEPDC5* gene, DEPDC5-R116L. Although the data collected at the time did not indicate the presence of a direct interaction between *DEPDC5* and *SCN5A*, they did not preclude the possibility that *DEPDC5* acts as a modulator of sodium current, especially given preliminary findings that *DEPDC5* knockout recapitulated BrS phenotype in murine models placed under pharmacologic stress.

Hypothesis: We hypothesize that a variant of the *DEPDC5* gene, DEPDC5-R116L, previously unassociated with Brugada syndrome, is mechanistically involved in BrS cases of unknown genetic origin, potentially via interactions with primary cardiac sodium channel $Na_V1.5$.

Methods: Previous efforts to functionally characterize *DEPDC5* in relation to $Na_V1.5$ via whole-cell patch clamping of HEK293T cells did not demonstrate a change in inward Na^+ current. Thus, our intention was to functionally characterize *DEPDC5* in more physiologic cell culture models. Wild-type DEPDC5 (DEPDC5-WT) and DEPDC5-R116L plasmids were transfected into Dudley cells—a HEK293T cell line overexpressing *SCN5A*—and freshly isolated neonatal rat cardiomyocytes (NRCMs). Both transfected cell types were later harvested for Western blotting and quantitative PCR analysis. Primary antibodies compatible with both cell types were identified and primers for qPCR analysis were generated. Both transfected cell types were additionally used in whole-cell patch clamp studies on inward Na^+ current. A DEPDC5 knockdown study utilizing shRNA viral plasmid for both cell types was also initiated.

Findings/Results: Western blot data suggest that DEPDC5-R116L reduces protein expression of DEPDC5 in comparison to wild type when normalized to a control protein in both Dudley cells and NRCMs. No difference in $Na_V1.5$ protein expression was observed in either cell type. qPCR analysis indicates no difference in cDNA levels between NRCMs transfected with DEPDC5-R116L and those transfected with DEPDC5-WT. Tentative qPCR data suggest cDNA levels may be reduced in Dudley cells transfected with DEPDC5-R116L compared to those transfected with DEPDC5-WT. Electrophysiological whole-cell patch clamp data proved inconclusive.

Conclusion: The reduced expression of DEPDC5 protein in Dudley cells and neonatal rat cardiomyocytes transfected with DEPDC5-R116L in comparison to DEPDC5-WT suggests that the identified mutation may exert an autoinhibitory effect on DEPDC5 protein synthesis. To draw a mechanistic link between this potential effect and the etiology of Brugada syndrome, further electrophysiological studies are required. Thus far, only the primary cardiac sodium channel $Na_V1.5$ has been studied. Future studies should investigate the effects of DEPDC5-R116L on other potential culprits for BrS etiology such as cardiac potassium and cardiac calcium channels. The completion of a knockdown study will also help paint a clearer picture of the potential role of DEPDC5 in BrS and BrS-caused SCD. Ultimately, functional characterization of novel BrS genes will help physicians provide more comprehensive genetic counseling for families and diagnoses for patients as well as improve the application of preventative treatments for at-risk individuals.

Abstract Title: Exploring the Links Between Cardiorespiratory Fitness and the Neurodegenerative Biomarkers Neurofilament Light Chain and Glial Fibrillary Acidic Protein in Older Adults.

Tuan Truong, BS, Liam Campbell, BA, Kelsey Baller, BS, Chris Oehler, MS, Li-Chun Lin, PhD, Gary Pierce, PhD, Michelle Voss, PhD

Introduction: Neurodegenerative diseases, such as Alzheimer's and related dementias (ADRD), pose major health challenges, particularly in older adults. Exercise, which can result in enhanced cardiorespiratory fitness (CRF), has been widely recognized for its potential to mitigate ADRD risk. Neurofilament light (NfL) and glial fibrillary acidic protein (GFAP) are biomarkers linked to neurodegeneration, with elevated NfL indicating neuronal damage and elevated GFAP indicating neuroinflammation. These brain-derived biomarkers can be measured in blood serum as a means to evaluate levels in the brain. Our study examines the relationship between CRF and these biomarkers, while also considering the effects of BMI, dilution effects, metabolic and vascular health, and medication use.

Hypothesis: We hypothesized that higher CRF would be inversely associated with serum concentrations of NfL and GFAP, suggesting a protective effect.

Methods: We conducted a cross-sectional study with 80 participants (mean age 63.3 $\pm$ 5.49 years, 64.2% female, mean education 16.5 $\pm$ 2.19 years) to investigate the relationships between CRF (measured by VO_2 max) and fasted blood serum concentrations of NfL and GFAP. Hierarchical linear regression models were used to assess the relationship of VO_2 max with NfL and GFAP with covariates that included BMI, age, sex, and education. Post hoc analyses examined the independent roles of CRF and BMI, and explored roles of cardiometabolic measures, medication use, and potential dilution effects. Similar regression models were also conducted using maximum wattage output on a stationary cycle as an alternative fitness measure not confounded by BMI. All analyses were conducted using Jamovi software, with significance set at $p < 0.05$.

Results: The hierarchical regression models revealed that VO_2 max did not significantly predict serum concentrations of NfL ($\beta = 0.189$, $p = 0.299$ and GFAP ($\beta = -2.200$, $p = 0.186$). Instead, BMI was a significant predictor, with increased BMI associated with decrease in both serum NfL ($\beta = -0.269$, $p = 0.014$) and GFAP ($\beta = -2.59$, $p = 0.010$). Additionally, BMI mediated the effects of VO_2 max on both NfL (Indirect Effect = 0.157, 95% CI [0.04, 0.333], $p = 0.036$) and GFAP (Indirect Effect = 1.8, 95% CI [0.691, 3.246], $p = 0.005$). Further exploratory analyses were conducted to assess these relationships. Accounting for differences in blood volume (EBV) across BMI in participants revealed that EBV did not mediate the inverse relationship between BMI and the biomarkers, suggesting that the observed effects were not primarily driven by a dilution effect. Additionally, incorporating analysis of metabolic and vascular measures, along with medication use, confirmed that BMI's impact on NfL and GFP was independent of such factors. This reinforces the robustness of the association between higher BMI and lower NfL and GFAP. When using wattage output as an alternative measure of fitness, wattage also did not predict serum concentrations of NfL and GFAP. When mediation analysis was conducted, we found no mediating effect of BMI on the relationship between wattage and the biomarkers NfL and GFAP.

Conclusion: Our findings suggest that cardiorespiratory fitness, as measured by VO_2 max, does not significantly predict serum concentrations of NfL and GFAP. Instead, BMI plays a more significant role, showing an inverse relationship with these biomarkers, which persisted even after considering potential confounding factors such as blood volume variance across BMI, metabolic and vascular measures, and medication use. While these results may appear to challenge the conventional view that higher BMI is associated with adverse health outcomes, they suggest that the relationship between BMI and neurodegenerative biomarkers may be more complex than previously thought. This highlights a need for further investigation into mechanisms underlying this association and the role of BMI in neurodegenerative processes, particularly given the absence of a mediating effect when using power output as an alternative fitness measure.

Revisiting the Lille Score: A Measure of Survival, rather than Steroid Response, in Patients with Acute Alcohol-Associated Hepatitis?

Student: Betty H Tu
Mentor: Kyle E. Brown

Introduction/Background:

Acute alcohol-associated hepatitis (AAH) is a common and serious complication of heavy alcohol use. Corticosteroids (CS) are the mainstay of treatment for AAH, however only about 60% of AAH patients respond to CS. Because of the adverse effects of high-dose CS, a metric called the Lille score was developed in 2007 to assess early response to treatment. The 2007 study reported that Lille score ≥0.45 was associated with decreased 6-month survival. However, all the patients whose data went into the formulation of the Lille score were treated with CS, thus equating patient survival with response to CS treatment. The assumption that survival in AAH is synonymous with response to CS is contradicted by the observations that some AAH patients survive despite their liver chemistries failing to improve while on CS or even having received no CS treatment at all.

Hypothesis/Objectives:

To assess whether a Lille score of <0.45 predicts survival in patients with AAH, independent of corticosteroid treatment status.

Methods:

Demographic, clinical, and biochemical data were collected from the electronic medical records of patients admitted to UIHC from January 1, 2010 to December 31, 2021 with a diagnosis of severe AAH (N = 603). These 603 patients represented 640 unique episodes of AAH. Lille scores, which incorporate change in total bilirubin and other laboratory parameters after starting CS, were calculated for each AAH episode either 4-7 days after CS initiation (in those treated with CS) or 4-7 days after admission in those who did not receive CS. Mortality within 28 days and within 180 days from admission were also recorded.

Results:

Of the 640 episodes of AAH, the Lille score was <0.45 in 320 episodes and ≥0.45 in the other 320 episodes. A significantly greater proportion of patients with Lille score >0.45 died within 28 days of admission compared to those with Lille score <0.45 (45.6% and 10.3% respectively, $p < 0.001$). Lille score ≥0.45 was associated with significantly greater odds of 28-day mortality than Lille score <0.45 (OR 7.30, 95% CI [4.79-11.13], $p < 0.001$). The relationship remained significant after adjusting for the variables used to calculate the Lille score and the presence or absence of steroid treatment (OR 2.33, 95% CI [1.22-4.48], $p = 0.011$).

Conclusions/Significance:

In patients with AAH, Lille score ≥0.45 is associated with greater 28-day mortality regardless of steroid treatment status. This data suggests that the Lille score is useful as a predictor of outcome, but not specifically as a metric for assessing response to CS treatment, in patients with AAH.

Surrogate Measures of Awareness during Endotracheal Intubation: A pilot observational study to evaluate patient anesthetic state during endotracheal intubation.

Laura Ulibarri, Yana Zemkova, Joseph Crum, Shannon Findlay, Anita Chazhikattu, Kevin Doerschug, Eliezar Santos Leon, Jacob Hampton, Brett Faine, Sydney Krispin, Sarah Hackbarth, Taylor Bentler, Sam Parnia, Brian Fuller, and Nicholas Mohr

Abstract

Study Objective: As sedation has become an important component of many medical procedures including rapid sequence intubation (RSI), there has been a growing concern for awareness during paralysis. These incidents have been shown to have lasting negative psychological impacts on patients. Our primary objective was to determine the depth and duration of sedation and paralysis associated with clinical doses of common RSI medications in the intensive care unit at the University of Iowa with a secondary objective to evaluate what proportion of these patients recall their experiences and demonstrate evidence of implicit learning.

Methods: This was a single site, observational, pilot study of participants who underwent rapid sequence intubation in the intensive care unit. Patients were excluded if they were non-English speakers, prisoners, or declined participation. During the period of sedation and paralysis, we obtained Bispectral Index (BIS) monitoring scores to assess sedation level and train of four (TOF) to assess paralysis duration (primary objectives). After obtaining delayed consent from the patient and/or LAR, we also obtained pertinent past medical history, laboratory analysis, and the medication administration via EPIC chart review. If a participant regained consciousness, we assessed patient recall of events utilizing the modified Brice questionnaire and implicit learning by asking patients to name three fruits (which were played via Bluetooth headphones during the RSI procedure and period of sedation/paralysis). These surveys were independently adjudicated by three independent, expert reviewers to determine the possibility of awareness with paralysis.

Results: Of the first 4 participants, 4/4 (100%) had a period with a BIS score greater than 60 (suggesting awareness) prior to the end of pharmacologic paralysis. The mean of the participants' highest BIS score prior to return of train of four was 82.5. The mean of the lowest was 39. The most used sedatives for induction included: ketamine and etomidate (each given to 2/4 (50%) of participants), and rocuronium was used as a paralytic for 4/4(100%) participants. The mean time elapsed prior to the start of a sedative infusion was 21.5 minutes.

Of the 3 participants who were extubated, 1 participant (33%) recalled events during their period of paralysis. No participants were able to name all three fruits played via Bluetooth headphones during their period of sedation and paralysis.

Conclusion: A significant proportion of patients who undergo RSI in the ICU have evidence of awareness during the period of paralysis, leading to the possibility of unpleasant memories. Our findings show the need for further investigation in to the awareness during paralysis so we may better understand how to prevent long-term psychologic sequalae of critical illness.

Conflict of Interest Statement:
There are no conflicts of interest.

Version 1 8/26/24

The relationship between hypertension and an epigenetic biomarker of alcohol use during alcohol withdrawal

Rachel Valente B.S., Allan Andersen M.D., Rob Philibert, M.D., PhD

Alcohol withdrawal syndrome (AWS) is a common and potentially fatal condition that affects millions of individuals annually. Symptoms of AWS include anxiety, autonomic hyperreactivity, tremor, and seizures, and severe alcohol withdrawal syndrome (SAWS) may lead to delirium, acute coronary syndrome, cerebrovascular accident, and death. Currently, clinical tools such as the Prediction of Alcohol Withdrawal Severity Scale (PAWSS) are used to predict the development of SAWS, with a PAWSS score of 4 or more, for example, being associated with a likelihood ratio of 174 for SAWS. However, better tools for predicting SAWS are needed. Recently, an epigenetic biomarker of alcohol use, the CpG cg07375256 located in *ZSCAN25*, a gene previously linked to hypertension, was shown to be a highly sensitive and specific predictor of SAWS including requiring phenobarbital treatment and the development of seizures. Here we examine whether *ZSCAN25* methylation may predict changes in blood pressure (BP) during the course of AWS. In a sample of n = 125 patients recruited from a large midwestern academic hospital, we demonstrate that *ZSCAN25* methylation predicts the change (maximum recorded BP – discharge BP) in diastolic ($p < 0.05$) but not systolic BP during hospitalization, after correction for age. In contrast, the PAWSS did not predict changes in systolic or diastolic BP during hospitalization. This finding suggests that measurement of *ZSCAN25* methylation may improve clinicians' ability to predict and manage exacerbations of hypertension during the course of AWS, potentially reducing morbidity and mortality.

Determinants of Neuropsychological Outcomes after Aneurysmal Subarachnoid Hemorrhage

Student: Alexander Van Dam, M1

Mentor: Edgar Samaniego, MD, MS
Collaborator: Elena Sagues, MD

Introduction: Aneurysmal subarachnoid hemorrhage (aSAH) is an event associated with high rates of mortality and morbidity. Despite evidence of cognitive deficits in up to 70% of aSAH survivors, factors contributing to cognitive decline remain unclear. The cognitive and behavioral changes observed following aSAH result in a substantial loss of productivity and a diminished quality of life. This is particularly devastating as aSAH primarily affects young patients with a mean age of 55.

Objective: The purpose of this study is to identify risk factors for cognitive deficits and aid in establishing criteria for predicting neuropsychological function following aSAH.

Methods: Acute comorbidities during hospitalization, and relevant clinical and radiological variables were collected for each patient. Hemorrhage volume was calculated using semi-automated software that analyzed head computed tomography (CT) scans obtained on admission. Cognitive function was evaluated using a brief telephone battery, including the blind version of the Montreal Cognitive Assessment (MoCA-22), and the Verbal Fluency Test (phonemic). Cognitive exam scores were normalized based on age, sex, and years of education. Behavioral and Quality of Life outcomes were assessed using the Beck Depression Inventory 2nd edition (BDI-II) and the Stroke Specific Quality of Life Scale (SS-QOL).

Results: We prospectively enrolled 165 patients with aSAH. The cohort was divided into two groups according to the time from aSAH to cognitive evaluation. The short-term follow-up group included 38 patients which underwent evaluation 3 to 12 months post-aSAH while the long-term follow-up group included 127 patients and underwent evaluation 1 to 15 years post-aSAH. In short-term follow-ups higher mRS at discharge ($p=0.006$) was significantly associated with impaired cognition. The multivariate model for short-term follow-ups achieved an AUC of 0.788, sensitivity 80%, specificity 77% and accuracy 79% for predicting cognitive recovery. In long-term follow-ups greater Hunt and Hess grades ($p=0.013$), greater modified Fisher grades ($p=0.010$), greater number of days hospitalized ($p=0.023$), and new ischemia during hospitalization ($p=0.013$) were significantly associated with impaired cognition. The multivariate model for the long-term follow-ups achieved an AUC of 0.706, sensitivity 85%, specificity 50% and accuracy 72% for predicting cognitive recovery. Of the 165 total patients, 133 patients had “good functional outcomes” with a mRS score of 0-2 at discharge. MoCA scores were significantly lower in patients with new ischemia during hospitalization ($p=0.042$). We also found that VFT z-scores were significantly lower in patients that developed intraparenchymal hemorrhage during hospitalization ($p=0.030$). A total of 44 patients returned completed SS-QoL and BDI-II questionnaires. Linear regression determined that radiological vasospasm (β -0.40, $p=0.006$, table 5), DCI (β -0.37, $p=0.012$) and higher Hunt and Hess grades (β -0.30, $p=0.053$) are the most relevant predictors of worse quality of life post-aSAH. When evaluating the entire cohort, we found that larger total hemorrhage volume at admission was significantly correlated with poor cognition post-aSAH ($\exp(\beta)$ 0.97, $p=0.048$).

Conclusions: In the first year after aSAH , mRS at discharge is an independent predictor of cognitive function. In the long-term, the utility of severity scales to predict cognitive outcomes diminishes while new ischemia during hospitalization emerges as an independent predictor. The trajectory of short-term and long-term cognitive outcomes are influenced by total hemorrhage volume. In addition to hemorrhage volume, patients who experience ischemia or vasospasm post-aSAH face greater deficits in cognition and quality-of-life even in cases of positive functional outcome metrics.

Correlation of Lymph Node Characteristics and Extranodal Extension in Oral Cavity Squamous Cell Carcinoma

Piper Wenzel, BS; Steven Van Meeteren, BA; Nitin Pagedar, MD MPH; Marisa Buchakjian, MD PhD

Background: Extranodal extension (ENE), defined as tumor extension beyond the lymph node capsule, is considered an important prognostic factor for recurrence and survival in oral cavity squamous cell carcinoma (OCSCC) (Snow et al 1982, Ghadjar 2010, Arun 2020). The 8th edition of the American Joint Committee on Cancer (AJCC) staging manual has incorporated ENE as a poor prognostic indicator, reflecting the significance of ENE for cancer management (Amin 2017). N-classification is affected by presence or absence of ENE but not by quantification of the size of ENE. Not only is the presence of ENE important, but also the extent has been shown to affect prognostic outcomes. Specifically, ENE classified as major (>2 mm) has been associated with worse overall survival compared to minor (≤2 mm) ENE (de Almeida 2024, Wreesmann 2016). Previous reports have documented the mean size of ENE to be 2 mm (range, 1-10) in head and neck SCC and 3.5 mm (SD 4.1) in OCSCC (Ghadjar 2010, de Almeida 2024). It has been suggested that future staging systems incorporate stratification by ENE extent (de Almeida 2024).

Lymph node ratio (LNR), defined as the ratio of lymph nodes positive for metastasis to total number of lymph nodes removed, has been reported to impact survival outcomes in oral cavity squamous cell carcinoma as well (Nocon 2021, Struckmeier 2024, Ding 2019). Specifically, LNR has been demonstrated to be significantly associated with overall survival, progression free survival, disease-free survival, and distant metastasisfree survival (Struckmeier 2024, Ding 2019). High LNR and presence of ENE have been associated in some studies while LNR was not found to be a predictor of ENE in Mair et al. (Ding 2019, Feng 2017, Sundaram 2023, Mair 2018). Additional studies are needed to further elucidate the relationship between LNR and ENE (Ding 2019). Size of metastatic deposit is another lymph node characteristic that has been reported to be correlated with presence of ENE (Snow 1982, Don 1995, Woolgar 2003, Ghadjar 2010, Arun 2021).

Much of the currently available literature identifying relationships between lymph node characteristics and ENE is dated, has a small sample size, or focuses broadly on head and neck squamous cell carcinoma rather than OCSCC. This study aims to include a sizeable group of patients to provide updated information focused specifically on OCSCC treated with upfront curative-intent surgery.

Aims: Identify correlations between lymph node characteristics and extranodal extension (ENE).

Materials and Methods: Patients who underwent neck dissection for oral cavity squamous cell carcinoma from 2004-2018 were included, with a starting sample of 496. The primary outcome was ENE in at least one lymph node. Additional variables included number of dissected nodes, positive nodes by level, positive lymph node ratio (LNR), and diameter of metastatic deposit and ENE focus. Univariate and multivariate binary logistic regression analyses were performed to determine correlations between included variables and ENE.

Results: Of the 496 patients, 233 had nodal metastasis (47.0%). 13,814 nodes were removed, with 714 (5.2%) containing metastasis. Of the positive nodes, 28.0% had ENE, 47.2% did not have ENE, and 24.8% were unknown. The mean ENE diameter was 5.1 mm (SD, 9.9). On univariate logistic regression analysis, ipsilateral neck LNR per 0.1 unit increase (OR 1.16, 95% CI 1.02-1.32, p=.02), metastatic deposit size per 1 mm increase (OR 1.06, CI 1.04-1.08, p<.0001), and clinical T- (p=.02) and N-class (p=.0003) significantly correlated with ENE. On multivariate logistic regression analysis, size of metastatic deposit (OR 1.06, CI 1.03-1.08, p<.0001) remained significantly correlated with ENE.

Conclusion: Controlling for confounding variables, size of metastatic deposit was an independent predictor of ENE, suggesting that as the metastatic deposit size increases, the odds of extension through the capsule also increases. This may be due to capsule thinning as the deposit grows or could represent the invasive nature of aggressive disease.

Comparative Outcomes of Kahook Dual Blade Goniotomy and Gonioscopy-Assisted Transluminal Trabeculotomy in Steroid-Induced/Uveitic Glaucoma vs. Other Open-Angle Glaucoma

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Steroid-induced glaucoma (SIG) and uveitic glaucoma are types of secondary open-angle glaucoma characterized by trabecular meshwork dysfunction, often leading to increased intraocular pressure (IOP). Minimally invasive glaucoma surgeries (MIGS) like Kahook Dual Blade (KDB) goniotomy and gonioscopy-assisted transluminal trabeculotomy (GATT) are designed to target the trabecular meshwork, making them potentially effective treatments for glaucoma characterized by trabecular meshwork dysfunction. While KDB goniotomy and GATT have been effective in treating other open-angle glaucoma (OAG), their specific efficacy in SIG and uveitic glaucoma remains unclear. This study investigates the long-term outcomes of KDB goniotomy and GATT in managing these challenging glaucoma subtypes compared to other OAG. Our findings demonstrate that steroid-induced and uveitic glaucoma are more likely to achieve surgical success over two years with KDB and GATT surgeries compared to other OAG. This study reinforces the effectiveness of MIGS in treating OAG, showing significant reductions in IOP and reliance on glaucoma medications postoperatively. Notably, the steroid-induced/uveitic glaucoma group presented with higher preoperative IOP and medication use, and experienced greater reductions in both IOP and medication needs at most postoperative timepoints. These results support the use of KDB goniotomy and GATT as effective, less invasive treatment options for managing IOP in open-angle glaucoma, particularly in steroid-induced and uveitic cases.

Cocaethylene and Other Cocaine Metabolites in Samples from Newborns and Young Children: Unraveling the Effects of Parental Substance Use

Student Name: Maria Vardapetyan
Mentor: Matthew Krasowski, MD, PhD – Department of Pathology

Introduction: Alcohol and other substance use in a family poses a significant threat to the safety and healthy growth of children. Currently, the most common tests that are used to identify potential drugs of abuse and metabolites include urine, hair, and blood. Umbilical cord tissue and meconium (first stools) can also be used in newborn drug testing. The utilization of these tests as a means of assessing exposure can facilitate appropriate medical intervention for managing intoxication and withdrawal symptoms. In suspected child abuse and neglect cases, detection of drugs in a child not prescribed by medical provider can provide child protective services with objective evidence to aid in difficult decisions related to child protection.
Hypothesis: Cocaine has multiple metabolites that may be detected in patient specimens. One of these metabolites, cocaethylene, is unusual in forming by metabolism when cocaine and alcohol are consumed simultaneously. We predicted cocaethylene would be seen in umbilical cords of newborns in settings of suspected or documented maternal cocaine and ethanol use during pregnancy, with other cocaine metabolites likely to be present. Cocaethylene in hair samples of young children was hypothesized to occur in setting of heavy parental/guardian cocaine and ethanol use, with external contamination of the hair being a likely mechanism.
Method: Following Institutional Review Board approval, a retrospective chart review of 63 cases that involved cocaine and cocaine metabolites in hair samples, and 20 cases that involved cocaine and cocaine metabolites in the umbilical cord of a newborn was conducted using Epic electronic medical record data for University of Iowa Health Care. The ages of the children ranged from newborns to 13 years old at the time of testing. The chart review was focused on data related to clinical presentation, history of parent/guardian substance use, and investigation of cases by the Child Protection Team. Given the sensitivity of data, security measures were taken to protect privacy.
Results: Cocaethylene was found in 2 of the 20 umbilical cord samples positive for other cocaine metabolites and likely occurred in the setting of the mother using both alcohol and cocaine. Cocaethylene was found more often in hair samples (7 of 63 hair samples positive for cocaine), with all 7 occurring in the setting of suspected child abuse or neglect, including apparent non-accidental injuries, burns, failure to provide adequate supervision, or delay in bringing to child to medical attention. There was no clear-cut history of children ingesting both cocaine and alcohol, consistent with the possibility that cocaethylene forms externally on hair.
Conclusion: It is possible that cocaethylene could form in a child's body from the absorption of both ethanol and cocaine by the child, but such a history was not evident in any of the 7 children with hair specimens positive for cocaethylene. The ethanol exposure could be from accidental ingestion of an alcoholic beverage or other sources such as mouthwash, hand sanitizer, or over-the-counter medications. Alternatively, the cocaethylene may be able to form externally by chemical reaction. More research needs to be done in this area to understand the underlying processes behind the appearance of cocaethylene in children's bodies and how these findings could assist medical and child protective services in making informed decisions about care and safety.

Title: Epidural anesthesia and postoperative coagulation disturbances after hepatic surgery: A retrospective single institution study, Ravina Vasanwala, Gabriel Vazquez, Dr. Nada Sadek, Dr. Franklin Dexter, Dr. Rakesh Sondekoppam

Introduction: Epidural analgesia (EA) has proven to be more effective in managing pain compared to systemic opioids following hepatobiliary surgeries. Considering the critical role of adequate pain control in influencing post-discharge pain outcomes, EA is often a cornerstone of pain management during the first 72 hours after these surgeries. However, the risk of blood loss and coagulation abnormalities (CD) associated with liver resections raises concerns, especially with the use of EA, due to the potential for bleeding complications or spinal epidural hematoma. To address this, we aimed to evaluate the frequency and progression of postoperative CD (characterized by INR >1.5, PTT >40 seconds, or platelet count <100,000/μL) in patients considered for EA. We also explored how patient factors (such as age, sex, BMI, and preoperative use of anticoagulants) and intraoperative variables (such as the duration of surgery and the volume of liver resected) are related to the development of coagulation disturbances.

Methods: Following approval from the institutional review board, we performed a retrospective chart analysis on patients who underwent liver resection at the University of Iowa between 2011 and 2023. The patients were identified using Healthcare Common Procedure Coding System (HCPCS) codes from the electronic health record. We examined records to gather data on patient demographics (including age, sex, BMI, ASA classification, recent use of anticoagulant/antiplatelet medications, or neoadjuvant chemotherapy), surgical details (such as the specific procedure, estimated duration, and mass/volume of liver resection), pre-operative coagulation tests (INR, PTT, and platelet counts) within 30 days before surgery, and post-operative coagulation tests up to seven days after surgery. The primary outcome was to determine the incidence of post-operative coagulation disturbances (CD). Exact Wilcoxon-Mann-Whitney tests were utilized to analyze which factors were predictive of post-operative CD.

Results: 684 patients were first identified for the study. Thirty-seven were excluded due to death within 7 days of surgery or pre-existing coagulation disturbances. In the remaining 647 cases, the incidence of postoperative coagulation disturbances (CD) was 24.9% (95% CI: 21.6%–28.4%), with thrombocytopenia being the most common, occurring in 20% of all cases. When using a platelet count of <85,000/mm as the threshold for coagulopathy, the incidence was 15.5%. Coagulopathy was observed in 11% of patients on postoperative day 1 and 22% on day 2. Patients who developed postoperative CD had a significantly greater volume of liver resected ($P < 0.0001$), with an area under the ROC curve of 0.61. No predictive value for CD was found in relation to patient sex, ASA physical status, weight, age, adjuvant chemotherapy, preoperative anticoagulation or antiplatelet use, estimated operative duration, or the year of data collection (all standardized differences <0.2). Classification tree modeling yielded a single node, indicating no useful preoperative predictors. Stepwise backward logistic regression, using a P-value of <0.05 for inclusion, identified only 2 patients with a predicted probability of postoperative CD below 10%, and none below 5%.

Discussion: Coagulation disturbances (CD) were frequently observed after open hepatic surgery, and retrospective analysis revealed a correlation with the extent of liver resection. Interestingly, the incidence of CD in our study was lower than what has been reported in previous studies. Thrombocytopenia emerged as the most common issue, while abnormalities in liver function markers (such as elevated INR/PTT) were less frequently encountered. The timing of these coagulation disturbances may align with the recommended schedule for epidural catheter removal as per best practices in ERAS protocols for hepatobiliary surgery.

Evaluating Biochemical Recurrence in Gleason 3+3 Prostate Cancer Patients

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Introduction: Prostate cancer is the predominant malignancy diagnosed in men and is amongst the five most common causes of cancer-related death. Traditionally, Gleason 3+3 prostate cancers (Gleason score of 6) have been regarded as indolent, yet have retained their malignant label given pathologic similarities with higher grade carcinomas. It remains unclear if Gleason 3+3 prostate cancer has no, or very low, metastatic potential given occasional cases of reported disease recurrent or metastatic spread. Given the impact of definitive therapies, including prostatectomy and radiation therapy, on patient quality-of-life, delineating the metastatic and recurrence potential of Gleason 3+3 adenocarcinomas would be valuable. This project aims to assess the clinical course of Gleason 3+3 prostate adenocarcinoma patients and delineate if definitive treatment is warranted.

Purpose: We aim to determine if Gleason 3+3 prostate cancers have the potential to demonstrate biochemical recurrence after prostatectomy. Identifying Gleason 3+3 recurrence potential would indicate the potential need for definitive therapy to optimize clinical course, while observing an inability to recur would support routine observation of all Gleason 3+3 patients to maintain quality of life.

Methods: This study involves generating a list of patients with Gleason 3+3 prostate cancer who underwent prostatectomy at the UIHC from Epic and the UI Oncology Registry. Qualifying patients were evaluated for biochemical recurrence by establishing pre-operative PSA and a post-operative PSA, with a post-op PSA of >0.2 indicating recurrence. Patients were also evaluated for PSA trends, prostate size on digital rectal exam and imaging, PI RADS lesions and subsequent therapies.

Results: Of 262 patients identified with Gleason 3+3 and having underwent prostatectomy at the UIHC dating back to 2008, 170 were noted as having incidentally identified disease after cystoprostatectomy for bladder cancer. Of the remaining 92 patients identified after radical prostatectomy, 17 were identified with a postoperative PSA of >0.2ng/ml, meeting the American Urological Association definition for recurrence. Our future plan is to confirm the pathologic diagnosis of Gleason 3+3 grade and followed by RNA analysis to identify potential biomarkers for cancer recurrence.

Microfragmented Adipose Tissue for the Symptomatic Treatment of Osteoarthritis

Nathaniel Wieting M.S., Ryan C. Kruse MD

Introduction

Osteoarthritis (OA) is one of the most common musculoskeletal conditions in the world, impacting hundreds of millions worldwide. A variety of conservative treatment options exist but are not typically long lasting. Once these treatments fail, historically, the only remaining alternative was joint arthroplasty. Patients who have exhausted conservative treatments and cannot or do not want an arthroplasty were left without treatment options. This has been termed the OA treatment gap. Now, orthobiologics, such as platelet-rich plasma (PRP) and microfragmented adipose tissue (MFAT), have been utilized to fill this gap for certain patients. The growing body of literature on the use of MFAT for OA includes many high level studies and is generally promising, albeit somewhat inconsistent.

Hypothesis

We hypothesized that the use of MFAT for the symptomatic treatment of OA would result in significant improvement in pain and function at 12 month follow-up without significant adverse events.

Methods

This prospective observational study included patients from July 2018-January 2023 with symptomatic OA who underwent treatment with MFAT. These procedures were done by the senior author at an outpatient sports medicine clinic. Standardized questionnaires, including but not limited to Patient-Reported Outcomes Measurement Information System (PROMIS), Knee Injury and Osteoarthritis Outcome Score (KOOS), Copenhagen Hip and Groin Outcome Score (HAGOS), Hip Disability and Osteoarthritis Outcome Score (HOOS), and Pain Catastrophizing Scale (PCS), were recorded at baseline and follow ups at 2 weeks, 6 weeks, 12 weeks, and 52 weeks. The primary outcome was PROMIS Physical Function at 12 months post-injection.

Results

40 joints were injected from 38 patients. The knee was the most commonly injected joint (72.5% of all joints). There was a statistically significant improvement in PROMIS Physical Function at 12 weeks and 52 weeks, with an average change of 8.89 ($p<.0001$) and 12.99 ($p<.0001$), respectively. Patients' mean average pain score also showed statistically significant improvement at 52 weeks, with an average change of 3.49 ($p<.0001$). Additionally, the KOOS pain score significantly improved at 12 weeks and 52 weeks, with an average change of 18.14 ($p<.0001$) and 21.20 ($p<.0001$), respectively. No significant adverse events were seen.

Conclusion

The findings of our study indicate that MFAT may be a safe and effective symptomatic treatment option for OA. Future high level studies are needed to confirm or refute our findings.

Artificial Intelligence-Derived Optical Coherence Tomography Image Analysis for Diabetic Macular Edema Shows Improved Retinal Fluid with Intravitreal Injections

Collaborators: Karl Wilson, Bernardo Bach, Zhi Chen, Srinivas Chava, Milan Sonka, Elliott Sohn

Background: Diabetic macular edema (DME) is the leading cause of visual impairment in the working-age population worldwide and is easily detectable by a human looking at a non-invasive retinal optical coherence tomography (OCT) scan. First-line treatment involves intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections, but is not always effective, particularly when the disease is mainly driven by unsuppressed inflammatory signals. In these scenarios, intravitreal corticosteroids (IC) are used due to their anti-inflammatory effects after incomplete response from anti-VEGF treatment. Previous studies have attempted to identify biomarkers to predict treatment responsiveness using OCT imaging, however current analysis methods are time and labor intensive. This study aimed to validate AI-derived OCT measurements and correlate them with visual acuity as the first step in predicting treatment outcomes for DME. We hypothesize that there are positive correlations between the automated, AI-derived total retinal thickness (TRT) and volumetric fluid measurements seen on OCT in DME, and best corrected visual acuity (BCVA).

Methods: This was a retrospective, comparative study that had IRB approval. We used TriNetX and SlicerDicer global health research networks to study the medical records of UIHC patients diagnosed with only non-proliferative diabetic retinopathy (NPDR) and DME who have received multiple intravitreal injections in the retina clinics from 2011—2024. These patients were categorized into 2 treatment groups: those who received only anti-VEGF injections and those who received IC at some point during their care but started with anti-VEGF injections before getting steroids. 613 patients between both treatment groups were obtained and evaluated. Following exclusions, a total of 70 patients were included, with 92 eyes analyzed. Raw OCT data for 70 patients that included 1655 visits were uploaded in de-identified manner for automated image analysis. OCT B-scans were cropped to the central 1mm diameter area centered on the fovea. For AI segmentation, we employed nnUnet network, trained on datasets from age-related macular edema patients and the RETOUCH public dataset. The hybrid framework integrates deep learning with graph search algorithms to segment intraretinal fluid (IRF), subretinal fluid (SRF), and other fluid measurements from patients with age-related macular degeneration. Pre-trained on a public dataset and fine-tuned for our setting, the model's performance was evaluated considering inter-observer variability. This same AI was used in this project to assess fluid in DME. We analyzed the correlation between BCVA and retinal fluid volumes, including intraretinal fluid (IRF), subretinal fluid (SRF), and total retinal thickness (TRT), at various time points after baseline injections in treatment-naïve eyes. Additionally, we compared BCVA and fluid measurements between the anti-VEGF and intravitreal corticosteroid (IC) groups at the time of their initial anti-VEGF injections. Mixed model analysis was employed to account for the correlation of data from both eyes of the same patient, with beta coefficients used for correlation analyses.

Results: For the anti-VEGF only group, from baseline to one-year post-injection (n=30 patients, 41 eyes), there was a significant reduction in TRT from baseline to one-year post-injection ($\Delta = -30 \pm 15$ mm, $p = 0.043$). For the anti-VEGF group from baseline to final injection (n=46 patients, 61 eyes), mean IRF volume significantly decreased from baseline to final visit, ($\Delta = -14.339 \pm 4.635\mu L$, $p = 0.003$), along with TRT ($\Delta = -97 \pm 13$ mm, $p < 0.001$) in these eyes. In the IC group (n=19 patients, 21 eyes), mean fluid reduced from baseline (i.e. treatment naive for anti-VEGF) to the first-ever IC showed a significant reduction in IRF volume ($\Delta = 63.526\mu L \pm 11.048$, $p < 0.001$) and in SRF ($\Delta = 13.265 \pm 6.527\mu L$, $p = 0.040$). When looking at the steroid group's first injection (treatment naive for anti-VEGF), there is a significant positive correlation between the IRF and BCVA (beta= 0.0016963342697299800, $p < .001$). All other correlation and mean analyses were not significant.

Discussion: This study highlights significant reductions in retinal fluid and TRT in both the anti-VEGF and IC groups. The demonstration that AI can be used for automated fluid segmentation is promising, and quality assurance of these novel methods are on-going to validate the results. This research is an important step toward the broader goal of using artificial intelligence (AI) to predict treatment outcomes in various retinal diseases.

Title: Comparison of Conflict-of-Interest Policies for Surgical and Medical Societies

Authors: Kathryn Wittrock, BS, and Hassan Aziz, MD

Objectives: Disclosing conflicts of interest maintains the integrity, independence, and objectivity of surgical and medical societies. This study analyzed the public accessibility of disclosure requirements for surgical and medical societies and the differences between these requirements.

Methods: An analysis of publicly available webpages of surgical societies in the United States was performed to find conflict of interest disclosure policies. These policies were analyzed to determine whether they addressed the identification, management, resolution, and administrative action related to conflicts of interest. The definitions of a significant conflict of interest were compared, and forms used to report possible conflicts of interest were identified. The primary outcome of this study relates to the significant variation in disclosure policies of different surgical societies.

Results: Publicly available websites from 78 surgical societies and 116 medical societies were accessed to find their conflict of interest or disclosure policies. Only 50% (39/78) of surgical societies and 52.6% (61/116) medical societies had clear requirements for disclosing conflicts of interest varying in length from a single paragraph to 21 pages, and a mere 38.5% (15/39) of policies from surgical societies defined a significant conflict of interest, while 72.1% (44/61) of policies from medical societies did the same. Of those with a clear conflict of interest statement, just 33.3% (13/39) of surgical meetings and 63.9% (39/61) of medical meetings provided a form for individuals to complete with the required disclosure information. Different surgical specialties had different numbers of surgical societies with different conflict of interest policies, with only 30.4% (7/23) of general surgical organizations having accessible guidelines.

Conclusions: Overall, there is a general lack of accessibility, accountability, and consistency in conflict-of-interest statements for different surgical meetings. Many policies do not contain detailed information regarding the management of conflicts of interest. To improve conflict of interest reporting, each surgical society should publish guidelines for making disclosures, provide a specific definition for a significant conflict of interest, and offer individuals a form to complete to provide disclosure.

2024 Medical Student
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The Effect of Pursuing Infertility Treatment on Weight Loss in Obese Patients

Lydia Yang, BA; Prapti Singh, DO; Karen Summers, MPH; Hakan Duran, MD

Introduction: The prevalence of obesity (BMI>30) is rapidly increasing in the United States. Many studies have found associations between obesity, infertility and decreased success in IVF treatment. Proposed mechanisms for this association include higher rates of ovulation dysfunction, menstrual irregularities, and need for higher doses of medications to induce ovulation. The American Society for Reproductive Medicine (ASRM) recommends focusing on decreasing preconception weight, preventing excess weight gain during pregnancy, and aiming for long-term weight reduction. The first-line approach in achieving these goals typically involves counseling on lifestyle changes; however, this has been shown to be not very effective by several studies. Desire for conceiving is a significant drive and may serve as an effective means to achieve these goals with appropriate counseling and guidance.

Purpose: We aimed to assess the impact of pursuing infertility diagnosis and treatment on weight loss in obese patients. As secondary outcomes, we were also interested in identifying how often these patients received weight loss counseling during clinic visits, and other factors that impacted prevalence of counseling.

Methods: A retrospective chart review was conducted on all patients with BMI > 30 seeking infertility treatment at the University of Iowa Hospitals and Clinics (UIHC) Reproductive Endocrinology and Infertility (REI) Clinics between 1/1/2020 – 12/29/2022. Using Epic query, we extracted patients that were seen as "New Infertility Patients" in all three REI clinic locations. Exclusion criteria were patients with BMI <30, not actively seeking infertility treatment, previously pursued in-vitro fertilization (IVF) treatment, and requiring the use of donor oocytes. Of note, REI clinics have a policy to not offer infertility diagnostic or treatment services to patients over BMI of 50 kg/cm^2. Demographic information such as date of birth, race, ethnicity, weight (kg), height (cm) was collected. We also collected past medical history (PMH), gravidity and parity, weight loss counseling, type of counseling received, referrals ordered, Assisted Reproductive Technology (ART) method used if any, pregnancy outcomes, and weight at each visit. All data was recorded using RedCap. Data refinement and analysis was completed with SPSS. For analysis purposes, patient BMI was stratified into six categories (30-34.99, 35-39.99, 40-44.99, 45-49.99, 50-54.99, 55+ kg/cm^2). Welch tests with Tukey post hoc tests and Chi-square analysis with post hoc z tests were performed to analyze changes in weight throughout treatment by BMI category. Chi-square analysis was also performed to analyze prevalence of weight loss counseling and types of weight loss strategies pursued (lifestyle changes, medical or surgical options).

Results: A total of 1880 patients were identified using Epic, of which,1046 met our inclusion criteria and were included in our review. At their initial visit, patients were on average 31.8 ± 5.38 (standard deviation) years old, with an average BMI of 38.7 ± 6.87 kg/cm^2. The highest proportion of patients had a BMI between 30-34.99 (35.6%) followed by BMI between 35-39.99 (28.1%). Thirty nine percent concurrently had PCOS, 15.2% had hypothyroidism, 11.7% had hypertension, and 6.1% had diabetes mellitus. Age, gravidity and parity were similar between patient groups who did and did not receive weight loss counseling. There was a statistically significant difference in prevalence of weight loss counseling at the initial visit between BMI categories, the higher the patient BMI, the more likely they would receive weight loss counseling ($p<0.001$) (BMI 30-34.99, 14%; BMI 35-39.99, 18%; BMI 40-44.99, 33.7%; 45-49.99, 44.8%; 50-54.99, 84.3%; BMI 55+ 91.7%). Patients that received weight loss counseling during their initial visit were more likely to lose weight (0.68 ± 4.55 kg lost between initial and final weight) during their further visits compared to patients that did not (0.27 ± 3.94 kg gained between initial and final weight) ($p=0.002$). Patients in the highest two BMI categories had greater weight loss compared to patients with BMI 30-34.99, 35-39.99, and 40-44.99 although the mean weight loss was less than 2 kgs.

Conclusions: This study shows an association between preconception weight loss counseling and weight loss observed in obese patients. Severely obese patients presenting to UIHC REI clinics with infertility are more likely to receive weight loss counseling than mildly or moderately obese ones. Weight loss counseling seems to be effective in this patient population, although the effect is modest in amplitude.

Title of the Presentation:
Investigating EFEMP1 Mutations in a Sub-Saharan African Cohort with Juvenile Open-Angle Glaucoma (JOAG)

Presenters:
Brian Young
Mentor: John H. Fingert, MD, PhD, Professor of Ophthalmology and Visual Sciences
Collaborators: Benjamin Roos

Introduction/Background:
Juvenile open-angle glaucoma (JOAG) is a rare and severe form of primary open-angle glaucoma (POAG) that affects individuals aged 3 to 40 years, often leading to irreversible blindness. JOAG is typically associated with an autosomal dominant inheritance pattern and is known to have a strong genetic component. While Myocilin (MYOC) mutations are the most common known genetic cause of JOAG, accounting for 8% to 34% of cases, the genetic basis for many other cases remains unidentified. Recent studies have reported mutations in the epidermal growth factor extracellular matrix protein 1 (EFEMP1) gene in JOAG pedigrees from various populations, suggesting that EFEMP1 could be a contributing factor in JOAG. However, the prevalence of EFEMP1 mutations in Sub-Saharan African (SSA) populations, who are disproportionately affected by JOAG, has not been thoroughly investigated.

Hypothesis/Purpose:
We hypothesized that there is a significant prevalence of disease-causing mutations in the EFEMP1 gene among Nigerian JOAG patients compared to a Nigerian control group without JOAG. The purpose of this study was to determine the role of EFEMP1 mutations in a cohort of Nigerian JOAG patients and to evaluate their potential contribution to the disease.

Method:
A case-control study was conducted, involving 55 Nigerian patients diagnosed with JOAG. DNA samples were collected from all participants, and Sanger sequencing was employed to analyze the coding regions of the EFEMP1 gene. Genetic polymorphisms were compared to the gnomAD database to assess for prevalence and potential pathogenicity. The data were analyzed statistically to assess the prevalence and significance of EFEMP1 mutations in the patient cohort compared to the control group.

Findings/Results:
Our study did not find any mutations in the EFEMP1 gene within the coding regions of the Nigerian JOAG patients. The variations observed in certain alleles were consistent with normal variation and had been previously documented in public databases, with no indication of pathogenicity. These results suggest that EFEMP1 mutations do not play a significant role in the etiology of JOAG in this Nigerian population.

Conclusion/Overall Significance/Broader Perspective:
The absence of pathogenic EFEMP1 mutations in this study suggests that other genetic factors or epigenetic mechanisms may contribute to JOAG in the Nigerian population. This finding emphasizes the need for further research to explore other candidate genes or regulatory elements that may be implicated in the development of JOAG. Understanding the genetic basis of JOAG in diverse populations is crucial for developing targeted interventions and improving early detection and management strategies, ultimately reducing the burden of blindness in high-risk groups. This study contributes to the broader effort of uncovering the genetic determinants of JOAG and highlights the importance of including underrepresented populations in genetic research.

Improving Patient Comprehension of Pathology Reports

Zahn, C.J. and Krasowski, M.

Abstract

In compliance with the 21st Century Cures Act, University of Iowa Health Care made all laboratory reports immediately available to patients upon posting to Epic. As a result, patients could view their pathology reports as soon as the pathologists completed them. Pathology reports are written at a reading comprehension level far above the average reading comprehension level of the average patient, thus leading patients feel to confusion, anxiety, and uncertainty about their health. This study explores options for making pathology reports easier to understand for patients of UI Health Care through assessing the readability score of various pathology resources available to patients as well as the implementation of patient-centered pathology reports (PCPRs). Patients in the intervention group will receive a PCPR in addition to their standard pathology report, a second group will receive the standard pathology report and links to pathology resources related to their conditions, and the comprehension of the medical conditions of both intervention groups will be compared with that of a control group that receives neither PCPRs nor additional pathology resources. Lastly, the PCPRs and the provided resources will have readability score assessed through Flesch-Kincaid readability scoring to explore a connection between medical information retention and readability.

Case Series on Patients with Dedifferentiated Chondrosarcoma

Amy Zeller, MS4; Benjamin J. Miller, MD, MS - Department of Orthopedics and Rehabilitation

Background/Rationale

Dedifferentiated chondrosarcoma (DDCS) is a highly malignant tumor that generally carries a poor prognosis, the 5-year survival ranges from 7 to 24%. It is also quite rare with an incidence of 0.44 new diagnoses per million people in the United States each year. Treatment typically consists of surgical excision of the tumor, while chemotherapy and/or radiation may also be utilized as adjunctive therapies. The rarity and heterogeneity of DDCS makes it difficult to predict any given patient's outcome. With a disease as deadly as DDCS any additional evidence has potential to make a significant impact on patient's lives.

Purpose

The aim of this project is to identify any potential factors that could impact patient prognosis. Ultimately the goal is for this to guide future prospective studies to more formally evaluate the relationships we find.

Methods

This study was a retrospective case series of all patients who were given a final pathological diagnosis of dedifferentiated chondrosarcoma of the extremity who were treated at University of Iowa between 2008 and 2024. Even with these broad inclusion criteria, the result was a cohort of 14 patients. Data was collected on each of these patients including demographic information, the presence of associated diseases such as Ollier Disease and Castleman Disease, as well as disease characteristics including tumor location and size. All data was sourced from Epic.

Statistical analyses included T-tests to determine the associations between patient survival and categorical variables, such as amputation, or the presence of pathologic fracture. Statistical significance level was set at $p < 0.05$. For quantitative variables, such as neutrophil/lymphocyte ratio (NLR) and mitotic rate of tumor cells, correlation coefficients were calculated to determine effect on patient survival.

Findings/Results

Of the 14-patient cohort, the median survival was calculated to be 2.23 years. Four patients outlived the five-year mark, yielding a five-year survival rate of 28.6%. The type of surgery a patient received (amputation versus limb salvage) did not yield a statistically significant difference in survival rate ($p = 0.21$), and interestingly neither did pathologic fracture ($p = 0.28$). Although not particularly strong, a positive correlation coefficient of 0.21 was calculated for NLR, while the correlation coefficient for mitotic rate was much stronger and calculated to be -0.46.

Conclusion

With a 16-year window at a large academic institution, the sample size of our study is consistent with the documented infrequency of patients with dedifferentiated chondrosarcoma. Our data showed that as mitotic rate increased, survival rate decreased, as would be expected due to the increased activity of tumor cells being more strongly correlated with worse outcomes. It's also important to note that our data showed that surgery type (amputation versus limb salvage) was not found to change a patient's survival rate, which can be an important talking point when discussing treatment options with patients moving forward.