Abstracts

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Effectiveness of computerized adaptive tests to screen for perinatal anxiety in underserved women of color

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Background: Black women are under-identified during the traditional screening process for generalized anxiety disorder (GAD). Past research has suggested that Black participants score lower on the GAD-7 questionnaire (a standard screening measure for anxiety) than participants of other race and ethnicities with similar symptoms. This is concerning in perinatal and postpartum women because of adverse effects of anxiety on the mother and the fetus. The Computerized Adaptive Test for Mental Health (CAT-MH) is a type of questionnaire that has been tailored to perinatal women. Testing of the CAT-MH shows an increased ability to detect more positive cases for depression than traditional questionnaires in the perinatal population in low-income women of color and Black women. However, the CAT-ANX, a subtype of CAT-MH questionnaire that screens for anxiety, has not yet been studied in this population against the GAD-7.

Objective: This study aims to show the correlation, if any, between the Computerized Adaptive Test for Anxiety (CAT-ANX), a computerized adaptive questionnaire, and GAD-7, a standard screening questionnaire for GAD in the perinatal and postpartum period for women of color.

Methods: 486 women (47.7% Black, 27.8% Hispanic) at the University of Illinois Hospital completed both the CAT-ANX and GAD-7 questionnaires at a minimum of two visits during their pregnancies and postpartum. Chi-squared analyses were performed to determine significant differences in positive scores between the two questionnaires stratified by race and ethnicity. Correlation concordance models were also completed to determine concordance in positive results between the two questionnaires across racial and ethnic groups. Linear mixed models were used to find and correct for socioeconomic factors.

Results: CAT-ANX scores were significantly associated with GAD-7 scores (CCC=.81, 95% CI=.75-.85). CAT-ANX screened positive 5.89% of women (2.7% Black, 4.67% Latina). GAD-7 screened positive 9.22% of women (6.26% Black, 5.27% Latina). There was an overall significant difference between positive screens on CAT-ANX and GAD-7 among all participants ($p < .005$). Furthermore, when stratified by race and ethnicity, the rate of positive screens on CAT-ANX scores was significantly lower than the rate of positive screens on GAD-7 in Black women ($p<.0005$), but not in White or Hispanic women.

Conclusion: The CAT-ANX questionnaire identified significantly less cases of anxiety compared to the GAD-7. Specifically, CAT-ANX screened positive 5.89% of women while GAD-7 screened positive 9.22% of women. Among all women, Black women screened positive at a rate significantly less with CAT-ANX than GAD-7. However, White and Hispanic women had no significant difference between the rate of positive CAT-ANX and GAD-7 scores. This is concerning considering the data that Black women are already under-identified for generalized anxiety disorder. More research and testing are necessary to use CAT-ANX as a screening measure for GAD in the perinatal population, especially in Black women.

Neuron Morphology Analysis in Human Autopsy Tissue

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Dementia is the loss of cognitive function and is often associated with tau and synuclein protein aggregates. Previous studies have shown that loss of dendrite complexity is correlated with cognitive problems, but it was unclear which protein aggregate, tau or synuclein, affects dendrite complexity more. We hypothesized that tau aggregates will impact dendrite complexity more than synuclein aggregates. Here we show that tau and synuclein aggregates negatively affect dendrite complexity, and both affect dendrite complexity similarly. Fresh human golgi-stained tissue from the anterior cingulate gyrus, a part of the brain that shrinks in most dementias, in three cases were examined: a patient with a higher proportion of tau, a patient with a higher proportion of synuclein, and a control patient with neither protein aggregate. Pyramidal neurons from layer II of the cerebral cortex in each case were imaged and subsequently manually traced. From these tracings, a quantitative sholl analysis was conducted to compare dendrite branching for the pyramidal neurons in each case, which is a measure of dendrite complexity. The results showed that there was a significant decrease in dendrite complexity when comparing the tau and synuclein patients to the control, but no significant difference in dendrite complexity between the tau and synuclein patients. These findings build upon existing evidence that loss of dendrite complexity is associated with decline in cognitive function, and that both protein aggregates contribute to this loss.

Role of SIN3A dysregulation in neural crest differentiation and Witteveen-Kolk syndrome

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Purpose: Childhood-onset glaucoma is commonly a manifestation of multi-organ syndromes, such as Witteveen-Kolk syndrome (WITKOS). WITKOS was defined in 2016 and is due to a loss of function mutation in *SIN3A*, which encodes a histone deacetylase scaffold and is critical to neural development. While ocular dysgenesis is not a common feature of WITKOS, a parent and two children presented to UIHC with early-onset glaucoma and a confirmed *SIN3A* mutation. We aimed to quantify *SIN3A* gene expression at the neural crest stage of anterior segment development. We also aimed to assess the gene's potential role in the establishment of neural crest identity.

Methods: Urine epithelial cells were collected non-invasively from all three family members and primary cultures were established. *SIN3A* frame-shift mutations were confirmed in patient DNA by Sanger sequencing; the gene was targeted for amplification by designing and optimizing PCR primers specific to the region of interest. Neural crest-like status was induced in human induced pluripotent stem cells (hiPSC) using a specialized growth factor medium. Flow cytometry against CD49d and p75/NGFR was used to evaluate neural crest identity. Lastly, *SIN3A* gene expression was assessed using real-time quantitative polymerase chain reaction (RT-PCR) in hiPSCs and the induced neural crest cells; this was performed pre- and post-knockdown using transfection with short interfering RNA (siRNA) designed to target *SIN3A* transcriptional products.

Results: Primary cell cultures were established from cells collected from the patients' urine samples. *SIN3A* frame-shift mutations were confirmed in DNA extracted from patient cells. Exposure of hiPSCs to an induction medium resulted in significantly increased expression of markers of neural development; yet, neural-crest identity was indistinguishable from other neural ectoderm cell types. Both neural-crest-like cells and iPSCs had minimal SIN3A expression levels relative to the housekeeping gene *ACTB*; levels of expression were slightly decreased after siRNA transfection.

Conclusions: This project evaluates SIN3A expression in induced neural crest cells to characterize anterior segment development in WITKOS. First, we found that collecting cells from patient urine is a viable approach to establishing primary cell lines and therefore allows a non-invasive method to collect human samples. Second, hiPSCs can be differentiated into neural-crest-like cells using specialized media. Third, siRNA transfection can be used to downregulate the expression of specific genes of interest in cell cultures. These techniques can be used to investigate molecular pathways disrupted by mutations in transcription factor genes like *SIN3A* as well as to model early ocular dysgenesis. Future goals include defining the changes in *SIN3A* expression levels in WITKOS patients during neural crest cell differentiation and simulating the complete timeline of development from stem cell to neural crest intermediate to mature anterior segment. These experiments can characterize potential anterior segment dysgenesis and/or dysregulation in WITKOS. In turn, these findings can inform potential gene therapy treatments as well as clinical interventions to treat glaucoma in WITKOS.

Challenges in Applying Drug Docking Software to Computational Models of Whole Cells

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Abstract

Molecular docking is a computational drug discovery method that is often used to evaluate the interactions of small molecules with individual macromolecular targets during high-throughput virtual screening. However, no molecular docking has been done on a whole-cell scale, limiting a fuller understanding of how drugs exert their effects *in vivo* and the predictive power of determining off-target drug binding events *in silico*. *AutoDock* is the most-cited molecular docking software, and its new implementation – *AutoDock Flexible Receptor* (ADFR) – allows users to specify flexible residues within a protein target to perform "induced-fit" molecular docking of flexible ligands. Here, I set out to test the use of ADFR in the blind molecular docking of antibiotics with known effectiveness against *Escherichia coli* and well-characterized intracellular targets. These antibiotics are Gentamicin, Coumermycin A1, Erythromycin, and Rifampin. My results reflect the inconsistent and unreliable performance of ADFR during blind molecular docking. ADFR struggled to successfully dock Gentamicin to its known binding sites – which may result from its extensive hydrogen bonding capacity – and failed with Coumermycin A1, perhaps due to the computational expense of sampling the conformational space of its 20 rotatable bonds. ADFR performed better with Erythromycin and Rifampin, but was still inconsistent. Correct drug docking predictions relative to crystallographic drug coordinates are often somewhere within ADFR's list of clustered results, but its #1 docking result only intermittently occupies the proper binding pose. Overall, there was no correlation between the success or failure of *AutoDock* and drug binding favorability, cluster size, or crystal structure resolution, preventing the creation of any standard to validate the performance of blind molecular docking on the whole-cell scale. ADFR seems to be a good molecular docker for select drug-target pairs but generally fails for other drug-target pairs outright (Gentamicin and Coumermycin A1), when docking to diverse crystal structures (Erythromycin), or by lacking the capacity to discriminate between correct and incorrect binding pockets within the same crystal structure (Rifampin). This project might be feasible in the future with a machine-learning neural net trained for blind molecular docking.

Abstract

Title: Targeting Lab Draws to Reduce Central Venous Catheter Manipulation

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Background: Central line-associated bloodstream infections (CLABSI) are a tracked metric across healthcare organizations and publicly reported, potentially impacting re-imbursement. Therefore, efforts are constantly made to prevent any CLABSI event. Patients with hematologic malignancy, stem cell transplant, and receiving chemotherapy are at a particularly high risk of CLABSI. CLABSI risk is also independently associated with the number of times the Central Venous Catheter (CVC) is accessed. We aimed at determining how often the CVC is accessed for routine blood draws in an immunosuppressed population.

Methods: This study took place in March 2023 at the University of Iowa Hospitals & Clinics (UIHC) over the course of 6 days. CVC accesses were tracked by nursing staff on the Stem Cell Transplant and Cellular Therapies Unit. Each Luer lock action was counted as one instance of “access” for this study. CVC accesses were tracked by minimum, maximum, and average values per day. The highest number of lab draws and IV med pushes were also tracked per patient, per day.

Results: There were 1106 total accesses over a 6-day period. Of this, lab draws accounted for 678 accesses (61.3%). Per patient, there was an average of 8.4 accesses per day, with a minimum of 0 per day and a maximum of 28 per day. In patients with the most CVC accesses, lab draws accounted for 11.8 instances of access on average, which was higher than the 8.8 average instances of access attributed to IV med pushes. Overall, in patients with the most CVC accesses, 56% of access was related to lab draws versus 44% related to medication administration.

Discussions: This data suggests that a large portion (61.3%) of CVC accesses are done for lab draws rather than IV med pushes. Given that most lab draws can be performed by peripheral venipuncture, we have identified a target for future study. By reducing overall CVC access, the total risk of CLABSI in this already higher-risk patient population may be lowered.

Dissecting the 16p11.2 hemi-deletion to study sex specific striatal phenotypes of neurodevelopmental disorders

Presenter: Emily Baldwin

Mentor: Ted Abel, PhD **Collaborators:** Ben Kelvington, Jaekyoon Kim, PhD

Background: Neurodevelopmental disorders (NDDs) like Autism Spectrum Disorder (ASD), Attention Deficit Hyperactivity Disorder (ADHD), and Intellectual disability (ID) create a wide range of changes in adaptive functioning, social communication, independent living, and more. Hemideletion of the 16p11.2 chromosomal region creates a high prevalence (up to 88%) of NDDs. NDDs also show sex bias, with males being 2-4x more likely to have a NDD diagnosis. Among 16p11.2 hemideletion carriers, males show greater impairment—making it a good model to study sex differences. A homologous hemideletion in mice (16pdel mice) creates a neurodevelopmental phenotype: hyperactivity male and female mice and male specific reward learning deficits. These phenotypes are also referred to as "striatal phenotypes", as the striatum is a neuroanatomic hub for these functions. Many studies have used single gene knockdown models to determine the effects of single genes out of the ~27 in this 16p11.2 region, but these have not recapitulated sex differences in these models. Therefore, it was important to study candidate genes whose combined effects could confer sex differences. In order to determine which genes play an important role in striatal phenotypes, gene expression maps were used to determine which genes whose expression overlaps with male specific anatomic changes in peristriatal fiber tracts. Out of this emerged 3 candidate genes within the 16p11.2 region: *Mvp, Sez6l2,* and *TaoK2*.

Purpose: The aim of this study is to determine if the combined effects of *Mvp*, *Sez6l2*, and *TaoK2* are sufficient to recapitulate the sex specific neurodevelopmental phenotypes seen in 16pdel mice.

Methods: CRISPR/Cas9 was utilized in C57BL/6J mice to create mice with hemideletion in the 3 candidate genes (3 gene mice). Knockdown was validated with qPCR. Home cage activity was measured using an infrared beam break system. Operant reward tasks with both a fixed ratio and progressive ratio were used to measure reward acquisition and motivation, respectively. We also measured protein expression in the striatum with Western Blot to further validate our model.

Results: The 3 gene mice show a significant decrease in TaoK2 and Sez6l2 protein expression in the striatum, while detection and quantification of Mvp is still ongoing. We observed male specific phenotypes in 3 gene mice: hyperactivity and reward motivation deficits. 3 gene males show significant hyperactivity in the 24 hour cycle and dark (active phase) cycle versus wildtype. Male 3 gene mice showed a deficit in reward motivation (progressive ratio) but no deficit in reward acquisition (fixed ratio). There is no significant difference in any of these behaviors in 3 gene females.

Discussion: The 3 genes, *Mvp, Sez6l2,* and *TaoK2* are sufficient to recapitulate striatal phenotypes seen in 16pdel mice. Hyperactivity and reward motivation deficits are both seen in male 3 gene mice, showing that the combinatorial effects of these genes are sufficient to create the sex differences seen in 16pdel animals. Reward acquisition is not impaired, and further work will examine differential regulation of reward acquisition versus reward motivation. We also see that the protein products of 2/3 genes are decreased in the striatum, a region of the brain that is very important for the studied phenotypes. Going forward, we will assess differential expression and activation of signaling proteins within the same pathways as Mvp, Sez6l2, and TaoK2. Current targets for this include ERK and JNK signaling. This could help us determine molecular mechanisms for complex neurodevelopmental phenotypes. Examining this differential expression can also help find candidates for why we see female protection / male resilience in neurodevelopmental disorders.

Preloaded DSAEK Corneal Allograft Injector with Wide-Lumen Storage: Exploring Endothelial Cell Loss Reduction in a Proof-of-Concept Study

Student: Evan Balk
Mentor: Christopher S. Sales, MD, MPH
Other collaborators: Luke Grandgenett

Introduction: Endothelial keratoplasty is the vision-saving standard of care for patients with corneal endothelial cell dysfunction and is employed in more than half of all corneal transplants today. Descemet stripping automated endothelial keratoplasty (DSAEK) is a minimally invasive, partial thickness transplant technique that transplants donor endothelial cells together with a thin layer of corneal stroma. DSAEK was introduced in 2006 but until 2022, surgeons lacked a device that would eliminate tissue preparation in the operating room by allowing DSAEK tissue to be preloaded at an eye bank, shipped to the hospital, and injected into the recipient's eye the next day. The first commercially available device in the U.S. has a 1.8mm internal diameter lumen to both store the DSAEK tissue and inject it into the eye. It is known that this device causes corrugations in the DSAEK tissue, which contribute to endothelial cell loss (ECL), a marker of pre-transplant tissue health that has direct repercussions on short- and long-term allograft survival. It has been postulated that this is due to the exposed collagen-filled stroma, which hydrates and swells in the storage medium, Optisol-GS, which is hypotonic. As the tissue expands in a small, confined space, the interior surface, where the corneal endothelium resides, buckles on itself causing irreparable damage to the endothelial cells.

Purpose: We hypothesized that storing DSAEK tissue in a large-diameter lumen would induce fewer corrugations and less damage to the corneal endothelial cells. We therefore sought to create a device that stores the tissue in a large-diameter "storage" lumen during overnight transport, before it is passed through a small-diameter "ejection" lumen into the eye during surgery. The purpose of this study was to ascertain whether or not the core design concept of the device – i.e. a large-diameter "storage" lumen – had the potential to improve ECL outcomes.

Methods: We created a 3D printed prototype test rig that employs three stages— loading, storage, and ejection— all with circular cross-sections. The internal diameters of the storage and ejection stage were 4.5mm and 1.8mm, respectively. Donor corneas were prepared as 75 μm thick DSAEK tissues and loaded into identical devices, one tissue in the 4.5mm diameter "storage" stage and the other in the 1.8mm "ejection" stage. The loaded devices were stored for 24 hours in Optisol-GS and then both tissues were pulled through the 1.8mm "ejection" lumen. The tissues were then stained with Calcein-AM and imaged. The ECL was calculated using trainable Weka Segmentation in FIJI ImageJ. Means were compared with independent T-Tests.

Results: Six DSAEK allografts were tested. There was no significant difference in initial allograft thickness between storage conditions (4.5mm lumen: 83 μm; 1.8mm lumen: 87 μm; $P = 0.64$). We found no significant difference in ECL between tissues stored in the 4.5mm lumen (25.2%) and the 1.8mm lumen (26.9%, $P = 0.79$).

Conclusion: We found that storing DSAEK tissue in a larger diameter lumen did not decrease ECL. One possible explanation is the difference in tissue thickness when it entered the "ejection" lumen. The tissues stored in the 1.8mm lumen entered at or close to their original thickness; however, the tissues stored in the 4.5mm diameter lumen swelled for 24 hours before entering. We postulate that the benefits of storing tissue in a less corrugated configuration are offset by the damage caused by forcing a swollen tissue into a small diameter lumen. Limitations of the study are the small number of replicates and due to the 3D polymer's opaqueness, lack of imaging to confirm the corrugations. Based on these results, we do not anticipate investing additional resources into this device.

Frameshift mutations in *mutL* that facilitate antibiotic resistance in *Staphylococcus aureus*

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Background: Chronic respiratory infections are the leading cause of mortality in cystic fibrosis (CF). Approximately 70% of patients with CF have persistent infections with *Staphylococcus aureus.* These infections require frequent antibiotics, but complete eradication of *S. aureus* is rare. Thus, surviving strains of *S. aureus* often evolve antimicrobial resistance (AMR). Our group recently reported the evolution of linezolid resistant *S. aureus* in a rare strain that was missing DNA mismatch repair genes *mutS* and *mutL*. This strain exhibited hypermutation owing to loss of DNA repair proteins and evolved a series of mutations affecting the 50S ribosome. We hypothesized that point mutations in *mutS* and *mutL* are prevalent in *S. aureus* from patients with CF and help facilitate AMR.

Methods: We collected 1452 isolates of *S. aureus* from patients with CF in retrospective (2008-2018) and prospective (2020-present) studies. We isolated DNA and performed short-read whole genome sequencing using the Illumina MiSeq platform. We used Bactopia to group isolates by sequence type (ST) and used Snippy for reference-based alignment of genomes within each ST to the nearest genomic reference. This allowed identification of potentially damaging mutations to *mutL*, *mutS*, or other genes affecting mutation frequency like *polC*, *polA*, and *dinB*. To confirm disruption of full length MutL protein, we probed a western blot using custom-synthesized rabbit anti-MutL antiserum. We constructed a phylogenetic tree using RAxML to determine the evolutionary relationship between isolates and clarify the order in which sequential mutations occurred in each strain.

Results: We identified a prevalent hotspot mutation in *mutL* (c.1019delA) predicted to frameshift the MutL protein (p.P340fs). This mutation occurred in the context of a conserved 9-adenine stretch of *mutL*. A total of 78 isolates with frameshift mutations were identified. While most ST had a 9-adenine stretch at the locus, there was a strong bias for *mutL* mutations occurring in clonal complex 5 (ST5 or ST105). 73 isolates with *mutL* indels were in the ST5/ST105 group ($P < 0.0001$). Deletion mutations were more common than insertions; 67 isolates had delA, 5 had delAA, and one had an insA mutation. A western blot showed the loss of full-length MutL in an isolate with a delA frameshift mutation. Disruption of *mutL* was associated with increased SNP frequency, a hallmark of hypermutation. Indels in *mutL* were strongly associated with mutations in *polC*, which encodes the major DNA polymerase PolIII ($P < 0.0001$). 66 isolates were double-mutant for *polC* and *mutL*. Of these, 51 contained a p.Thr31Ile substitution in *polC*. Phylogenetic analysis indicated that *polC* mutations typically preceded *mutL* frameshift mutations, whereas *polA* mutations generally followed *mutL* frameshifts.

Discussion: Frameshift mutations in *mutL* are highly prevalent in ST5/ST105 *S. aureus*. We confirmed these mutations disrupt MutL and are associated with hypermutation. Frameshift mutations in *mutL* were strongly associated with *polC* mutations. Because these *polC* mutations preceded the *mutL* frameshift, we suspect that *polC* p.Thr31Ile allows more minus-1 frameshifts in homopolymeric DNA stretches such as the c.1019 position in *mutL*. Thus, *polC* mutations may allow *mutL*-dependent hypermutation in chronic *S. aureus* infections.

Risk factors for development of programmed death 1 (PD-1) inhibitor bullous pemphigoid

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Introduction

Immune checkpoint inhibitors targeting PD-1 (programmed cell death 1) have rapidly become the standard of care for advanced cancers. While beneficial in leading to antitumor immune responses, they increase risk for autoimmune disorders, including the autoimmune blistering disease bullous pemphigoid (BP).

BP is triggered by autoantibodies to the cell-substrate adhesion molecule BP180 (AKA Col XVII) Established risk factors for BP not associated with PD-1 inhibition ("Classic" BP) include advanced age and pre-existing neurologic disease (dementia, Parkinson's disease, and stroke), and certain medications: furosemide, spironolactone, and gliptins.

Hypothesis/Purpose

Based on previous work, we hypothesized that the PD-1 inhibition alone was not sufficient for the development of PD-1 inhibitor BP and that other pre-existing factors are present in those patients who develop BP autoantibodies upon PD-1 inhibition. *The purpose of this study was identification of those risk factors*.

Method

We performed a retrospective cohort study to identify demographic features of PD-1 BP patients with the goal of identifying risk factors. Sixteen patients with PD-1 BP were compared to 2764 patients who received a PD-1 inhibitor but did not develop BP. Their PD-1 inhibitor(s) exposure, cancer diagnosis, age, sex, and self-identified race and/or ethnicity were collected.
Exact logistic regression models were used to assess the effect of patient and disease characteristics on the odds of developing BP. Variables statistically significant on univariable analysis were included in the multivariable model. All statistical testing was two-sided and assessed for significant at the 5% level using SAS v9.4 (SAS Institute, Cary, NC).

Findings/Results

Age ($p=0.02$), male sex ($p=0.01$) and RCC/Urothelial indication ($p<0.01$) were all independently associated with the development of PD-1 inhibitor BP.

Patients 75 years of age or greater 75 had a 3.14 times risk of developing BP compared to those under 75. Males were at 8.69 times increased odds of developing BP compared to females. Patients who had RCC or uroepithelial indication were 3.81 times more likely to develop BP.

Conclusions

Patients who developed PD-1 inhibitor BP resembled classic BP patients with respect to age (74.6y vs 71.6y) rather than the mean age of PD-1 treated patients without BP (64. 6y). This suggests that changes in the immune system related to aging are also important for the development of PD-1 inhibitors.

Male patients were strongly over-represented in our cohort of PD-1 inhibitor BP compared to those who did not develop BP (16/17, $p=0.01$). Classic BP has been reported to have an equal M:F ratio to slight male predominance.

RCC/Uroepithelial cancers were also over-represented in the PD-1 inhibitor BP group. While, these neoplasms are more common in males, the multivariate analysis indicates that neoplasm type was an independent risk factor. Interestingly, BP180 is expressed in the kidney and the bladder epithelium is generally not symptomatically involved in classic BP.

Title: Reoperation rates of isolated meniscus repair with and without marrow stimulation

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Introduction: The meniscus is a critical component of the knee, providing both chondral protection and stability. Meniscus injury can cause significant disability and limit overall knee function. Successful meniscus repair provides consistent improvement in function while also restoring the chondral protective and stabilizing role within the joint. However, it remains unclear whether biologic augmentation via marrow venting for isolated meniscus repairs improves the success of meniscus repair. This study aims to identify whether bone marrow stimulation reduces meniscal repair re-tear rates. The hypothesis was that marrow stimulation will lead to reduced re-tear rates.

Methods: We retrospectively reviewed meniscus repairs from 2012-2022. Cases with root repairs, cartilage restoration, osteotomy, or other concurrent ligament repair or reconstruction were excluded. We recorded type of tear (medial vs. lateral) and technique used at index surgery (all inside vs. inside-out). We defined repair failure as subsequent meniscectomy (reoperation rate) or clinical evidence of re-tear with MRI confirmation. A Fisher's two-tailed exact test and Chi-square test were used to determine significance.

Results: Sixty-four isolated meniscus repairs (32 medial, 32 lateral) were included of which 34 (53.1%) received bone marrow venting and 30 (46.9%) did not. Eight patients (12.5%) underwent reoperation and 10 (15.6%) had evidence of re-tear. Cumulative failure rate was 15.6% (10/64). Medial tears accounted for 70% (7/10) of re-tears, lateral for 30% (3/10). Four re-tears (40%) came from all-inside technique and 6 (60%) from inside-out. Repairs with bone marrow venting had a reoperation rate of 11.8% (4/34) and a clinical re-tear rate of 11.8% (4/34). Repairs without venting had a reoperation rate of 13.3% (4/30) and a clinical re-tear rate of 20% (6/30). There was no significant difference in reoperation rate (11.8% vs. 13.3%, $p>0.05$) or clinical re-tear rate (11.8% vs. 20%, $p=0.54$) with or without bone marrow venting, respectively.

Conclusions: We found no significant difference in meniscal re-tear or reoperation rates with and without bone marrow ventilation. Further biologic techniques should be investigated to improve healing of isolated meniscus repairs in young athletes.

Body Composition Changes Following Revision Total Joint Arthroplasty

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DISCLOSURES:

INTRODUCTION: Although total joint arthroplasties (TJA) are of the most successful surgeries in medicine, occasionally replacements fail and subsequently require revision surgery. Most commonly, this is due to infection, instability, fractures, or stiffness of the replaced joint. By comparison, revision TJAs are highly physically taxing events for patients to endure since they require a larger incision, specialized equipment, a more complicated procedure, and a lengthier recovery. Hence, one would expect to observe more dramatic consequences to a revision patient's body, ultimately diminishing their functional capacity and further complicating their recovery. Insights regarding this impact can be investigated through the use of bioimpedance analysis (BIA) to collect and follow body composition data such as skeletal muscle mass (SMM), percent body fat (PBF), phase angle (PA), and more. It is assumed that patients with a less favorable baseline body composition more often require a revision TJA following a primary TJA. The purpose of this study is to identify the baseline body composition parameters of revision TJA patients to contrast with a similar cohort undergoing primary TJAs. Further, this study aims to quantify the consequences of revision TJAs on patients' body composition and overall functional capacity. Insights gained from this study can be leveraged to guide clinical decision making for patients undergoing primary and revision TJAs.

METHODS: This prospective cohort study, which was approved by our institution's IRB, aims to enroll 100 participants undergoing revision TJA surgery. Body composition data is obtained via BIA pre-operatively and at each post-operative follow-up visit (3 weeks, 6 weeks, 12 weeks, 6 months, and 1 year). Additionally, maximal hand grip strength (HGS) is collected at the same intervals and is used as a surrogate measure for skeletal muscle function. Data is evaluated in comparison to pilot data on a similar cohort of patients who underwent primary TJA. Furthermore, retrospective review of BIA data in patients schedule to undergo revision BIA was reviewed. Primary outcomes for this study include baseline and changes in SMM, PBF, PA, and HGS. Secondary outcomes include baseline and changes in weight, skeletal muscle index (SMI), and body fat mass (BFM). Descriptive statistics and t-tests were calculated for body composition metrics of interest for each population with significance set at $\alpha = 0.05$.

RESULTS SECTION: To date, 12 subjects undergoing revision TJAs have been enrolled. 10 subjects have completed their pre-operative scan and HGS test, 2 subjects have completed their 3- and 6-week follow up visits. 34 additional patients were retrospectively reviewed for baseline analysis. The two patients who did not complete baseline measurements have been excluded from further analysis. The pilot study, to which this data is being compared, enrolled 84 subjects undergoing primary TJAs. Current analysis shows that the primary and revision cohorts shared similar baseline SMM ($p = 0.23$), PBF (0.28), SMIT (0.30), and PA (0.19). Additionally, 6-week postoperative analysis shows that weight decreased postoperatively in the primary cohort but increased in the revision cohort ($p < 0.01$). Further, the revision cohort demonstrated a much more dramatic decrease in SMM (0.28) and increase in PBF (0.27) than did the primary cohort on 6-week follow up. Finally, analysis shows the revision cohort had much larger reductions in hand grip strength 3-week (0.04) and 6-week (0.13) follow up compared to the primary cohort.

DISCUSSION: Baseline analysis has not yet revealed any dramatic differences between these two populations. The revision population has demonstrated similar baseline measures of SMM, BFM, PBF, SMI, weight, and PA without statistical significance. Despite lack of significance, PA, a measure of cellular health, trended lower in revision patients. This may indicate that the primary population has more favorable overall biological health and cell integrity than that of the revision population. Although the dataset remains in its infancy, preliminary results have begun revealing the dramatic impact felt by patients undergoing revision TJAs as compared to those undergoing primary TJAs. While both primary and revision populations experienced a 6-week post-operative decline in skeletal muscle mass, for example, the revision population did so to a much greater degree. Further, while the primary population had almost no change in their body fat percentage post-operatively, the revision population has experienced a dramatic increase in their body fat percentage. These two body composition parameters, in particular, are thought to be key players in a successful surgical recovery and in quality of life beyond recovery. However, despite current results demonstrating multiple substantial differences in these populations, limited conclusions should be drawn until sufficient data has been obtained.

SIGNIFICANCE/CLINICAL RELEVANCE: Conclusions drawn from this study can be used to inform clinicians and their patients on the impact revision TJAs have on physical health and in doing so will once again demonstrate the clinical utility of bioimpedance technology for orthopedic clinical practice.

TABLES AND FIGURES:

Table 1: Mean baseline body composition parameters for primary and revision subjects w/ SD and p values. **Denotes statistical significance*

	Weight (kg)	SMM (kg)	SMM (%)	BFM (kg)	PBF (%)	SMI (kg/m^2)	PA (°)
Primary (n=84)	98.9 ± 25.3	31.6 ± 8.3	32.2 ± 5.7	41.6 ± 17.0	41.1 ± 10.0	8.4 ± 1.5	4.8 ± 0.9
Revision (n=46)	102.3 ± 26.6	33.6 ± 9.8	33.2 ± 5.9	40.8 ± 16.5	39.1 ± 10.3	8.7 ± 1.8	4.6 ± 0.9
p	0.48	0.23	0.36	0.80	0.28	0.30	0.19

Table 2: Mean change by 6-week follow up in body composition parameters for primary and revision subjects w/ SD and p values.

	Δ Weight (%)	Δ SMM (%)	Δ PBF (%)	Δ PA (%)
Primary (n=69)	-0.76 ± 2.66	-0.18 ± 0.97	-0.01 ± 1.72	-2.61 ± 4.92
Revision (n=2)	0.62 ± 0.24	-3.16 ± 2.00	5.19 ± 3.38	-4.08 ± 9.94
p	0.0013*	0.28	0.27	0.87

Table 3: Mean baseline HGS and mean change in HGS by 3 and 6-week follow up for primary and revision subjects w/ SD and p values.

	Baseline HGS	n	Δ_{3wk} HGS	n	Δ_{6wk} HGS	n
Primary	27.3 ± 9.8	84	0.8 ± 4.5	58	-0.3 ± 4.8	30
Revision	31.0 ± 13.7	12	-6.0 ± 7.0	3	-5.7 ± 6.2	2
p	0.22		0.042*		0.13	

Aspirin Specifically Targets Triglyceride and Copeptin Levels in the Development of Preeclampsia

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Objective: Preeclampsia has been associated with elevated triglyceride levels, often above the expected physiologic increase in pregnancy. Low-dose aspirin (81mg) is routinely prescribed in pregnancy to prevent the development of preeclampsia, however, the mechanism of this remains poorly understood. The objective of this study was to determine if aspirin is effective in lowering triglyceride levels in association with preeclampsia.

Study Design: In this retrospective case control study, subjects were selected from our established Perinatal Family Tissue Bank (IRB#200910784) based on aspirin use and preeclampsia in pregnancy. Demographics were collected from the electronic health record using the Intergenerational Health Knowledgebase. Statistical analysis was performed with aspirin use and preeclampsia as dependent variables. Alpha was set at 0.05.

Results: In patients with preeclampsia, 22 patients took aspirin during their pregnancy compared to 25 who did not. Similarly, in those without preeclampsia, 132 took aspirin and 404 did not. These populations did not differ in demographic measures (ex. maternal age, race/ethnicity, BMI, gravida). When comparing triglyceride levels from the first to third trimester of pregnancy, patients with preeclampsia who took aspirin had a smaller overall increase in triglycerides compared to those who did not take aspirin (3.7 ± 46.2 vs. 32.0 ± 61.2 mg/dL, $p = .22$). In addition, these patients had a smaller increase in copeptin, a precursor peptide associated with preeclampsia, compared to those who did not take aspirin (-0.1 ± 0.5 vs. 0.7 ± 1.9 pmol/L, $p = .21$). This effect was not seen in those without preeclampsia; there were not significant differences in triglycerides (28.7 ± 60.6 vs. 14.6 ± 44.3, $p = .09$) nor copeptin (2.0 ± 9.8 vs. 0.6 ± 6.6 pmol/L, $p = .27$) in patients who took aspirin compared to those who did not take aspirin.

Conclusion: This data suggests that aspirin specifically targets triglycerides and copeptin in pregnancy in patients who develop preeclampsia. Exploring this mechanism further may lead to a more efficacious preventative for preeclampsia.

Incidence of frailty in midlife adults and its impacts on outcomes

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Introduction. Unintentional injuries are a serious problem in the US, with unintentional falls being perhaps the most significant cause of hospitalization for injury in adults. Despite this, current CDC guidelines for fall screening only address the older adult population. Midlife adults (50-64 years) may also face serious risk of unintentional falls and related injury and thus require proper risk identification and prevention strategies. A potential metric to identify increased fall risk is frailty, a multidimensional syndrome of loss of physical and cognitive function, commonly leading to increased vulnerability. The incidence and impact of frailty on outcomes in midlife trauma patients remains understudied, with lack of multicenter studies on this population.

Purpose. Herein, we assessed the incidence of frailty among midlife and older trauma patients from 2012 to 2021 as well as the impact of frailty on the outcomes of midlife trauma patients. We hypothesized that the incidence of frailty among midlife adults has increased over time while remaining stable in older adults and that frailty is associated with an increased hospital length of stay, discharge requiring higher level of care, and increased risk of mortality in midlife trauma patients.

Methods. This is a 10-year retrospective cohort study (2012-2021) using data from the American College of Surgeons Trauma Quality Improvement Program (ACS TQIP) database. A total of 4,692,222 patients 50 and older who suffered traumatic injuries, excluding burn injuries, were included to assess the incidence of frailty over the 10-year period. The impact of frailty on outcomes in midlife adults was assessed using TQIP data from 2021. After excluding patients with burn injuries and those missing continuous variables, 190,038 patients 50 to 64 years with traumatic injuries were included. This de-identified dataset is nationally representative. Demographics (age, sex, race), injury information, comorbidities, pre-injury anticoagulants, Injury Severity Score (ISS), ventilator days, ICU length of stay (LOS), and complications including, but not limited to, acute respiratory distress syndrome (ARDS), severe sepsis, and unplanned readmission to the ICU, hospital LOS, and discharge disposition were evaluated. Frailty was scored using the modified frailty index-5 (mFI-5), which uses a 0-5 scoring system based on the presence of 5 comorbidities: diabetes mellitus, congestive heart failure within 30 days before surgery, hypertension requiring medication, history of COPD or pneumonia, and functional health status before surgery--partially or totally dependent. Descriptive statistics were obtained. Frailty was assessed as both a bivariate (mFI greater than or equal to 3 considered frail) and ordinal variable (frailty assessed by mFI-5 point increase from 0-5). Trends in frailty incidence in midlife and older adults over the 10-year period were assessed using Poisson regression analysis while adjusting for demographics. Using the 2021 TQIP dataset, univariate and multivariate analyses were performed to 1) assess differences between frail and non-frail midlife adults and 2) assess the impact of frailty on patients' outcomes. Our primary endpoints were hospital LOS and discharge disposition; secondary endpoints included ICU LOS, days on a ventilator, complications, and mortality

Results. The proportion of frail midlife adults increased from 2.40% to 5.09% from 2012 to 2021. Similarly, the proportion of frail older adults increased from 6.42% to 14.70%. Upon adjustment for demographics, the incidence of frailty increased by 6% per year (incidence rate ratio (IRR) = 1.06 [95% CI 1.06, 1.07]). In older adults, upon adjustment for demographics, frailty incidence increased by 11% (IRR = 1.11 [1.10, 1.11]).

Looking at the 2021 midlife adult subgroup population, 5.1% were frail. Compared to non-frail patients, frail midlife adults were more likely to be female (47.4% vs. 34.9%) and older (medians: 60 y vs. 58 y). Frail midlife adults stayed longer in hospital (medians: 5 vs. 3 days) and in the ICU (medians: 3 vs. 2 days). There was no difference between ventilator days between these two groups. Frail patients were more likely than their counterparts to be readmitted to the ICU (4.58% vs. 1.67%). Compared to non-frail patients, frail individuals were more likely to require higher level of care at discharge (43.1% vs. 21.8%). Mortality rate was higher (3.8% vs. 2.3%). On multivariate analysis adjusting for age, sex, insurance status, ISS, vitals on arrival, and mode of transportation, frailty in midlife adult trauma patients was associated with increased risk of death (OR = 2.272 [2.006-2.574]), longer hospital stay (MR = 1.458 [1.427-1.489]) and ICU stay (MR = 1.297 [1.242-1.355]), and discharge requiring higher level of care (MR = 2.270 [2.163-2.383]).

Conclusion. Frailty has increased in both midlife and older adult trauma patients over the 10-year period studied. Moreover, frailty is associated with several negative health outcomes for midlife adults. These results highlight the need for further exploration into preventative efforts regarding frailty.

Trigonometry of the hand and wrist under full body weight loading using functional upper extremity load-bearing CT imaging

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Collaborators: Ignacio Garcia Fleury, MD, Natalie Glass, PhD

Introduction

The effect of full body weight loading of the upper extremity on the kinematic relationship between the bones of the hand and wrist is not well understood, which presents challenges in diagnosing and treating injuries. However, the use of weight bearing CT (WBCT) on the foot and ankle has improved our understanding of injuries that are not easily identified using other forms of imaging. Injuries to the hand and wrist account for 3% to 9% of all injuries in athletes and are one of the most expensive injury types. Currently, there are no studies evaluating full body weight loading of the upper extremity using functional CT imaging methods. Other studies are limited in that only one particular bone or joint was evaluated, minimal loading was applied to the upper extremity, and 3D simulations used to represent full body weight loading were not validated against patient or cadaver data, thus demonstrating the need for functional upper extremity loading CT (FUEL CT) and imaging under full body weight loading conditions.

Purpose

We believe the impact that weight bearing CT has had on the understanding of foot and ankle pathology can be translated to the upper extremity using our FUEL CT method. In order to support the use of FUEL CT, we must first identify and describe the trigonometric relationships between bones of the hand and wrist under full body weight loading. We believe FUEL CT will give insight into the hand and wrist bone relationships during full body loading, which will improve our ability to both diagnose and treat these injuries. This study aims to demonstrate the changes that occur within the hand and wrist in full body loading conditions, which can be used as a foundational tool for clinical use and further research.

Methods

Informed consent was obtained from fourteen past or present competitive gymnasts for analysis of handstands using a WBCT scanner. Age, sex, height, weight, previous injuries, current wrist pain rating, dominant writing hand, and cartwheel hand dominance were documented for each participant. Four participants were excluded because their images had significant motion artifact and were unable to be analyzed. A neutral, unloaded image was obtained for each participant. Then, participants performed a handstand (with standardized hand placement) inside the WBCT scanner. Finally, two parallel handlebars were attached to the scanning platform and participants performed a handstand-like action in the parallettes position. Images were converted to NIfTI files for analysis using the Disior Bonelogic® Hand and Wrist module (Bonelogic Hand and Wrist, version 2.0, Disior Ltd, Helsinki, Finland). The software identified bony anatomic landmarks and computed 2D radiographic measurements. Each measurement's calculation methods were defined. Representative 3D models were created based on the CT images. Measurements in the Handstand and Parallettes position were compared with those in the neutral position. Wilcoxon signed rank test and paired t-tests were used to analyze results.

Results

Radiolunate Angle, Capitolunate Angle, Scapholunate Angle, Lunotriquetral Angle, Radiotriquetral Angle, Radiotrapezoidal Angle, Radiotrapezial Angle, and Radiometacarpal III Angle all tilted dorsally in both the Handstand and Parallettes conditions compared to Neutral (all $p<0.05$). Carpal Height Ratio, Ulnar Translation Ratio, Radioscaphoidal Joint Minimum Gap (mm), Radiolunate Joint Minimum Gap (mm), Scaphotrapezial Joint Minimum Gap (mm), Lunocapitate Joint Minimum Gap (mm), and Carpometacarpal I Joint Minimum Gap (mm) were smaller in the Handstand and Parallettes conditions compared to Neutral (all $p<0.05$). In the Parallettes condition, Radial Inclination (°) had a volar tilt, Radial Height (mm) was larger, and Ulnar Variance (mm) shifted distally compared to Neutral (all $p<0.05$). In the Handstand condition, Scaphotrapezoidal Joint Minimum Gap (mm) was smaller compared to Neutral ($p<0.05$).

Conclusion/Discussion

We successfully demonstrated, both trigonometrically and visually with 3D models, the ways in which the relationship between bones of the hand and wrist change during loading conditions. This study supports that FUEL CT may be a better tool to measure hand and wrist parameters compared to traditional imaging. We have laid the foundation for future FUEL CT research, and the development of a dedicated FUEL CT device is warranted. The research is limited due to a small sample size, so more participants need to be recruited in future studies to further validate our findings. Future research could include applications to everyday activities, such as falling onto an outstretched hand or pushing yourself up from the sitting position using the arms of a chair. Future analysis of this data could include stratification based on age, sex, height, prior injury, and wrist pain to see if any of these factors have bearing on the hand and wrist measurements.

Low shunt burden from PDA is not associated with adverse outcomes in premature infants

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Introduction: Patent ductus arteriosus (PDA) is a common diagnosis in premature infants affecting approximately 1/3 of infants born <30 weeks gestational age. Persistence of the ductus can lead to excessive flow through the pulmonary circuit resulting in hemodynamic consequences. PDA in the setting of prematurity has been associated with increased mortality and morbidity including bronchopulmonary dysplasia (BPD), chronic pulmonary hypertension (CPH), intraventricular hemorrhage (IVH), and pulmonary hemorrhage. Randomized controlled trials based on diameter of PDA show no benefit to treating the PDA or have mixed results. The use of targeted neonatal echocardiography (TnECHO) allows for a more comprehensive evaluation of overall shunt burden and hemodynamic significance. Higher shunt volume of the PDA evaluated with a PDA score has been shown to be associated with increased risk of BPD. Early identification of infants with a PDA score > 6 (moderate to high volume shunt) and early treatment of the PDA is associated with improved outcomes. There is limited data on infants with a low PDA score (<6).

Hypothesis: Patients with low PDA burden will not have higher incidence of the composite of death or adverse respiratory outcome compared to those with no PDA burden.

Methods: A retrospective cohort study was conducted in premature infants born < 30 weeks gestational age ($\leq 29^{+6}$) who were admitted to the NICU at the University of Iowa Stead Family Children's Hospital between August 2018 and May 2023. Those with congenital anomalies or anatomic cardiac disease other than PDA, patent foramen ovale/atrial septal defect, or small (<1mm) muscular ventricular septal defect and those without TnECHO performed within the first postnatal week were excluded. The Iowa PDA score was used to determine PDA status on TnECHO, and patients were divided into two groups: no PDA burden (closed PDA on initial or follow up screen if done in the first postnatal week) or low PDA burden (PDA score <6 on initial screen and continued for at least 2 weeks with no medical therapy for PDA during hospitalization). PDA status on TnECHO and postnatal complications associated with prematurity and PDA were compared between groups including length of stay, IVH, CPH, and BPD. The primary outcome was the composite of death or adverse respiratory outcome defined as a diagnosis of CPH prior to discharge and/or Grade 2/3 BPD by Jensen criteria. Univariate analysis was performed to analyze demographics and clinical characteristics according to group. The p-value was set at 0.05.

Results: A total of 112 premature infants met inclusion criteria (69 in the no PDA burden group and 43 in the low PDA burden group). There were no differences between the two groups with regard to demographics or in the primary outcome of death or adverse respiratory outcome (p=0.239). There was also no difference in the occurrence of CPH (p=0.296), pulmonary hemorrhage (p=0.523), systemic hypertension (p=0.284), or need for supplemental oxygen at time of discharge (p=0.559).

Conclusions: Prolonged exposure to low volume PDA shunt was not associated with increased risk of death or abnormal respiratory outcome. These data further highlight the importance of comprehensive evaluation of PDA shunt volume, particularly in the setting of interventional clinical trials.

Gene Transfer Efficiency in Models of Increased Secreted Airway Mucins

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Abstract

Airway mucus is essential for lung health by trapping inhaled small particles and transporting them out of the lung via mucociliary transport. Given the role of airway mucus in host defense, one can easily envision mucus as a barrier to efficient viral vector mediated gene transfer, particularly in the airways of people with cystic fibrosis (CF). The goals of this study are to: 1) advance physiologically relevant in vitro and in vivo models of mucus barriers to gene therapy; 2) determine the degree to which mucus prevents viral vector mediated transduction; and 3) determine if mucolytic interventions can improve vector transduction of airway epithelial cells. We first compared transduction of well-differentiated primary airway epithelial cells from CF and non-CF human donors because CF primary cells produce increased levels of Muc5AC. We next tested tracheal explants from CF and non-CF pigs. Explants remain capable of Muc5AC and Muc5B mucus secretion from goblet cells and submucosal glands. Lastly, we investigated vector transduction in a mouse model of goblet cell metaplasia. Although these models do not fully recapitulate the complex inflammatory environment of the CF lung, the results suggest that mucus hypersecretion is not a substantial impairment to vector transduction, especially in conjunction with delivery enhancing vehicles.

Developing Resources to Fill Gaps in Dermatological Training in Bagamoyo, Tanzania

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Background: The Bagamoyo District in Tanzania is home to more than 300,000 people but lacks a trained dermatologist. A pilot study in 2017 identified the need for dermatologic care in the Bagamoyo District, with further research affirming the effectiveness of a secure teledermatology platform as an efficient and cost-effective method to address this need. The majority of skin conditions in the Bagamoyo District continue to be evaluated and treated by general practitioners. Knowledge of the presentation, prevalence, and treatment of common dermatologic conditions remains important for general practitioners.

Purpose: Medical schools worldwide often devote very few curriculum hours to dermatology education. Case-based educational modules have been proposed as a way to address the gaps in dermatologic knowledge for clinical students. The objective of the current study is to create educational modules using deidentified dermatologic patient cases that have been uploaded to the secure teledermatology platform (africa.telederm.org) from the Bagamoyo District.

Methods: A survey was administered to second-year medical students gaining clinical experience at Bagamoyo District Hospital. The survey collected participants' demographic information as well as questions about the amount of dermatology information they had received. The survey also assessed students' confidence in their ability to diagnose common dermatologic conditions, their beliefs on the importance of dermatology training, and their preferences for additional training.

Results: 121 Medical students responded to the survey, representing Excellent College, City College, Nyaishozi College, and Ununio College. 87% of students indicated that they had received no more than 3 hours of training in dermatology, with 56% of students stating that they had received 1 hour or less. On a scale of one to five with one being not confident and five being very confident, on average, students ranked their confidence in diagnosing skin diseases as a 3.76 and their confidence in treating skin diseases as a 3.72. Over 90% ranked the importance of learning about dermatology as a five on a scale of one to five. Finally, students ranked what resources they would find helpful on a scale of one to six, with a video lesson from a specialist and an atlas of skin diseases available on the phone as the most popular options.

Conclusion: This research illustrates gaps in dermatological training and provides a novel understanding of the educational needs of general practitioners in Bagamoyo. Based on input from local students and providers, we plan to develop educational resources, including a skin disease atlas of local cases. We will also provide online learning modules with a pre- and post-test to evaluate effectiveness.

Weight-Bearing CT-Based RSA of Post-Operative Implant Migration in Primary TKA Patients

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Background: The primary treatment for osteoarthritis of the knee, one of the leading causes of disability in the U.S. population, is a total knee arthroplasty (TKA). Surgical implant micromotion, which defines the movement of the implant relative to the surrounding bone, serves as a predictor of the long-term prosthetic survival in arthroplasty. With approximately 790,000 TKAs being performed annually in the U.S. and a growing elderly population, the need for an efficient method of characterizing implant micromotion continues to grow. Historically, radiostereometric analysis (RSA) has served as the standard for measuring implant migration. However, conventional RSA is a complex process that requires specialized implants, x-ray equipment, and trained radiology personnel. In contrast, CT-based RSA is a method that utilizes CT imaging to identify micromotion of the implant, eliminating many of the obstacles present with RSA. To compare RSA and CT-based RSA in 2016, Broden et al. discovered that low-dose 3D CT provides comparable precision to traditional RSA in measuring the migration of acetabular cups in total hip arthroplasties in an experimental setting. In 2022, Angelomenos et al. determined that low-dose 3D CT and traditional RSA demonstrate similar precision in actual patients up to 1 year. These studies demonstrate that CT-based RSA and traditional RSA possess comparable levels of precision, supporting the use of CT-based RSA in assessing implant migration.

Purpose: Weightbearing CT (WBCT) technology is a type of imaging that has not been used for CT-based RSA. This study will utilize WBCT imaging and subsequent CT-based RSA to identify early surgical implant micromotion in primary TKA patients.

Methods: This study was approved by our institution's IRB. This prospective study aims to recruit 200 adult patients with severe osteoarthritis presenting to our clinic for TKA. Subjects who are capable of becoming pregnant and are not currently on contraceptives, who are wheelchair-bound, and who have an active infection or other medical conditions are excluded. Implant micromotion data was collected using a cone beam CT (CurveBeam HiRise). All patients will undergo one pre-operative WBCT scan and post-operative WBCT and non-weight-bearing CT (nWBCT) scans at 3 weeks, 6 weeks, 12 weeks, and 1 year. The inclusion of nWBCT scans utilizing the same scanner assesses whether implant micromotion is due to the weight-bearing load and provides information about implant performance under a weight-bearing or non-weight bearing condition. A logistic and frequency analysis will be used to analyze the data by examining the patients' demographic variables such as patient age, sex, and body mass index (BMI). From the WBCT imaging, the translational rotation along the x-axis, y-axis, and z-axis were extracted in SECTRA's CT-based RSA (CTMA) software and used to quantify a subject's implant micromotion across post-operative time points.

Results: The age of the subjects ranges from 61-74 years with the average age being 67.11 yrs. This study includes 4 biologically male and 5 biologically female subjects. Pre-operative scans for 7 of the patients have been completed, and two patients have undergone the 6-week post-operative scans. Due to the lack of any 12-week scans being completed yet, there has not been enough imaging to establish a relationship of implant micromotion over different post-operative time points using CTMA software. With IRB approval of 3-week scans and non-WBCT scans occurring recently, observations on the effect of weightbearing and non-weightbearing on implant performance have also yet to be obtained.

Conclusion: Due to the lack of post-operative WBCT imaging at this time, there are not any substantive conclusions that can be reported regarding the use of WBCT technology as an imaging technique for CT-based RSA. However, based on previous studies on CT-based RSA, the novel use of WBCT with CT-based RSA offers an opportunity to better understand how implants in primary TKA patients migrate over time. This study can potentially demonstrate the utility of WBCT imaging and CT-based RSA as a method of understanding surgical implant micromotion over time, which would encourage the growth of safer and more effective imaging techniques for osteoarthritic patients.

Significance of alkaline phosphatase elevations in alcoholic hepatitis

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Introduction: Alcoholic hepatitis (AH) is a common manifestation of alcohol-associated liver disease that is associated with high short-term mortality. The diagnosis of AH is made on the basis of a history of heavy alcohol intake and a specific pattern of laboratory abnormalities including elevated bilirubin and prothrombin time (PT). The severity of AH is estimated using Maddrey's discriminant function (MDF). Raised levels of alkaline phosphatase (AP) indicate cholestasis, which can be seen in various forms of liver injury, but which is not typical of AH. However, for unknown reasons, significant elevations of AP are seen in a proportion of AH cases. It is possible that AP acts as an acute phase reactant (APR) in AH, as has been suggested in other contexts. APRs are serum proteins whose concentrations change in response to inflammation.

Purpose: The goal of this research project is to determine if AP behaves in a manner consistent with other APRs that are routinely measured in patients with AH, such as albumin, transferrin, and ferritin. Secondly, we proposed that elevations in AP may be more common in AH patients with infections.

Methods: Patients age $\geq$18 admitted to the University of Iowa Hospital and Clinics with a primary diagnosis of AH from January 2012-December 2022 comprised the study population. Chart review was performed of the 500 most recent admissions. From this, 332 patients with a confirmed AH diagnosis were identified. Comprehensive chart review was performed. The patients were split into 3 groups, based on initial AP levels: AP $\leq$ the upper limit of normal (ULN, 104 U/L) [group 1: no AP elevation], AP > ULN but $\leq$ 2x ULN [group 2: mild AP elevation], and AP > 2x ULN [group 3: significant AP elevation].

Results: The average age of patients overall was 48+/-11 yrs. The male: female ratio was about 2:1. AP levels ranged from 45 to 1392, with 28 subjects in group 1, 235 in group 2 and 69 in group 3. Group 1 had the highest mean MDF (66+/-65.6), followed by group 2 (48+/-47.6) and group 3 (41+/-40.9); (group 1 vs group 3, p=0.01). Significant correlations between AP and APRs were found only for transferrin (r_s 0.13, p=0.03) and ceruloplasmin (r_s 0.22, p=0.002). The frequency of bacteremia was significantly higher in group 3 (23%) vs group 2 (8%, p=0.0005) but did not differ from group 1 (11%). No significant differences in the frequency of acute kidney injury or hepatic encephalopathy were found among the groups.

Discussion and Conclusion: This is the first study to evaluate the frequency of AP elevations in AH. We found 2-fold or greater elevations of AP in 20% of hospitalized AH patients. AP levels were low/normal in the group with the highest MDF, indicating that severity of AH is not a predictor of increased AP levels in this condition. AP levels correlated only weakly with those of two other known APRs. Although our data suggest that AP levels does not behave as a classical APR in AH, the significantly increased frequency of bacteremia in group 3 suggests that raised AP may be a marker for infection. Further analysis is planned to evaluate whether changes in AP levels are predictive of treatment response, spontaneous improvement, or mortality in AH.

Surgical management of symptomatic vertebral hemangiomas: a single institution experience and literature review

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Mentor: Patrick Hitchon, MD

Introduction:
Vertebral hemangioma (VH) is the most common benign spinal tumor. Most remain asymptomatic and only need monitoring, but some may rapidly grow, extending beyond the vertebral body and invading the paravertebral and/or epidural space, compressing the spinal cord and/or nerve roots ("aggressive" VHs).

Purpose:
There are many treatments for VH, but the efficacy of techniques such as embolization, radiotherapy, and vertebroplasty as adjuvants to surgery are unclear. We sought to summarize treatments and outcomes to guide VH management plans. We shared our institution's experience in managing symptomatic VHs, reviewed the literature on presentation and management options, and proposed a management algorithm.

Method:
We retrospectively reviewed craniospinal VH patients treated at UIHC from January 2005 to May 2022. We retrieved demographic and clinical data from the database and documented neurologic status using pre- and post-operative Frankel scores. X-ray, CT, and MRI were used for radiographic evaluation. Imaging assessed lesion location and appearance, spinal structures, and neural element compression. Surgical treatments included vertebroplasty, decompressive laminectomy with/without instrumentation, and endovascular embolization. Operative complication and morbidity rates were also retrieved.

Results:
Out of 75 patients, 14 underwent surgery and 61 did not. Among non-operative patients, 17 were male, 44 female, aged 14-75 years (median 52); 13 had back/neck pain, others were asymptomatic with incidental diagnoses. They deferred surgery due to minimal pain or no neurologic deficits. Out of 14 surgical cases, 6 were male and 8 were female, aged 18-71 years (median 52.5). Symptoms included neurological deficits (n=9), pain (n=4), or no symptoms (n=1). Thirteen patients underwent tumor resection, 2 had vertebroplasties, and 4 had preoperative embolization done. The median follow-up was 14.5 months. Three patients had radiotherapy, but only one had a recurrence post-surgery. Embolization often reduced intraoperative blood loss, but cohort sizes were insufficient for definitive proof.

Conclusion:
VHs are often found incidentally during routine spine imaging obtained for workup of back or neck pain, most often from typical findings on CT and/or MRI. Observation is suitable for asymptomatic VHs. Vertebroplasty is effective for moderate-to-severe pain. Embolization, decompression, and stabilization are necessary for VHs with neurological deficits/radiculopathy. Radiation is used for recurrent VHs.

Prevalence of Sarcopenia in Patients Undergoing Elective Spine Surgery

Student: Gage Christenson M1

Mentor: Catherine Olinger MD

Contributors: Sarah Ryan MD, Alex Coffman BS, Mike Mariner MD, Cassim Igram MD, Andrew Pugely MD, Department of Orthopedics and Rehabilitation

Background: Degenerative spinal disease is increasing in the aging US population, resulting in an increase in spinal surgery patients. Sarcopenia, defined as generalized, progressive decrease in skeletal muscle mass or function, poses a risk to this geriatric surgical population. Sarcopenia increases with age and is an independent predictor of adverse orthopedic surgery outcomes. In conjunction with elevated BMI, this is termed 'sarcopenic obesity'. Current studies quantifying the presence and risk of sarcopenia in spinal surgery cohorts rely on imprecise or outdated body composition measurements like BMI or the cross-sectional area of the psoas muscle. Bioimpedance analysis (BIA) is a non-invasive, accessible, and efficient tool that provides a more detailed quantification of body composition.

Objective: The purpose of this study is to establish the prevalence of sarcopenia and sarcopenic obesity among patients indicated for elective spine surgery at a single academic institution using BIA.

Methods: A total of 82 patients (40 male, 42 female) indicated for elective spinal surgery between ages 27-100 were enrolled. During their preoperative visit, BIA was used to collect patient body composition, including weight, BMI, and appendicular skeletal muscle index (aSMI). Preoperative patient reported outcomes were also collected. Sarcopenia is defined as aSMI <8.5 kg/m2 for men and 6.3 kg/m2 for women. Obesity was defined as BMI >30.

Results: At the preoperative time point, 22.0% of patients in this study met criteria for sarcopenia, and 3.6% patients met criteria for sarcopenic obesity. The mean age, BMI and aSMI for study participants was 62.29 years, 31.72, and 8.14 kg/m2. The most common procedures performed on enrolled patients was thoracolumbar PSIF <3 levels (n=26), thoracolumbar PSIF > or = 3 levels (n=21), and ACDF (n=14). Sarcopenia was evenly distributed between patients undergoing fusions less than three levels and fusions greater or equal to three levels. Eighty percent of the sarcopenic patients were male (n=12/15). Obese patients averaged 3.49 lbs. more skeletal muscle mass ($p=0.056$) and a significantly higher aSMI ($p<0.0001$).

Conclusion: Sarcopenia is prevalent among preoperative spinal surgery patients at our institution, especially in male patients. This data identifies patients who may benefit from increased surveillance and preoperative nutritional and exercise intervention. Further data collection during postoperative visits will be used to investigate correlation of body composition with surgical and patient reported outcomes.

Expression of RcrB confers resistance to hypochlorous acid in uropathogenic *Escherichia coli*

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To eradicate bacterial pathogens, neutrophils are recruited to the sites of infection, where they engulf and kill microbes through the production of reactive oxygen and chlorine species (ROS/RCS). The most prominent RCS is antimicrobial oxidant hypochlorous acid (HOCl), which rapidly reacts with various amino acids side chains, including those containing sulfur and primary/tertiary amines, causing significant macromolecular damage. Pathogens like uropathogenic *Escherichia coli* (UPEC), the primary causative agent of urinary tract infections (UTIs), have developed sophisticated defense systems to protect themselves from HOCl. We recently identified the RcrR regulon as a novel HOCl defense strategy in UPEC. The regulon is controlled by the HOCl-sensing transcriptional repressor RcrR, which is oxidatively inactivated by HOCl resulting in the expression of its target genes, including *rcrB*. *rcrB* encodes the putative membrane protein RcrB, deletion of which substantially increases UPEC's susceptibility to HOCl. However, many questions regarding RcrB's role remain open including whether *(i)* the protein's mode of action requires additional help, *(ii) rcrARB* expression is induced by physiologically relevant oxidants other than HOCl, and *(iii)* expression of this defense system is limited to specific media and/or cultivation conditions. Here, we provide evidence that RcrB expression is sufficient to *E. coli*'s protection from HOCl and induced by and protects from several RCS but not from ROS. RcrB plays a protective role for RCS-stressed planktonic cells under various growth and cultivation conditions but appears to be irrelevant for UPEC's biofilm formation.

Bacterial infections pose an increasing threat to human health exacerbating the demand for alternative treatment options. UPEC, the most common etiological agent of UTIs, are confronted by neutrophilic attacks in the bladder, and must therefore be well equipped with powerful defense systems to fend off the toxic effects of RCS. How UPEC deal with the negative consequences of the oxidative burst in the neutrophil phagosome remains unclear. Our study sheds light on the requirements for the expression and protective effects of RcrB, which we recently identified as UPEC's most potent defense system towards HOCl-stress and phagocytosis. Thus, this novel HOCl-stress defense system could potentially serve as an attractive drug target to increase the body's own capacity to fight UTIs.

NCC phosphorylation is inhibited by feeding-induced hyperkalemia independently from long-term Potassium intake regulation of NCC expression in mice

Tim Davie, Jim Young, Jonathan M. Nizar

Introduction: Hypertension is a treatable disease that affects approximately half of Americans and maintains a high prevalence worldwide. Sodium chloride cotransporter (NCC) is apically expressed in the distal convoluted tubule of the kidney, is inhibited by thiazide diuretics to reduce blood pressure, and is known to play a role in regulating blood pressure through sodium reabsorption. High potassium intake increases urinary sodium excretion and therefore decreases blood pressure, in part by decreasing NCC activity via dephosphorylation and reduced membrane abundance. Dephosphorylation (inactivation) is stimulated by high basolateral (plasma) potassium concentrations by increasing cytosolic Cl efflux, and this dephosphorylation event has been hypothesized to suppress apical NCC expression over the long-term. Previously, mouse models of potassium-relevant NCC regulation have focused on the effects of chronic feeding. These experiments tested the effect of very short (minutes) and long term (weeks) of potassium intake on NCC phosphorylation and abundance.

Purpose of this study: Elucidate the effect of chronic high-K feeding on physiological response to short term K-feeding in mice with regards to changes in NCC phosphorylation and abundance.

Methods: We fed mice normal or high K diets for 2 weeks. Prior to sacrifice, mice were further divided into 3 sub-groups, (1) 4 hour fast followed by water gavage, (2) 4 hour fast followed by KCl gavage equivalent to 5% of daily K intake (i.e. “meal"), or (3) no fast followed by water gavage. Kidneys and plasma were collected and western blotting was used to determine total NCC and phosphorylated T53 NCC abundance. Serum electrolytes were measured using i-STAT Alinity blood analyzer. We analyzed the relative changes in NCC phosphorylation, abundance, and plasma potassium between groups.

Results: We found that both plasma K or NCC phosphorylation were not altered by chronic high K feeding, as differences between normal and high K-fed mice were only found in mice in the non-fasted group. Total NCC, however, was decreased in the chronic high K-fed mice in both the fasted and non-fasted groups. In mice who were given a KCl “meal” after fasting, a normal K diet “meal” did not alter plasma K or NCC phosphorylation, but the high K diet “meal” resulted in hyperkalemia and reduced NCC phosphorylation, without altering total NCC abundance.

Conclusions: We conclude that the cumulative effects of chronic potassium feeding primarily alters sodium reabsorption through decreasing total NCC abundance rather than decreasing phosphorylated NCC. Also, mice chronically fed a high-potassium diet that are later given a high KCl meal develop repeated feeding-induced episodes of hyperkalemia, which continues to reduce NCC phosphorylation over minutes, a novel observation incongruent with the prior working model of NCC regulation, and expanding our understanding of renal sodium transport regulation and blood pressure control.

Title: Nystagmus recordings and correlation with underlying diagnosis in children

Presenter: Kristin Davis
Mentor: Dr. Alina Dumitrescu, MD
Contributors: Joel Vandelune and Veronica Peotta Jacobsen

Introduction: Nystagmus is uncontrolled, repetitive movements of the eyes. Nystagmus is a clinical symptom associated with a multitude of diseases ranging from neurological causes, such as periventricular leukomalacia or congenital malformations of the brain, to ophthalmic etiologies such as albinism, retinal diseases with onset in childhood, to benign causes. Nystagmus can be clinically described based on its amplitude, frequency, direction of oscillations, and variation with the gaze direction. The diagnostic workup to identify the cause of nystagmus is inclusive and targeted simultaneously, including imaging, electrophysiology, and genetic testing.

Purpose: Despite extensive work done to classify nystagmus, an objective method has yet to be. This study aims to evaluate eye movement recordings' role in the correct and complete diagnosis of patients with nystagmus.

Methods: Patients with nystagmus evaluated in the pediatric ophthalmology and pediatric inherited eye disorder clinics at the University of Iowa were prospectively enrolled in this study. In addition to their regular workup, patients underwent video recording of their nystagmus using the Neurolign Dx 100. This device is an FDA-cleared eye-tracking device previously used for other eye conditions and is currently under investigational use for recording nystagmus. It consists of VR-style goggles worn by the patient. Horizontally and vertically moving targets are displayed, while multiple infrared cameras record the eye movements and oscillations. This painless, noninvasive procedure does not require anesthesia and roughly takes 10 minutes. The recordings are then analyzed to measure nystagmus direction, frequency, amplitude, intensity, and waveform morphology. The nystagmus characteristics will then be compared with the etiology as determined by the clinical workup for correlation.

Results: This is a prospective study that started enrolling patients in 2021. Thus far, our study has enrolled 40 patients, 22 males, and 18 females between the ages of 4 and 18. Nystagmus recordings were successfully obtained from all patients. We were able to analyze all the recordings. Ten individual waveform morphology patterns were identified. The classification and waveform morphology analysis obtained using automatic eye-tracking recordings was more detailed and reproducible than the clinical description. Four different categories of underlying nystagmus etiology were identified in our cohort. Of those enrolled in the study, 45% had oculocutaneous albinism, 22.5% had optic nerve anomalies, 20% had retinal dystrophies, and 12.5% had congenital motor nystagmus. Visual acuity was grouped into 3 categories: good (20/40 or better), moderately decreased (20/40 to 20/100), and poor (worse than 20/100). The underlying etiology correlated with the severity of visual acuity. However, no correlation between the nystagmus waveform morphology or pattern and the underlying diagnosis or visual acuity (as a prognosis factor) has been established so far in this cohort.

Conclusion: So far in this study, we demonstrated that automated nystagmus recording and classification is possible and reliable. This is an ongoing study, and a larger number of recordings are required before drawing the final conclusions on these recordings' clinical applicability and usefulness.

Umbilical cord drug testing and associations of positive test results with PHQ-9 scores

Student: Abby Davison
Faculty Mentor: Abbey Hardy-Fairbanks, M.D., Department of Obstetrics and Gynecology

Background:
Substance use during pregnancy can lead to poorer pregnancy outcomes, including increased maternal and infant morbidity and mortality. In fact, the CDC has identified "mental health conditions (including deaths to suicide and overdose/poisoning related to substance use disorder)" to be the leading cause of preventable pregnancy-related deaths. There remains a critical need for reducing substance use rates during pregnancy. In the general population, substance use is often associated with co-existing mood disorders and polysubstance use is associated with a high likelihood of depression. However, little is currently known about the association between perinatal substance use and maternal depression screening in the antepartum and early postpartum period.

Methods:
A retrospective chart review was completed for neonates and their birthing parent whose umbilical cord underwent drug screening following delivery from January 2022 to February 2023. Demographic data, obstetrical/neonatal outcomes, drug screening results and other health history information were collected from the electronic medical record. UIHC screens for depression using Patient Health Questionaire-9 (PHQ), which is a validated screening tool for depression in pregnancy and PHQ data was also collected. A screening score $\geq$10 is considered concerning for a mood disturbance. Descriptive statistical methods were used to summarize collected data. Chi-square or Fischer exact tests, and t-tests tests were used when appropriate to analyze the associations between drug screening results and PHQ-9 scores. Statistics were calculated using OpenEpi Version 3.0.

Results:
Demographics: The cohort of pregnant persons (n=170) included 112 people who identified as white (65.9%), 34 Black (20.0%), 11 were Hispanic (6.5%), and 13 who identified as other (including multiple races) (7.6%). 113 pregnant persons (66.5%) had public insurance, 41.4% were married at time of delivery. 42.0% reported active tobacco use in pregnancy, while 25.6% reported substance use during pregnancy, with THC being the most reported substance.

Umbilical cord drug screening results: Of the 170 umbilical cords tested, 40 (23.5%) returned positive for substances. 7 of the 40 positive tests (17.5%) showed legally prescribed substances, but 39 (97.5%) showed illicit substances that were not prescribed. Of these 39 positive tests showing illicit substances the most common substance found was THC (n=33, 84.6%), stimulants were found in 10 subjects (25.6%) were positive for stimulants and 6 tests were positive for multiple substances.

PHQ-9 scores: Throughout the ante- and postpartum period, pregnant persons whose umbilical cords screened positive for substances had PHQ-9 scores that trended higher than those whose cords screened negative. Mean and positive PHQ scores were significantly higher and had higher rate of a positive screen in pregnant persons with positive cord tests at NOB visit and in 3rd trimester.

Conclusions:
PHQ-9 scores obtained at all points in the antepartum and postpartum period tended to be higher among pregnant persons whose babies had positive umbilical cord drug screenings, as opposed to those whose screenings were negative. Patients who endorse current or a history of substance use would benefit from additional mental health screening and intervention. Additionally, people identifying as Black only make up about four percent of Iowa's population, and approximately one-third of Iowans have publicly funded insurance. This cohort of patients who underwent umbilical cord screening had a demographic make-up that much higher proportion of patients who identify as Black and those with public insurance. This may be due to associations of lower socioeconomic status with increased risk for substance use in pregnancy, but the possibility of bias in choosing persons for whom drug testing is indicated cannot be eliminated. Considering that less than 25 percent of the cord tests in this study screened positive for substances, these demographic groups are likely being over-tested for substance use. In February 2023, the list of possible indications for providers to order umbilical cord drug screening narrowed substantially in hopes to decrease unconscious bias in ordering and to allow for testing of the appropriate patient population. Our project is only examining data from umbilical cords tested prior to that change, so future study is needed to compare data collected in this study to those collected after the policy change.

Title: Baseline Differences of Body Composition Between Patients with Femoroacetabular Impingement versus Hip Dysplasia.

Authors: Irving Delgado-Arellanes, Steven Leary, Elle McCormick, Aspen Miller, Nicholas Bender, Courtney Seffker, Jenna Jenison, Michael Willey, Robert Westermann.

Presenting Author: Irving Delgado-Arellanes

Objective
Body composition and sarcopenia have an increasingly recognized impact on outcomes following orthopedic surgery but have not been studied in hip preservation patients. This study aims to compare preoperative body composition in patients undergoing hip arthroscopy for femoroacetabular impingement (FAI) versus periacetabular osteotomy (PAO) or femoral osteotomy (FO) for hip dysplasia and to assess its impact on baseline patient-reported outcome measures (PROs).

Methods
We prospectively enrolled patients indicated for arthroscopy or arthroscopy with PAO/FO and measured preoperative body composition using bioelectrical impedance analysis (BIA). We collected skeletal muscle mass (SMM), percent body fat (PBF), dry lean mass (DLM), lean body mass (LBM), extracellular water/total body of water ratio (ECW/TBW), and appendicular skeletal muscle mass index (ASMI). We measured alpha angle for FAI patients and lateral center edge angle (LCEA) for dysplasia patients to assess severity. Finally, we collected baseline international Hip Outcome Tool (iHOT) score. Results are reported as mean ± standard deviation. Student's t-test and linear regression were used to assess significance.

Results
We enrolled 40 FAI subjects (33 female, 82.5%) and 35 dysplasia subjects (32 female, 91.4%). Preoperative alpha angle and LCEA were 67.41±9.04° and 23.85°±8.47°. For FAI subjects, body composition was: SMM 28.18±6.94kg, PBF 30.06±8.84%, DLM 13.60±3.05kg, LBM 49.91±13.62kg, ECW/TBW 0.380±0.01, and ASMI 7.22±1.18. Body composition for dysplasia subjects was: SMM 26.29±4.67kg, PBF 31.31±10.15%, DLM 12.81±2.09kg, LBM 47.81±7.75kg, ECW/TBW 0.380±0.01, and ASMI 6.93±0.84. Body composition did not differ between groups. Preoperative iHOT scores were 29.78±16.20 for FAI and 27.86±13.86 for dysplasia subjects (p=0.589). SMM demonstrated a significant correlation with iHOT score (**r=0.245, p=0.034**).

Conclusions
BIA is a reliable tool to establish body composition in hip preservation patients. Preoperative body composition did not differ among dysplastic or FAI subjects. Higher preoperative SMM was associated with higher PRO scores. Future studies are warranted.

Machine Learning with Multiple Modalities of Brain Magnetic Resonance Imaging Data to Identify the Presence of Bipolar Disorder

Student: Lubin R. Deng
Mentor: Vincent A. Magnotta
Collaborators: Gail I. S. Harmata, Ercole John Barsotti

Background: Bipolar disorder (BD) is a chronic psychiatric mood disorder that is solely diagnosed based on clinical symptoms. These symptoms often overlap with other psychiatric disorders including major depression and schizophrenia, which can lead to misdiagnosis. An increasing number of studies has attempted to use machine learning (ML) to create predictive models for BD based on data from brain magnetic resonance imaging (MRI). Most ML studies have focused on a single modality of MRI data (e.g., functional connectivity) and typically excluded the cerebellum. These studies commonly reported classification accuracies of 60%-85%. Stronger prediction performance may be achievable by combining information from multiple modalities of MRI data and including the cerebellum.

Purpose and hypothesis: In this study, we used ML to differentiate between participants with and without BD type I by combining information from structural, functional, and diffusion-weighted imaging of the forebrain and cerebellum. We hypothesized that a moderate prediction performance would be observed using each of the modalities individually, and high accuracy would be achieved by combining information from all three modalities. We also hypothesized that features from the cerebellum would play a key role in the prediction.

Methods: Participants with BD type I and matched controls were recruited into a multi-sequence MRI study. We obtained volumetric data, resting state functional connectivity data, and diffusion-weighted (NODDI) imaging data on 186 participants (108 BD I, 78 control), 38 of whom were randomly selected as test subjects. For each of the three modalities of MRI data, a ML model was selected by performing holdout validation on the non-test subjects. The selected model was then trained on all non-test subjects and used to generate a prediction of the class of each test subject. Voting was performed with the three models' predictions; the final predicted class of each test subject was the one predicted by at least 2 of 3 models. The prediction performance was determined, and the most important predictor variables were explored.

Results: The selected ML model for each modality and its performance were (modality—model, test accuracy/F1 score/ROC AUC): volumetric—neural network, 0.816/0.851/0.770; connectivity—logistic regression, 0.842/0.857/0.868; NODDI—AdaBoost of decision trees, 0.763/0.791/0.744. Voting resulted in an accuracy of 94.7%, F1 score of 0.955, and ROC AUC of 0.978. Voting with any 2 of the 3 modalities did not achieve metrics as high. Important predictors included cerebral gray and white matter volumes, functional connectivity involving the cerebellum and nodes of the emotional control network, and diffusion metrics in the inferior cerebellar peduncle and tracts of the emotional control network.

Conclusion and significance: It is possible to identify BD with high accuracy in our sample by combining structural, functional, and diffusion-weighted MRI data. All modalities were integral to the strong performance. Our results also highlight the key role of the cerebellum in identifying BD. As predictive models for BD with MRI data are further refined and tested, they may transform clinical practice in the future.

Assessing the efficacy of Tec kinase inhibition in alopecia areata

Olivia DiGioia, Maddison Lensing, Ali Jabbari

Background Information

Alopecia areata (AA) is a prevalent autoimmune disease that is characterized by the loss of immune tolerance of the hair follicle, which leads to hair loss. During its growth phase, the hair follicle is in what is known as an immune-privileged state. In AA, the immune-privileged state of the hair follicle is compromised, allowing T cells to attack the follicle and inhibit hair growth. In association with the collapse of the immune privilege of the hair follicle, there is a release of IL-15, which activates NKG2D-expressing CD8 T cells. Stimulation of these cells by T Cell Receptor (TCR) and IL-15 triggers them to release IFNγ. TCR signaling is partially mediated by the Tec kinase family which consists of Itk, Tec, and Rlk. Ritlecitinib is one of the two FDA-approved treatments for AA. It is a dual JAK3 and Tec kinase family inhibitor that has demonstrated efficacy in patients with severe disease. This efficacy suggests that both JAK/Stat signaling elicited through cytokines such as IL-15 and Tec kinase signaling elicited through TCR engagement may be contributing to the pathogenesis of AA. It is as of yet unclear, however, what role Tec kinases play in AA pathogenesis, and whether or not Tec kinase inhibition alone is sufficient to treat AA.

Hypothesis/Purpose

We hypothesize that the pathogenic CD8 T cell population relies on Tec kinase signaling in order to elaborate effector functions such as IFN-γ production, and blockade of this signaling will prevent AA onset.

Methods

We used qPCR analysis to compare the gene expression of Tec kinases in AA and unaffected (UA) C3H/HeJ mice. Lymph nodes and skin samples were isolated from both groups, then CD8+ T cells were isolated; RNA was extracted and used to generate cDNA for analysis. We examined genes for the Tec kinase family members of Tec, Rlk, and Itk, as well as effector-related genes including IFNγ, CXCR3, and NKG2D. Lymph nodes from AA mice were also collected for a proliferation assay and a culture inhibitor test. For the proliferation assay, CD8+ T cells were sorted and cultured for three days. The cells were aliquoted and treated with (1) ritlecitinib, (2) ibrutinib, a pan Tec-kinase family inhibitor, (3) JTE-051, a pan-Tec kinase family inhibitor with high specificity for Itk, and (4) vehicle and dyed with Cell Trace Violet to visualize the amount of proliferation that occurred through analysis with flow cytometry. The CD8 T cells used for the culture test were further sorted into NKG2D+ and NKG2D- populations. The cells were separated into the four treatment groups and cultured for three days in the presence of TCR stimulation. Flow cytometry was utilized to analyze the frequency of cells in each group expressing IFNγ, perforin, granzyme, and CD107a.

Findings/Results

Quantitative PCR analysis suggested that expression trended higher for Itk, Rlk, NKG2D, IFNy, and CXCR3 in AA skin. Tec kinase gene expression was comparable in both groups. For the proliferation assay, the treatment groups had significantly less proliferation than the vehicle group, with lower CD69 expression and proliferation indices. In the culture inhibitor test NKG2D+ group, ritlecitinib and ibrutinib had significantly lower levels of IFNγ, CD107a, perforin, and granzyme than the vehicle group. JTE-051 was trending closely with ritlecitinib, suggesting a similar reduction in effector cell function.

Conclusion

The inhibition of proliferation and inflammatory markers by JTE-051 suggests that it has the potential to prevent alopecia areata onset. Based on the results of the three experiments, Tec kinase family inhibition should be explored further through in vivo murine model experiments to observe potential for therapeutic efficacy of JTE-051.

Determining Which Pediatric Bowel and Bladder Dysfunction Symptoms are Best Treated with Constipation Therapies and Anticholinergics

Presenter: Jackson Dunning
Mentor: Douglas Storm, MD
Collaborators: Christopher Cooper, MD

Background: Bowel and bladder dysfunction (BBD) is a common, heterogeneous problem that accounts for upwards of 40% of all pediatric urology clinic visits. BBD describes a spectrum of lower urinary tract and bowel symptoms that typically manifest in children as urinary and stool incontinence, urinary urgency and frequency, painful urination, and constipation. These children may also suffer from recurrent urinary tract infections, which may cause renal scarring and a reduction in kidney function. In addition to the urinary and gastrointestinal issues, BBD also has a profound impact on a child's mental health, self-esteem, social development, and overall quality of life. Given these issues, it is important not only to properly diagnose BBD, but also to provide an effective treatment plan. The pediatric urology division at UIHC previously developed a validated questionnaire that objectively differentiates the various manifestations and symptoms of BBD. Two common treatments utilized in this population include the treatment of constipation, using various medications, and the use of anticholinergic medications. Unfortunately, it is not clear which BBD presenting symptoms are best treated by these interventions.

Purpose: To identify which BBD symptoms respond best to the use of constipation medications and anticholinergics.

Hypothesis: We hypothesized that certain pediatric BBD symptoms may best respond to treatment with constipation therapies or anticholinergics.

Methods: A retrospective chart review analyzing questionnaire and treatment data from patients aged 5-10 years who presented to University of Iowa Hospitals and Clinics (UIHC) pediatric urology division for evaluation and treatment of BBD over the last 5 years was performed. Patients must have attended at least 2 clinic visits to be included. We collected demographic data, BBD questionnaire data, and prescribed treatments. This data was stored in a RedCap database. In patients who received medical treatment for constipation and those treated with anticholinergics, the BBD questionnaire results collected from a patient's initial visit were compared to the questionnaire results collected from their final follow up visit(s) to assess the efficacy of these treatments.

Results: Data from 300 patients was reviewed and included in the study. Average patient age was 6.1 years and included 89 males (30%) and 211 females (70%). 190 (63%) patients received constipation treatment while 56 patients (19%) were treated with anticholinergics. Compared to their initial visit, patients who received constipation treatment were 37% more likely to report fewer episodes of nocturnal enuresis ($p=0.07$). Patients who received anticholinergics were 54% more likely to report fewer instances of daytime incontinence ($p=0.02$). These patients were also 52% more likely to report less frequency of incomplete bladder emptying ($p=0.03$).

Conclusions: Patients who suffer from nocturnal enuresis often benefit from treatment of underlying constipation, while patients suffering from daytime urinary incontinence and those with the feeling of incomplete bladder emptying may best benefit from anticholinergic therapy.

Title: NREM Sleep Manipulations and Memory Consolidation

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Spatial and declarative memory is strengthened by sleep and weakened by sleep loss. This type of memory requires the hippocampus for learning and consolidation. Previous works suggest that NREM sleep might be most beneficial for memory consolidation in the hippocampus. For that reason, it was hypothesized that elevating NREM sleep duration in mice might strengthen their hippocampus-dependent memory. In this study we targeted the parafacial zone, a nucleus in the brain that has been implicated in generating NREM sleep, in order to increase NREM sleep in mice and assess their changes in memory consolidation. To increase NREM sleep we expressed an excitatory receptor (hM3Dq) in the inhibitory neurons of the parafacial zone. Mice had been trained in a hippocampus-dependent contextual fear conditioning task and then allowed to either sleep normally, or be stimulated for increased NREM sleep. What we found is that our targeting of the parafacial zone did not improve memory consolidation, and the increases in NREM sleep were not as potent when combined with the memory manipulation. Moreover, we found a correlation of poorer memory consolidation with increased NREM sleep. These results may be explained by the projections from the parafacial zone to the parabrachial nucleus. The parabrachial nuclei have a role in contextual fear conditioning, particularly in conveying the pain/noxious sensation from training. We explore the difference in activation in the parabrachial nuclei as a potential explanation for the inverse relationship between parafacial zone activation and memory consolidation. Results are still being analyzed and only preliminary analysis has been done which currently shows increased activation of the caudal parabrachial nuclei. These results were surprising given our predictions on NREM sleep and memory consolidation, although they were complicated by the methodology used. There is still more research to be done into what aspects of sleep play a role in hippocampal memory. Future works on this topic may consider using different manipulations of memory, or alternative targets to study NREM sleep.

Student - Bridget Easler
Mentor - Nicole Novak PhD. Research Assistant Professor. University of Iowa College of Public Health.
Other Collaborators: Heather Dron PhD, Marie Kaniecki MPH, Elyse Thulin PhD
Project title: Examining Dynamics of Consent and Coercion in Sterilization Cases Reviewed by the Iowa Board of Eugenics.
Introduction with background/rationale: Iowa's 1929 sterilization law established the Iowa Board of Eugenics (BoE) to implement its state-run eugenic sterilization program. The BoE, which was composed in part by physician superintendents of Iowa's state institutions, ultimately oversaw the sterilization of 1,910 Iowans between 1934-1974. Upon the BoE's dissolution in 1977, members asserted that they had acted only under the voluntary components of the law by obtaining signed consent forms from the person whom sterilization was proposed for, or their next of kin, family member, or personal friend. However, the 1929 legislation outlined an alternate process to allow a state-appointed guardian to give consent. This and other elements of the operation of Iowa's formal sterilization program call into question whether this "consent" obtained by the board was freely given and fully informed. Further investigation will correct distorted or superficial notions of how and to what degree of voluntariness consent was obtained and operationalized in eugenic sterilization programs and yield better understanding of how everyday patients and Iowans experienced eugenic sterilization and coercive consent practices.
Hypothesis/Purpose: This project aims to investigate processes used to obtain signed forms for sterilization cases overseen by the Iowa BoE, including factors that undermined the ability of individuals and families to give free and full consent to the procedure. This will be accomplished by examining from whom consent was sought and obtained and elements of resistance, objection, and coercion in BoE cases.
Methods: An iterative mixed methods study design was undertaken using restricted Iowa Board of Eugenics records accessed through a research agreement with the State of Iowa Archives. For the qualitative arm, transcribed case files containing correspondence and medical records were reviewed. Thirty oversampled case files containing evidence of overt coercion or objection to sterilization and 10 random cases were included. Predefined codes and categories were developed to identify instances and elements of coercion, objection, and resistance in each case. Additional codes were developed inductively after preliminary case review to ensure that important aspects of the data were not overlooked and to consider less overt aspects of the cases that did and did not allow for free and full informed consent. A matrix was used to organize cases, codes, and illuminating quotes and to compare across and within cases to identify patterns in consent and coercion. Dominant patterns were used to elucidate overarching themes. The quantitative arm utilizes data abstracted from the entire collection of 2,421 case index cards containing documentation of the identity of who signed sterilization forms and their relationship to the sterilization subject. In 94 cases, index cards included signatures from an unclear source and required additional review of the full case file at the state archives to confirm the identity of the signer. These data were then categorized by signature type: self, family, spouse, and state. The demographic and descriptive characteristics of those who were referred to the BoE for sterilization were quantitatively analyzed across these signature type categories.
Findings/Results: Consent was often obtained in the context of significant power differentials, including between families and affiliates of state institutions, the latter responsible for making decisions on when patients could be released. These employees could grant release conditionally and inducement to sign forms agreeing to sterilization emerged as one clear theme in this context. Additionally, signatures were sometimes obtained with the use of aggressive tactics such as persuasion through numerous visits and correspondence and misrepresentation of the purpose and necessity of the procedure. The BoE's professed adherence to the components of Iowa's sterilization that required "consent" is referenced in cases of successful resistance and several public statements. In addition, this objective is evident in the program's routine practice of obtaining signatures from numerous individuals for single cases. However, 30 sterilizations were carried out with consent documented only from a state affiliate or state appointed guardian alone and just 11.3% of cases have documentation of a signature from the person for whom sterilization was proposed. Many of the individuals who signed permission forms for themselves were referred from the community, reflecting a general perception that institutionalized individuals inherently lacked the capacity to consent or participate in reproductive decision making.
Conclusion/Overall significance/Broader perspective Quantitative findings largely reflect BoE assertions that signed forms were obtained in the majority of cases; however, these forms were most commonly signed by family members and signatures were often obtained in context of coercive power dynamics and with the use of aggressive tactics and misrepresentation. Furthermore, this program was bureaucratic and ritualized in the efforts and resources put forth to obtain signatures. These procedures, undertaken to proactively distance the board from potential liability, effectively provided the perception of the BoE acting with "consent" while implicating families and other agencies and people.

Investigating the role of CD4 cells and interferon-gamma in alopecia areata pathogenesis using the C3H/HeJ mouse model

Authors: Yumeng T. Engelking, Samuel J. Connell, Cristina Dix, and Ali Jabbari

Background: Alopecia areata (AA) is an autoimmune disease of the hair follicle (HF) that results in nonscarring hair loss, often seen as defined circular patches on the scalp. Affecting approximately 2% of the population, AA is often associated with reduced quality of life due to increased distress, depression, and anxiety. Healthy anagen stage HFs are in a state of immune privilege (IP), characterized by minimal to no expression of MHC class I (MHCI) molecules of the follicular epithelium. AA is believed to develop as a result of the collapse of IP leading to infiltration of CD4 and CD8 T cells around the HF, suggesting roles for both cell populations. Previous work has focused on the contributions of CD8 T cells in the pathogenesis of AA, however, what role CD4 T cells are playing is still unknown. Interferon-gamma (IFN-γ), a pro-inflammatory cytokine, is believed to contribute to the development of AA, in part by disrupting the IP site of HFs by upregulating MHCI. Activated T cells, including T helper 1 CD4 T cells, are potent producers of IFN-γ, suggesting a contribution of these cells in promoting AA pathogenesis. However, further research is needed to fully understand the role of CD4 T cells and CD4 T cell derived IFN-γ in the pathogenesis of AA.

Purpose: To determine whether IFN-γ production by CD4 T cells contributes to the development of AA.

Methods: Preliminary studies were performed using wild-type or two transgenic strains (10bit/IFN-γYFP and CD4CreERT/IFN-$\gamma^{fl/fl}$) of C3H/HeJ mice, with and without AA. In the first experiment, skin was taken from unaffected and AA affected mice to evaluate for gene expression of MHCI and IFN-γ by RT-qPCR and serum was collected to assess for IFN-γ protein levels by ELISA.
In a separate study, blood and lymph nodes were collected from unaffected 10bit/IFN-γYFP mice to assess for YFP expressing CD4 T cells by flow cytometry. In a third study, CD4CreERT/IFN-$\gamma^{fl/fl}$ mice were injected with tamoxifen or vehicle control. One week later, cells were collected from the lymph nodes and were activated for 7 days *in vitro*. Production of IFN-γ by CD4 T cells was assessed pre- and post-culture by flow cytometry.

Results: Mice with AA showed increased gene expression of MHCI and IFN-γ in the skin and increased protein levels of IFN-γ in the serum as compared to unaffected control mice. We found that in 10bit/IFN-γYFP mice, YFP expression is increased in the T cells following stimulation with PMA/Ionomycin when compared to steady state levels. Furthermore, following injection of tamoxifen, IFN-γ production was deleted from CD4 T cells in CD4CreERT/IFN-$\gamma^{fl/fl}$ mice, that maintained after *in vitro* activation.

Conclusion: We found that AA affected mice exhibit increased mRNA and protein levels of IFN-γ and that we can successfully delete IFN-γ production in CD4 T cells in our transgenic mice. These results provide the framework for future studies in which we can address the importance of CD4 T cell derived IFN-γ in the pathogenesis of AA.

Differences in Comorbidities and Outcomes of Primary Total Joint Arthroplasty of the Hip and Knee Based on Referral Type at an Academic Center

Bennett Feuchtenberger B.S., Michael Marinier M.D., Ayobami Ogunsola, M.D., MPH, Kyle Geiger M.D., Natalie Glass PhD., Jacob Elkins M.D. PhD.

INTRODUCTION: Primary total joint arthroplasty (TJA) of the hip and knee are some the most successful and common orthopedic surgeries as they give patients pain relief and restore function. Total hip (THA) and total knee arthroplasty (TKA) make up a significant amount of yearly healthcare expenditures. Over the past decade, TJA surgeons have participated in value-based payment models to incentivize reducing cost for an episode-of-care (EOC), defined as the 90-day period following a procedure. Hospitals and physicians are reimbursed with a set fee for care during this time leaving the leaving the HC system to cover any costs related to services subsequent to the surgery within this timeframe. These efforts have been highly effective at reducing the cost of EOC, improving outcomes, and decreasing complication. However, recent target pricing methodology such as that put forth by Centers for Medicare and Medicaid Services (CMS) in the Bundled Payment for Care Improvement- advanced (BPCI-A) has decreased margins and physician reimbursement. There is concern that this has the potential to incentive surgeons to inappropriately refer more complex patients to academic tertiary care centers causing patients to experience more inconveniences post-surgical complications. This can potentially burden not only the tertiary care center but also the patient. This study sought to determine if patients undergoing TKA/THA have different comorbidities and complication rates based on referral type :referrals from non-orthopedic providers, self-referrals, and outside orthopedic referrals. Hypotheses include that patients with an outside orthopedic referral will have more comorbidities and higher rates of complications.

METHODS: This study was approved by our institutional review board. Records of patients referred for primary total hip or knee arthroplasty (THA, TKA) to a single tertiary care center from September 2019 to January 2020 were reviewed. Data included referral type, procedural details, primary insurance, demographics, Charleston Comorbidity Index (CCI), and American Society of Anesthesiology (ASA) classification. Additionally, complications following TJA were noted, including: perioperative fracture, transfusions, surgical site infection, wound complications, unplanned antibiotics, prosthetic joint infection, instability, hip dislocation, pulmonary embolism/deep vein thrombosis, cardiovascular adverse event, revision surgery, number of admissions within 90 days of postoperative period, and total complication rate. A statistician performed Kruskal-Wallis, Wilcoxon, Rank Sum, t-test, and chi- square tests were performed. P-values were adjusted for multiple comparisons using the Stepdown Bonferroni approach.

RESULTS SECTION: In total there were 393 patients included in this study 249 (63%) were non-orthopedic referrals, 104 (26%) outside orthopedic referrals, and 40 (10%) self-referrals. body mass index (BMI, $p=0.02$), percent obese ($p=0.005$), ASA score ($p=0.006$), percent ASA score ≥ 3 ($p=0.009$), length of stay ($p=0.04$) and duration of surgery ($p=0.01$) differed significantly between referral cohorts. Complications differed significantly by cohort in wound complications ($p=0.045$), blood transfusions ($p=0.027$), unplanned antibiotics ($p=0.046$) and patients with ≥ 2 complications ($p=0.001$), .

DISCUSSION: This study compared patients who underwent primary THA and TKA at a tertiary care center based on referral type. Patients referred from outside orthopedic surgeon tended to be more complex given the higher BMI, percent obese, higher ASA score, longer duration of surgery and length of stay. These comorbidities are likely part of the reason for higher rates of complications such as unplanned antibiotics, wound complications, blood transfusion and people with more severe complications. While this data does validate orthopedic surgeons' ability to perform the "eyeball test," it simultaneously strengthens prior literature demonstrating local orthopedic surgeons tend to refer their more complex patients to tertiary care centers. Limitations of study are that it is unknown the motivating reason behind the referral. Additionally, it is impossible to retrospectively know whether the patient would have done better at their local orthopedic doctor versus going to a tertiary care center. However, it does show that tertiary care centers are being burdened with more complex patients by referral from local orthopedic surgeons.

SIGNIFICANCE/CLINICAL RELEVANCE: This study demonstrates local orthopedic surgeons are referring more complex patients to tertiary care centers, resulting in more severe post-surgical complications for the patients undergoing operation by tertiary care surgeons. Current reimbursement policies should be updated to risk stratify patients to avoid incentivizing referring complex patients inappropriately.

Project Title: Artificial Intelligence to Predict the Age of a Hand
Medical Student: Madeline Fitzhugh, M3
Mentor: Dr. Jennifer G. Powers, MD
Collaborators: Dr. Kevin Chu, PhD; Ananya Munjal, MS, BS; Nora Bensellam, BA; April Zhang; Nicole Tin; Hannah Zhang

WHAT A HAND CAN TELL US: ARTIFICIAL INTELLIGENCE TO PREDICT THE AGE OF A HAND

Introduction
Previous age prediction research has combined facial landmarks and texture features to improve age prediction. Characterizing aging is important for both health and aesthetic reasons, but no AI study has sought to predict age based specifically on dermatological signs of aging such as reduced laxity, photoaging, irregular pigmentation, and telangiectasias. Hands provide a unique opportunity to study aging as it relates to vehicle associated sun exposure, occupational exposure, and handedness.

Hypothesis
Demographic differences in particpants such as gender, occupation, and geographic region impacts sunscreen usage. Females and those in certain occupations use more sunscreen. An AI algorithm can predict a person's age within +/- 5 years from visual patterns of hand photographs in a controlled environment.

Methods
Participants were given a survey gathering demographic and sun exposure information. Photographs were standardized using an LED photo box (Light Box Photography, Nezababy Photo Box 9x9 x 72 LED Dimmable Light Portable Folding Studio Light Box) with a green background to control for lighting differences, and distance from target and taken using Apple iPhones and iPads. The dorsal aspect of right and left hands were photographed separately. Images were processed using Local Binary Patterns and combined into a histogram ultimately creating at texture "fingerprint" which is run through AutoML.

Results
Data collection measures have sourced sourced 312 participants, with a distribution of 40% male and 59% female. The majority of participants reported living in the Midwest Region, and are Caucasian/White (70% and 78.5% respectively). Handedness of participants was 89.7% right, 8.7% left, and 1.6% both. In regard to sun exposure, 35% of participants report less than 30 minutes of sun exposure daily. Almost 44% of participants reported "never" wearing sunscreen SPF 30 or greater on their hands. Early statistical anaylsis demonstrated that participants who reported using sunscreen "Almost always" or "Always" on their hands were 52.3% women and only 38.6% men. Gender predicted sunscreen use ($X^2(4)=51.53$, $p<0.001$). Survey participants in the healthcare field reported sunscreen usage at 61.5% while the occupation with participants that reported the lowest rates of sunscreen usage on hands are those in the service industry at 33.3%. The relationship between occupation v. sunscreen usage is statistically significant ($X^2(20)=79.14$, $P<0.001$). Respondents in the South reported highest levels of sun exposure than counterparts in other geographic regions, with a 29% variance in average daily exposure, ($F(3,96)=13.39$, $p<0.001$) indicating a significant statistical association between sun exposure and geographic location. Photographs generated have demonstrated typical signs of photoaging including lentigines, erythematous lesions, hyperlinearity as well as swollen joints, nail changes secondary to chronic disease.

Conclusion
Photographs of hands reveal much more than just signs of aging. Texture and irregular pigmentation are often the first signs of changes, yet size of joints and vascular changes were less anticipated sources of aging identification. . Data sources >300 participants will be able to inform age prediction algorithms, and allow us to compare board-certified dermatologists against their computerized counterparts in the next phase of this study.. We envision age prediction based on texture and irregular pigmentation will allow us to create malignancy prediction timelines and encourage healthier skin practices.

Erica Fossee

Mentor: Dr. Shoshannah Eggers

Collaborators: Vishal Midya

Title

Associations between lead exposure, the microbiome, and cognitive function in adults

Background

Any level of lead exposure is dangerous and can lead to detrimental health effects such as neurological deficits and psychiatric conditions. Previous research has also found connections between lead exposure and changes in gut microbiome composition and diversity. The gut microbiome is composed of many microorganisms residing in the gastrointestinal tract that metabolize nutrients and release metabolites that can affect health throughout the human body. The gut microbiome has also been linked to neurological health, with previous research finding an association between greater gut microbiome diversity and higher cognitive function in adults.

Purpose

The aim of this study was to estimate the association between lead exposure and cognitive function in adults, and the role of the gut microbiome along this pathway.

Materials & Methods

375 participants from the Survey of the Health of Wisconsin were included in this cross sectional analysis. Lead was measured via urine samples, gut microbiota composition was assessed using 16S rRNA sequencing, and cognitive function was measured using the mini-cog assessment. Regression analyses were done to analyze the associations between lead exposure and cognitive function, lead exposure and individual taxa, and cognitive function and individual taxa. A mixture modelling approach was also used to examine the relationship between the microbiome as a whole and lead exposure and cognitive function, with one model representing the lead associated microbiome and the other representing the cognitive function associated microbiome. Models were adjusted for appropriate covariates and analyses were completed in R.

Results

There was no significant association between lead exposure and cognitive function in unadjusted and adjusted models. There were significant positive and negative associations between 29 individual taxa and lead exposure, and between 50 individual taxa and cognitive function. Two taxa (Bacteroides, Oscillospiraceae) were significantly associated with both lead exposure and cognitive function. Both mixture models were significantly and positively associated with both lead exposure and cognitive function. One taxon was common to both the regression and mixture models.

Conclusions

While we did not see a significant association between lead and cognitive function, we saw overlap among the taxa associated with lead and cognitive function as well as associations in the microbiome mixture models. Therefore, it is possible that lead did not affect cognitive function, but the joint effect of lead and the microbiome could have an effect on cognitive function. This knowledge can help us better understand the effects of lead exposure and how we can mitigate its health effects.

Title: Alterations in neonatal immune profiles following chorioamnionitis exposure
Student: Christopher M. Franke
Mentor: Jennifer R. Bermick, MD

Introduction with Background/Rationale: The leading cause of morbidity and mortality in the neonatal period are infections. Neonatal increased infection risk has been thought to be a result of "immature" immune systems and dampened pro-inflammatory responses. These dampened responses are beneficial to the *in utero* fetus, as excessive inflammation is associated with spontaneous abortion and intrauterine growth restriction. Due to limited antigen exposure in utero and major deficiencies in adaptive immunity, neonates rely almost exclusively on innate immune cells for protection against pathogens. Chorioamnionitis is infection and inflammation of the chorion, amnion and placenta and complicates up to 70% of preterm births. Chorioamnionitis exposure causes an early inflammatory response that alters the fetal immune system and dampens responses to secondary pathogens. Chorioamnionitis exposure is known to increase the risk of developing both early and late onset neonatal sepsis. Bulk sequencing methods have shown chorioamnionitis-induced differences in neonatal monocyte RNA expression and epigenetic patterning, but some chorioamnionitis-induced changes are likely too small to be detected using bulk sequencing approaches.

Hypothesis/purpose: Due to the possibility of small changes caused by chorioamnionitis, we utilized single cell sequencing to characterize differential chromatin accessibility and gene expression profiles in neonatal mononuclear immune cells at different degrees of prematurity.

Method: Following the IRB protocol on this NIH-funded project with the Bermick lab and informed parental consent, umbilical cord blood and residual whole blood from routine clinical blood draws were collected. Placentas were analyzed by histopathology to determine the exposure of chorioamnionitis. Mononuclear cells were isolated from whole blood by Ficoll-Isopaque density gradient centrifugation and processed using the 10X Genomics Multiome ATAC + Gene Expression Kit. Samples were sequenced using next generation sequencing and aligned using 10X Genomics Cell Ranger ARC software. Downstream analyses were completed using R packages "Seurat" and "Signac".

Results: After filtering for high quality cells, we analyzed a total of 52,830 cells across three degrees of prematurity defined by the World Health Organization: term (greater than 37 weeks' gestation), very preterm (28 0/7 – 31 6/7 weeks' gestation) and extremely preterm neonates (22 0/7 – 27 6/7 weeks' gestation). Samples were mapped to a reference using gene expression and assay for transposase-accessible chromatin (ATAC) data to infer cell identity. There were 24 different immune cell types identified. The samples were then mapped in an unsupervised analysis showing distinct expression and accessibility patterns across degrees of prematurity and exposure to chorioamnionitis within each immune cell identity.

Conclusions: There are distinct changes in gene expression and chromatin accessibility with exposure to chorioamnionitis, however, more analyses need to be done to determine what is changing in the cells and how it is altering the immune cells and dampening inflammatory responses.

Title: Predictors of Tissue Infarction from Distal Emboli after Mechanical Thrombectomy
Student: Emily Fuller
Mentor: Colin Derdeyn

Background: Distal embolization after endovascular thrombectomy (EVT) is common. We aimed to determine factors associated with tissue infarction in the territories of distal emboli.

Methods: This is a retrospective cohort study of consecutive patients with anterior circulation large vessel occlusions who underwent EVT from 2015-2021. Patients with TICI2b reperfusion after EVT and follow-up imaging were identified. Baseline characteristics, procedural details, and imaging findings were reviewed. Primary outcome was categorized according to the occurrence of infarction at the territory at risk owing to the distal embolus on follow-up DWI-MRI sequence.

Results: From 156 subjects, 97 (62%) had at least 1 infarction in the territories at risk. Hypertension was significantly more prevalent in the infarct group (83% vs. 53%, p=.001). General anesthesia was more commonly used in the infarct group (60% vs. 43%, p=.037). Median number of distal emboli and diameter of the occluded vessel were similar. After adjusting for confounders, hypertension (aOR: 4.73, CI: 1.81-13.25, p=.002), higher blood glucose (aOR: 1.01, CI: 1.00-1.03, p=.023), and general anesthesia (aOR: 2.75, CI: 1.15-6.84, p=.025) were independently associated with infarction. Presence of angiographic leptomeningeal collaterals predicted tissue survival (aOR: 0.13, CI: 0.05-0.33, p<.001). 90-day modified Rankin scale (mRS) scores were worse for the infarction patients (mRS 0-2: infarct, 39% vs. 55%; p=.046).

Conclusions: Nearly 40% of patients with TICI2B reperfusion had no tissue infarction in the territory of a distal embolus. The association of infarction with hypertension and general anesthesia suggests late or post-procedural blood pressure management could be a modifiable factor. Patients with poor leptomeningeal collaterals or hyperglycemia may benefit from revascularization.

Clarity from Chaos: Cataloguing the incidence of chaotic PGT-A results and creating a standard protocol for response

Annie Galloway BA, Ginny L. Ryan MD MA

Introduction: Pre-implantation genetic testing for aneuploidy (PGT-A) is a common adjunct for individuals pursuing fertility treatment through in vitro fertilization (IVF). PGT-A testing assesses the chromosomes in biopsied trophectoderm cells of blastocyst embryos for aneuploidy. This helps determine which embryo might be best for implantation and live birth. Results are typically categorized as euploid (all cells have a normal number of chromosomes), aneuploid (all cells have an abnormal number of chromosomes), or mosaic (a mix of ploidies in tested cells). In 2018, some genetic testing companies created a new PGT-A result category called "chaotic." This was initially considered the most severe category of abnormality, with 6 or more aneuploidies in the biopsied cells, and disposition of these embryos would follow patient disposition directions for other abnormal embryos. In 2022, however, a team at the University of Rochester Medical Center transferred a chaotic embryo to a patient's uterus that resulted in the live birth of a male infant. Several studies have subsequently documented significant rates of euploidy (normal chromosomes) when these embryos were re-biopsied. These new findings add to the rapidly evolving understanding of PGT-A testing, and clear communication and shared decision-making with patients are vital in this scenario. The University of Washington (UW) Reproductive Endocrinology and Infertility (REI) Division wanted to catalogue how many chaotic embryos they had in storage, how many patients were affected, and what the latest science suggested, in order to provide up-to-date counseling and evidence-based care for their patients.

Purpose: Our primary purpose was to catalogue UW's PGT-A test results and look into trends in the data since 2017. Our secondary purpose was to collaborate with Igenomix, the primary PGT-A testing company used by UW, to better understand the latest science and determine an appropriate protocol for communicating chaotic embryo results and offering treatment options to patients.

Method: PGT-A results are stored in a shared file in a secured, HIPAA compliant server. We created a database that documented each PGT-A testing result along with patient DOB, testing company used, number of embryos tested, and any additional PGT-M (pre-implantation testing for monogenic disease) results. We then looked for trends using summary statistics. We met with Igenomix to better understand their implementation of the "chaotic" result in 2018 and their understanding of the science behind these complex outcomes. Finally, the REI Division met to discuss how best to address chaotic PGT-A results moving forward and communicate retroactively to patients who have "chaotic" embryos in cryostorage.

Findings/Results: Rates of euploid, aneuploid, mosaic, and "limited amplification" were similar across different PGT-A testing companies. The addition of the chaotic result categorization did not change Igenomix's rates. Trends have stayed relatively similar since 2017. In our meeting with Igenomix, they explained that initially using the cutoff of six aneuploidies to categorize a result as chaotic was to prevent patients from having to see so many aneuploidies listed. Igenomix only has hypotheses as to the cause behind so many aneuploidies in one embryo. They state that because of observed differences in rates of chaotic embryos across clinics, it may be due to differences in biopsy technique. However, it may also be due to the amplification process within Igenomix as well. Generally, they believe that as you see more aneuploidies they observe, the less likely the result reflects the actual genome. Notably, they report that 38% of chaotic embryos are euploid upon re-biopsy, which indicates that re-biopsy might be an appropriate offering as part of a chaotic embryo result protocol. The REI Division decided that "chaotic" test results will be treated prospectively as non-diagnostic, and patients will be offered re-biopsy or transfer after careful counseling that includes genetics counselors. Patients with these embryos in cryostorage will be counseled similarly and their cryopreserved embryos will be removed from the routine disposition process for abnormal embryos.

Conclusion/Broader Perspective: Emerging and evolving reproductive technologies require attention to continuing provider education and nuanced, multidisciplinary patient counseling. It is vital to take into account a patient's emotional response to information about genetic test results on their embryos.

The Story of Stories: A Qualitative Analysis of Non-Healthcare Frontline Workers' Experiences with COVID-19 Protocols and Health Communication During the Pandemic

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Introduction: The COVID-19 pandemic exacerbated enduring health disparities among frontline workers, including many workers in occupations outside of large healthcare organizations. To ensure an equitable response to the pandemic's long-term health impacts and prepare for future public health emergencies, research is needed to understand the social and structural factors affecting the health of frontline workers. Research incorporating the firsthand experiences and perspectives of frontline workers is scarce, yet crucial to this effort.

Purpose: This project aimed to identify and interpret qualitative themes among frontline workers' experiences with COVID-19 protocols and health information during the pandemic.

Methods: Open-text responses from a community-engaged survey of frontline workers in the Midwestern United States were qualitatively analyzed. The survey covered multiple topics about the COVID-19 pandemic, including personal protective equipment (PPE), vaccines, and healthcare. Of 889 total survey respondents, more than three-quarters of participants provided one or more open-text response. More than 2,500 total open-text responses were provided by respondents in either Spanish or English. A codebook was developed based on the original survey instrument and literature review, and the codebook was then iteratively revised as needed based on emerging topics in the data. Each response was independently coded by two study team members who were fluent in the original language in which the response was written. Analysis was conducted using the MAXQDA software to identify themes, experiences, and perceptions among respondents.

Results: Common themes included PPE usage, vaccines, health communication, regulatory mandates, occupation-related challenges, interpersonal challenges, and trust/distrust. Respondents frequently commented on COVID-19-related health communication. "There are so many conflicting reports about the infection, vaccine, and care," one respondent shared, that it was difficult "to decipher what was real—and caused a lot of anxiety." Respondents were also concerned that the pandemic "became a political game" that made "the medical community so divided." They urged future health messaging to "present facts" rather than "judgment" that makes people feel "less than" about their health decisions. Some respondents expressed gratitude to healthcare providers, while others reported mistreatment when they sought care or needed a medical interpreter. Respondents also reported occupational challenges, including a lack of PPE at their job site, paying out of pocket for PPE, and being "penalized" for time off work. One worker wrote in summary, "We saw over and over again how we and our families' lives were not made to be a priority."

Conclusion/Significance: This research provides firsthand insight into the challenges and perceptions of non-healthcare frontline workers regarding PPE use, COVID-19 vaccines, and pandemic management in workers' own words. This study provides essential guidance to ongoing public health messaging and community health promotion efforts, including those intended to protect the health of persons who work in frontline occupations.

Novel FoxO-targets in the regulation of Diabetes-related muscle weakness

Student: Ryan Gannon
Collaborators: Christie Penniman, Jayarani Putri
Mentor: Brian O'Neill, MD, PhD, Department of Internal Medicine

Background: Decreased muscle strength and mass is a common finding in individuals with poorly controlled diabetes. This decline negatively affects this patient population's ability to function independently, contributes to disability and mortality, and has been linked to an inability to adequately recover from surgery. The O'Neill lab and others have previously shown that in type 1 diabetes, loss of insulin action results in high muscle turnover rate, loss of muscle mass and a decrease in mitochondrial respiration and expression of the mitochondrial proteins crucial to this process. Furthermore, muscle atrophy and mitochondrial dysfunction in mouse models of type 1 diabetes were rescued by muscle-specific FoxO deletion. Unfortunately, systemic inhibition of FoxOs can lead to cancer in non-muscle tissues as FoxOs are tumor suppressors. Given this, our project sought to characterize a muscle-specific protein downstream of FoxO called Lrrc2.
Lrrc2's expression is limited to cardiac and skeletal muscle tissue, is dysregulated in diabetes, and is highly associated with mitochondrial genes in human heart failure. Otherwise, little is known about Lrrc2.
Purpose: To use a three-pronged approach to describe the role of Lrrc2 in diabetes related decline of muscle strength and mitochondrial function.

1. Evaluate the subcellular localization of Lrrc2 in muscle.
2. Establish an in vitro *diabetic milieu* in C2C12 muscle cells to evaluate the effect of Lrrc2 overexpression and knockout on mitochondrial respiration and uncoupling.
3. Determine the protein interactions and subcellular localization of Lrrc2 in muscle under normal and diabetic conditions in C2C12 muscle cells.

Methods: Approach 1 was sought with immunofluorescent confocal microscopy using samples previously collected. Plasmids containing either Lrrc2-GFP or GFP (control) were introduced into diabetic (STZ) and non-diabetic mice by an injection and electroporation method. A mito-BFP plasmid (a fluorescent protein know to localize to mitochondria) was co-electroporation for mitochondrial co-localization. After 14 days, these mice were sacrificed, and tissues were harvested and prepared for confocal imaging. In Approach 2 we used various treatments (palmitate + high glucose, palmitate alone, CCCP) in C2C12 muscle cells after 4 days of differentiation into myotubes. The effect of these conditions on mitochondrial respiration and uncoupling was evaluated using a Seahorse Bioanalyzer. Approach 3 is being elucidated by generation of a stable C2C12 cell line which selectively expresses a TurboID-Lrrc2. TurboID is a novel proximity labeling (PL) enzyme that attaches biotin markers to nearby proteins.
Results: In approach 1 we saw that Lrrc2-GFP and mito-BFP show clear co-localization. Interestingly, our control GFP-cassette and mito-BFP show co-localization as well. No differences in localization or co-localization were seen between diabetic and non-diabetic mice. In approach 2 we've found that palmitate and high glucose conditions—after optimizing and testing various doses and delivery vehicles—were unable to consistently affect mitochondrial respiration and uncoupling in differentiated C2C12 myotubes and therefore, cannot be used to establish a *diabetic milieu* for these experiments. In approach 3, TurboID constructs—TurboID-Lrrc2 (n-terminal and c-terminal) and TurboID-GFP (control)—have been designed, successfully transfected into HEK293 cells, and their PL activity has been confirmed by western blot. TurboID-Lrrc2 (n-terminal) has been selected as the construct with the greatest transfection efficiency, expression, and retains high-levels of enzyme activity.
Conclusions: In our imaging studies, Lrrc2-GFP looks to be consistently located in the mitochondria of diabetic and non-diabetic mice. We cannot firmly conclude this because our control-GFP also shows strong co-localization to the mitochondria as well. Further studies with higher fidelity microscopy will be completed to elucidate this relationship. From experimental results performed under approach 2, we've concluded that high glucose + palmitate and palmitate alone does not disrupt mitochondrial function in C2C12 myotubes. Given this, CCCP—a known uncoupler which our lab has previously shown can negatively affect mitochondrial function—will be used in future assays. Lastly, we've shown the necessary quality control steps to ensure our PL enzyme constructs—TurboID-Lrcc2 and TurboID-GFP—show high expression, and retain their PL enzyme activity in HEK293 cells. Lentivirus containing these constructs have been made and will be used to generate a stable C2C12 cell line for future experiments.

Assessing the Mechanical Properties of Acutely Injured Lungs: A Comparative Study of Traditional and Novel Ventilation Techniques Utilizing Computed Tomographic (CT) Imaging

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Introduction: Acute Respiratory Distress Syndrome (ARDS) is a severe, often life-threatening condition characterized by an acute inflammatory lung injury that impedes effective gas exchange. Mechanical ventilation, while essential for ARDS management, often struggles to ensure uniform gas exchange due to the structural heterogeneity of the lungs. Moreover, prolonged or inappropriate use of mechanical ventilation can lead to ventilator-induced lung injury (VILI), exacerbating pulmonary dysfunction in ARDS patients. A promising technique developed by Kaczka and colleagues, termed multi-frequency ventilation (MFV), seeks to address these issues. In this study, we used quantitative computed tomographic (qCT) imaging to delve into the pathophysiology of ARDS using a porcine model and compared the effects of two ventilatory strategies: conventional mechanical ventilation (CMV) and MFV.

Hypothesis: We hypothesize that MFV will outperform CMV in optimizing gas exchange and mitigating lung injury within the context of ARDS.

Method: Twelve large pigs, with weights between 36.7-70.0 kg, were pre-anesthetized and subsequently randomized to either the CMV or MFV groups. After acquiring baseline data using lung injury-associated biomarkers and initial CT scans, a lung injury resembling ARDS was induced via oleic acid administration. This was followed by a 9-hour ventilation session, after which a comprehensive post-injury assessment was conducted. Lung parenchyma segments from the 3D-CT image scans were extracted using a convolutional neural network. The Pulmonary Analysis Software Suite was then employed to analyze the quantitative details of lung textures and aeration patterns in both groups.

Results: Baseline comparisons between the CMV and MFV groups revealed no significant disparities. After 9 hours of ventilation post-injury, the MFV group showed a pronounced reduction in respiratory rate and a marked improvement in the PaO_2: FiO_2 ratio, suggesting less respiratory stress and more efficient gas exchange compared to the CMV group. Aligning with these observations, qCT images demonstrated a homogenous lung aeration pattern and diminished tissue consolidation in the MFV group. Further texture analysis confirmed that the MFV strategy preserved a larger proportion of normal lung textures and significantly minimized tissue consolidation compared to CMV.

Conclusion: Our study highlights the potential advantages of MFV over CMV in ARDS management. With indications of improved oxygenation, reduced respiratory stress, and better lung tissue preservation, MFV is a promising ventilatory strategy. These insights deepen our understanding of ARDS and offer potential improvements in its management. Continued research is needed to evaluate the effectiveness of MFV in human ARDS patients and to incorporate these promising findings into clinical settings. Our work is a significant step towards improving patient outcomes in ARDS, an enduring clinical challenge globally.

Investigating the Effects of Complement on Choroidal Endothelial Cells

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Age-related macular degeneration (AMD) is a major cause of vision loss in older adults worldwide with over 200 million people affected. People with AMD experience a loss of central vision that can impair their ability to read, write and recognize faces leading to a significantly decreased quality of life. One challenge in treating AMD is the complex disease pathogenesis with multiple environmental and genetic components affecting disease progression. As a result, there is significant interest in learning more about AMD disease pathogenesis to identify novel targets for therapeutic intervention.

One hallmark of AMD disease pathophysiology is a significant decrease in choriocapillaris density which is seen in AMD and even more severely in geographic atrophy (GA). Immunofluorescence staining of the choriocapillaris for membrane attack complex (MAC), the terminal step in the complement cascade, showed that MAC deposits preferentially within the choriocapillaris and not surrounding structures such as the RPE, indicating a possible mechanism for choriocapillaris loss in AMD. High power confocal microscopy was used to confirm this finding. As such, we hypothesized that this complement deposition within the choriocapillaris leads to alterations in endothelial cell behavior that may be contributing to the development of AMD.

One key feature of endothelial cells is their ability to migrate during vasculogenesis and vessel repair so we assessed the effect of complement on cell migration using a c166 mouse endothelial cell line. Cell injury was induced using a scratch model and cells were treated with either complement-intact human serum, c9-depleted serum or a PBS control. It was observed that cell migration was significantly impaired in c166 cells treated with normal, complement-intact serum when compared to both the c9-depleted and PBS control groups. Immunofluorescence staining verified the deposition of MAC only in the normal serum group but not the c9-depleted or PBS control groups suggesting the impaired cell migration is due to MAC deposition on the endothelial cells. This has important implications for AMD disease pathophysiology suggesting complement deposition may have a role in impairing key endothelial cell functions that may ultimately contribute to the development of AMD.

Title: Disinfecting Luer-lock Syringe Tips of ST-5 *S. aureus* for Anesthesia Intravenous Access

Participants: Stephanie Gibbons, Dr. Randy Loftus, Dr. Franklin Dexter

Abstract

Background. Luer-lock syringe tips in the OR have been coming back positive for contamination. Contamination of these tips allows for nosocomial infection, which poses a threat to patient health and safety. Outlining a disinfection method for luer-lock syringe tips that is both effective and practical is of utmost importance to reduce the likelihood of bloodstream infections introduced by syringe tips since bloodstream infections have been shown to increase patient morbidity and mortality. 70% isopropyl alcohol (IPA) is commonly used in OR room to disinfect syringe tips. On the market, two notable devices that use 70% IPA are Curos tips and DOCit. These devices can be compared to 70% IPA pads in disinfecting syringe tips. **Hypothesis**. Due to DOCit's additional disinfection method of physical friction, it is expected to perform better than 70% IPA pads and Curos tips in disinfecting syringe tips. **Methods**. This randomized, controlled laboratory-based study compares five different disinfecting methods using 70% on a particularly robust strain of *S. aureus*, ST-5. The methods include 70% IPA pad with a dry time of 10 or 60 seconds, Curos tips with a 60 second dwell time, and DOCit with 10 or 60 second dwell times. **Results**. Multivariate analysis revealed that DOCit applied for 10 or 60 seconds reduced CFU counts by at least 63% relative to 70% IPA pads ($P < 0.0001$) and by at least 41% relative to Curos ($P < 0.0001$). Using univariate analysis, it was determined that the dry time (10 seconds verses 60 seconds) for 70% IPA pads performed the same with 0% of the syringe tips achieving <10 CFU (0/48, $P > 0.99$). Similarly, dwell time for DOCit (10 seconds verses 60 seconds) performed the same with 25% of syringe tips achieving <10 CFU (12/48, $P > 0.99$). Lastly, more than half the syringe tips remained contaminated with ST-5 *S. aureus* ($P = 0.0004$). **Implications**. These results show that between 70% IPA pads, Curos tips, and DOCit, DOCit is the most effective in reducing CFU. However, none of the treatments were able to completely eliminate growth due to the robust nature of ST5 *S. aureus*. Other disinfecting solutions or treatments must be explored to achieve complete disinfection of luer-lock syringe tips.

Evaluating tissue specificity of RNA aptamers discovered via whole-organ cardiac SELEX

Student: Trent Gilbert
Mentor: William Thiel **Collaborators:** Li-Hsien Lin, Jennifer Streeter, Yani Chen, Mary Wilson, James Byrne, Dominic Reddin

Introduction: Cardiovascular disease is the leading cause of death in developed countries, yet the number of new cardiovascular drugs entering the market in the past twenty years has decreased significantly. Currently, about 10% of FDA-approved drugs are approved as cardiovascular therapies and about one third of those drugs target a novel mechanism. Therefore, there is much importance in pursuing novel methods to aid in diagnosis and treatment of cardiovascular disease. RNA aptamers are synthetic, single-stranded oligonucleotide ligands that recognize targets with similar specificity and affinity as antibody/antigen interactions. Aptamers that are found to target cardiac tissue with specificity can then be used to deliver therapeutics in a manner that is specific to the heart. There has been much investigation into conjugation of oligonucleotides to antibodies for targeted gene therapy. In a similar manner, one promising avenue of therapeutic delivery is conjugation of a therapeutic siRNA to a cardiac aptamer. RNA aptamers differ from antibodies in development via a selection process, SELEX, that can ideally result in greater tissue specificity and reduced off-target effects.

Hypothesis: An enriched cardiac aptamer library will exhibit significant specificity for cardiac tissue as compared to non-cardiac tissue.

Methods: The enriched cardiac apatamer library was generated following the SELEX process. An aptamer library was perfused through mouse hearts via a Langendorff heart model and apatamer present in cardiomyocytes was purified and amplified for use in subsequent rounds. We separately performed *in vivo* selection rounds with tail vein injections: mice were injected with purified aptamer and after 1 hour anesthesized. In subsequent experiments, tissues collected after tail vein injections were evaluated for presence of aptamer. To evaluate presence of aptamer in tissues collected, a trizol extraction method was optimized to recover aptamer and enzymatically degrade endogenous DNA and RNA. The optimized isolation protocol involved reinforced ceramic bead homogenizing tubes with the Precellys 24 homogenizer and 20 microliters TRIzol per milligram of collected tissue. Recovered aptamer was then amplified using an RT-PCR procedure, and then quantitative PCR was used to evaluate aptamer present. In doing so, we were able to evaluate selectivity of aptamer that had been amplified from selection rounds. Subsequent investigation will involve conducting high throughput sequencing to identify aptamer sequences most specific for cardiac tissue. To assist with analyzing the sequencing data, three python programs were written to process data from high throughput sequencing. These programs together consolidate fastq data for selection rounds, combine fasta data from all selection rounds to create a non redundant database and enable evaluation of overall read count patterns for better informed aptamer evaluation. These programs were written with memory utilization in mind so as to support increasingly large datasets produced by high throughput sequencing.

Results: The optimized trizol extraction of aptamer was able to more consistently isolate aptamer RNA from tissue compared to previous methods. The selected-for aptamer library from the Langendorff heart selection rounds exhibited significant specificity for cardiac tissue and skeletal muscle. Liver, stomach and brain were all evaluated and demonstrated a significantly lower presence of aptamer. The python programs for assistance with analysis were able to process data at a scale previously unattainable from tools previously utilized by the lab.

Conclusion: Leading cardiac aptamers from the selection round did demonstrate greatest specificity for cardiac tissue. The secondary affinity for skeletal muscle was unsurprising, as components for which aptamers may have affinity in cardiomyocytes could have analogs in skeletal muscle. In comparison to leading cardiac antibodies, the aptamers were not found in high concentration in the liver and further were not elevated in smooth muscle.

Preliminary data from the largest prospective cohort study of neuroendocrine tumors (NET-PRO)

Authors: Alyxandra Golden, Brian Gryzlak, MSW, MA Rhonda DeCook, PhD, Michael O'Rorke, PhD

Introduction: Neuroendocrine tumors (NETs) are tumors that originate in neuroendocrine cells. They can occur anywhere in the body, but they are most common in the GI tract and lungs. Initially, patients with NETs may not experience significant symptoms, which may explain why 40% of NET patients have metastases at the time of diagnosis. By the time the disease is diagnosed, patients can start experiencing more severe symptoms such as carcinoid syndrome. This is caused by the tumor's ability to synthesize and hypersecrete hormones that result in symptoms such as diarrhea, bronchospasm, hypotension, and cardiac defects. Patients with NETs typically have prolonged survival with the disease, so they experience these symptoms for a long time. NETs are relatively rare with 12,000 cases diagnosed in the US each year. Perhaps as a result of this, there is limited data on patients' health-related quality of life. This is concerning considering the significant symptom burden these patients often experience. There's also a lack of data on the optimal sequencing of treatments. Optimal sequencing is challenging because many NET therapies result in toxicity, so patients may lose their ability to withstand toxicity before they run out of treatment options.

Purpose: NET-PRO is a prospective cohort study designed to address the lack of data on NET patients' health-related quality of life and optimal treatment sequence. This is the largest ever prospective NET study.

Methods: NET-PRO plans to enroll 3010 total patients from 14 clinical sites across the country with the University of Iowa as the coordinating center. The study started recruiting patients in July of 2021 and patient recruitment is scheduled to end in June of 2024. Each patient will complete 4 surveys administered at 0, 6, 12, and 18 months. These surveys collect general health information, information about patients' experiences with NET symptoms and treatments, and demographic information. As of July 2023, 1037 patients have completed survey 1. Although patient enrollment and survey administration is not complete, we wanted to take a preliminary look at what patients were reporting on survey 1.

Results: Initial analysis of patient demographics showed the age of male patients at diagnosis was statistically different from female patients. 35.6% of female patients were younger than 50 at diagnosis compared to only 18.4% of males (male mean age = 59.5, female mean age = 54.7). Next, patients were categorized based on whether their overall health-related quality of life had been impacted by their NET based on a set of 42 measures. Of the impacted patients, 62% were female and 38% were male. Furthermore, 70% of patients with an income less than $100K were impacted compared to only 55% of those making $100K or more.

Conclusion: Although performed on preliminary data only, this analysis indicates that meaningful differences exist in the NET patient population. Further study with data collected from NET-PRO will help identify those differences, why they exist, and how they can be addressed. This knowledge could help improve treatment and quality of life for patients living with this disease.

Title: Fever as a protective factor for development of lung injury and kidney injury in patients with sepsis

Presenter Name: Klaudia Golebiewski, BS
Mentor Name: Nicholas Mohr, MD, MS
Collaborators: Priyanka Vakkalanka, PhD, Sydney Krispin, MPH, MA, Katie Schneider, MSN, RN

Introduction: Sepsis is a severe inflammatory response to infection leading to multiple organ dysfunction and high risk of mortality. Sepsis patients are at risk for developing specific organ failures, such as lung injury and acute kidney injury, which complicate recovery and lead to higher mortality. Fever has been associated with lower mortality in sepsis, more robust immune response with fewer secondary infections and prolonged organ dysfunction, but the role of fever in the development organ failure is unclear.

Purpose: We aimed to determine the association between fever and the development of lung injury and kidney injury. We hypothesized that higher maximum fever, rather than cumulative fever, would be associated with lower incidence of lung and kidney dysfunction in patients with sepsis.

Methods: This was a retrospective cohort study of patients diagnosed with severe sepsis or septic shock in the University of Iowa emergency department between May 2020-October 2022. We manually extracted vital signs, laboratory findings, and diagnoses from the electronic health record. We defined lung injury as $PaO_2/FiO_2<300$ and kidney injury as serum creatinine of ≥0.3 mg/dL or ≥50% within 2 days, less than 0.5 mL/kg/h urine production, or dialysis initiation. We stratified patients into fever categories (<37, 37-38, 38-39, >39°C) for maximum fever within 24 hours and calculated cumulative fever as (temperature minus 37°C) x time (within 4 days). We evaluated the association between fever and organ failure within 7 days.

Results: Of the 518 patient hospitalizations for sepsis, 227 met inclusion criteria (52% male). The prevalence of lung injury was 37% (n=85) and kidney injury was 89% (n=202). Moderate fever (37-38°C) on Day 1 was associated with increased lung injury relative to no fever (odds ratio [OR] 1.80, 95% CI 1.15-2.82), and high fever (>39°C) was associated with an even higher risk (OR 2.02, 95% CI 1.01-4.05). We found no relationship between fever and kidney injury.

Discussion: Fever was associated with increased incidence of lung injury. Future work will use covariate adjustment and mediation analysis to understand to what extent fever contributes to organ failure development and timing.

Abstract Title: Risk of vision threatening complications with sports in Juvenile X-linked Retinoschisis
Presenter: Kaitlyn Grimes
Mentor: Arlene Drack, MD
Collaborators: Alina Dumitrescu, MD

Background/Introduction: Juvenile X-Linked Retinoschisis (JXLRS) is a hereditary retinal disorder caused by pathogenic variants in the gene *RS1*. *RS1* encodes retinoschisin, necessary for cell adhesion and structure in the retina. Lack of a fully functioning protein leads to separation of the retinal layers, known as retinoschisis. The result is progressive vision loss with onset in childhood. Patients with JXRS may experience complications like retinal detachment (RD), vitreous hemorrhage (VH), and posterior vitreous detachment (PVD), which can result in vision loss or blindness. These complications are more common with ocular trauma, so many ophthalmologists recommend that patients with JXLR avoid contact sports. However, many patients with JXLRS make the decision to play contact sports and are counseled on the importance of wearing protective eyewear such as sports goggles or face guards while participating in sports.

Aims/Hypothesis: To evaluate and compare the risk of developing ocular complications as a result of eye trauma that is related to sports and eye trauma that is unrelated to sports in a cohort of patients with JXLRS. We hypothesize that patients with JXLRS who play contact sports without safety goggles will have more vitreous hemorrhages, posterior vitreous detachments, and retinal detachments than those who do wear safety goggles.

Methods: This was a retrospective IRB-approved study of 53 patients with JXLRS who were followed at the University of Iowa Department of Ophthalmology. The information collected and analyzed from chart review includes age, gender, ethnicity, history of participation in sports, history of wearing safety goggles/face guards, diagnosis and cause of ocular complications, and the age at which ocular complications occurred.

Results: 53 patients, all boys, met the inclusion criteria for the study. Out of 53 patients, 22 were confirmed to participate in sports currently or previously. Of these 22 patients, only 2 were evaluated due to ocular trauma during participation in sports. 1 of these patients was diagnosed with a complete PVD in the left eye with small vitreous hemorrhage due to sports-related trauma during wrestling. The other patient had a significant enough sports-related eye trauma during baseball to cause angle recession but was not found to have RD, PVD, or VH. Of these 22 patients, 8 were confirmed to wear safety goggles or face guarding while participating in sports, 0 of which were evaluated for sports-related eye trauma. 2 of the 22 patients were confirmed to not wear protective eyewear while participating in sports, 1 of which was the patient evaluated for sports-related (baseball) eye trauma and not found to have PVD, RD, or VH. We were unable to confirm the protective eyewear status for 12 patients playing sports, 1 of which was the patient evaluated for sports-related (wrestling) eye trauma and diagnosed with partial PVD in the right eye and complete PVD in the left eye with small vitreous hemorrhage. Out of 53 patients in the study, 6 were evaluated for trauma to the eye that occurred outside of sports, 3 of which were diagnosed with RD and 3 of which were diagnosed with VH. The traumatic ocular events include 2 head collisions, 1 self-poke, 1 fall from a bike, 1 water balloon strike, and 1 unspecified trauma.

Conclusion: RD, VH, and PVD occurred due to trauma but not necessarily trauma related to sports. Of the 8 patients who did wear goggles when playing sports, none were evaluated for a sports-related eye injury, however 1 was evaluated for an eye injury that occurred outside of playing sports when not using protective eyewear. This suggests that boys with JXLR should be encouraged to wear glasses daily for protection as well as sports goggles and face guarding during sports because they may experience trauma to the eye during daily life, even when they are not playing sports.

Associations between NIH Toolbox Emotional Battery measures and previous suicide attempt in bipolar disorder type I

Noah M. Gritters, Gail I. Harmata, Ercole John Barsotti, Jess G. Fiedorowicz, Aislinn Williams, Jenny Gringer Richards, Leela Sathyaputri, Samantha L. Schmitz, Gary E. Christensen, Jeffrey D. Long, John A. Wemmie, Vincent A. Magnotta

Abstract

Introduction: Suicide attempts are much more common in people with bipolar disorder type I (BD-I) than in the general population. In an attempt to explain and reduce this risk, multiple emotional measures have been individually associated with suicide attempts in BD-I. However, utilizing a brief set of multidimensional measures has not been explored. We used the NIH Toolbox Emotional Battery (NIHTB-EB) to assess various emotional measures and determine which ones were associated with a prior suicide attempt in participants with BD-I.

Methods: The study consisted of 56 controls, 50 BD-I non-attempters, and 42 BD-I attempters. All participants completed the NIHTB-EB, which consists of 17 emotional measures in four subdomains. The subdomains are Psychological Well-Being (PWB), Social Relationships (SR), Stress and Self-Efficacy (SSE), and Negative Affect (NA). Suicide attempt status was determined using the Columbia-Suicide Severity Rating Scale.

Results: There were eleven emotional measures associated with suicide attempts after correcting for multiple comparisons. These were general life satisfaction (PWB), emotional support (SR), instrumental support (SR), friendship (SR), loneliness (SR), perceived rejection (SR), self-efficacy (SSE), perceived stress (SSE), sadness (NA), anger-hostility (NA), and anger-physical aggression (NA). The six measures not associated with suicide attempts were positive affect (PWB), meaning and purpose (PWB), perceived-hostility (SR), fear-affect (NA), fear-somatic arousal (NA), and anger-affect (NA).

Conclusion: Our results suggest the NIHTB-EB is largely in concordance with previous studies looking at individual emotional measures. In particular, Social Relationships and Stress and Self-Efficacy subdomains have a high proportion of measures associated with suicide attempts in BD-I. As such, these areas could be promising targets for further longitudinal studies or interventions aimed at reducing the risk of suicide attempts in people with BD-I.

Retrospective Review of Swallowing Outcomes for Oropharynx and Larynx Patients after Chemoradiation

Student: Austin Halupnik, BS
Mentor: Carryn Anderson, MD, Department of Radiation Oncology
Other Collaborators: Brian Peterson, MA, CCC-SLP, Bradley Loeffler, MS, Shri Rajan, MD

Background

Head and neck cancers (HNC) are among the most common global malignancies, with high rates of mortality. Although the utilization of chemoradiation has led to increased survival among those with HNC, many patients suffer from dysphagia as a result of the treatment. This ranges from difficulty swallowing solid foods to a dependency on feeding tubes. Dysphagia predisposes individuals to increased medical comorbidities, increasing their likelihood of pneumonia, prolonged use of a feeding tube, and weight loss. Dysphagia also affects patient quality of life, as individuals may require changes in eating patterns and experience pain and discomfort. Considering the consequences of dysphagia, it is important to detect dysphagia promptly to allow for swallowing rehabilitation and nutritional assistance. There are a variety of datapoints that aid in holistically describing the course of dysphagia prior to, during and following chemoradiation treatment.

Purpose

To collect our institutional experience and assess dysphagia prior to, during and after chemoradiation for oropharyngeal and laryngeal cancer patients. This data can be used for future comparison with patients treated with newer radiation therapy techniques that are designed to decrease cumulative dose to swallowing structures.

Methods

We conducted a retrospective review of oropharyngeal and laryngeal cancer patients who were treated with chemoradiation with curative intent at the University of Iowa Hospitals and Clinics (UIHC) from 2019-2022. Manual chart review was completed using Epic electronic health records. Charts were reviewed retrospectively for patient demographics, tumor characterization, treatment, the use of feeding tubes, and current cancer status. Speech therapy visits were reviewed for multiple outcomes. The EAT-10 scale (scaled 0-40: 0 = no swallowing problems, 40 = severe dysphagia) was used to assess the patients' self-perceived issues with dysphagia. The Penetration and Aspiration Scale (PAS, scaled 1-8: 1 = no penetration, 8 = aspiration with no attempt to clear) and impairment of swallowing phases from oropharyngeal motility studies (OPMS, scaled from normal to severe impairment) were used to assess dysphagia from swallowing imaging. The Functional Oral Intake Scale (FOIS) was used to assess functional oral intake of food and liquids (scaled 1-7: 1 = nothing by mouth, 7 = no restrictions). Linear mixed effects regression was used to estimate the rate of change in mean swallowing assessment scores from baseline, and to assess differences in baseline scores and the rate of change across disease and clinical characteristics.

Results

There were 109 patients who qualified for this study. 89 patients were treated for oropharyngeal cancer and 20 patients were treated for laryngeal cancer. There was a statistically significant increase in the mean EAT-10 scores from baseline to initial follow-up (10.14 vs. 13.27, $p=0.03$) for all patients. The rate of change in EAT-10 scores also significantly differed ($p<0.01$) based on whether the baseline EAT-10 assessment was prior, during or before radiation therapy. Mean PAS scores were significantly greater at initial follow-up compared to baseline (3.94 vs. 3.14, $p=0.04$) for all patients. Additionally, the mean baseline PAS scores were found to significantly differ between larynx and oropharynx patients (4.63 vs. 2.81, $p=0.01$). Larynx patients with a baseline and follow-up OPMS displayed improvements in the pharyngeal and cervical esophageal phases, while oropharynx patients displayed a decline in each of these phases, although these differences were not statistically significant. Patient-reported dysphagia via EAT-10 scores generally mirrored clinician assessments via PAS and OPMS.

Conclusion

Retrospective review of swallowing outcomes at UIHC indicates that dysphagia worsens in oropharyngeal and laryngeal cancer patients in the months immediately following chemoradiation. During this period, patients experience more self-perceived issues with swallowing and have higher degrees of penetration and aspiration. Patients treated for laryngeal cancer have higher degrees of penetration and aspiration than oropharyngeal cancer patients at baseline. Additional data, including FOIS data, is yet to be interpreted. Future prospective studies will continue to evaluate swallowing outcomes at UIHC for oropharynx and larynx cancer patients treated with newer radiation techniques.

Measurement of Health Utility in Reconstructive Urologic Surgical Procedures

Student: Samuel Hansen, M2
Primary Mentor: Bradley A. Erickson, M.D., M.S., Professor, Department of Urology
Secondary Mentors: Dan Shane, PhD Associate Professor, Department of Health Management and Policy; Charles H. Schlaepfer, M.D. (Uro-4)

Introduction
Health state utility value (HSUV) research is designed to quantify the perceived impact of a certain health condition through questions about hypothetical scenarios. Tools to assess these health states typically use a visual analogue scale (VAS), the standard gamble (SG), time trade off (TTO), and willingness to pay (WTP). To our knowledge, these tools have not been widely utilized for benign urologic reconstructive procedures. Applying these tools for surgical procedures that may not extend lifespan but will likely improve quality of life offers benefits including improved patient counseling, resource allocation, and awareness of the burden of these conditions on society.

Purpose
The purpose of our study was to define the HSUV of several urologic conditions, and avenues to improve those conditions, that may result from the treatment of prostate cancer (CaP). We sought to define the degree of negative impact a health state has on the individual, specifically focusing on patients with CaP. Defining the HSUV of these conditions and treatments would serve as a basis for objective measures of patient satisfaction and perceptions on outcomes and resulting quality of life.

Methods
Eligible study participants were identified by a medical records search for patients with CaP that had urology clinic appointments in July and August, 2023 and were between the ages of 50 and 80. Eligible patients were contacted via email and asked to complete a survey designed to assess HSUV associated with benign urologic conditions. Demographic and medical history were abstracted from medical records. Patients were given a brochure in the clinic if they had previously been emailed but did not submit a survey response. Surveys using VAS, SG, TTO, and WTP included scenarios about the following health conditions and treatments: blindness (mono-/binocular), osteoarthritis, erectile dysfunction (ED), inflatable penile prosthesis (IPP), stress urinary incontinence (SUI), and artificial urinary sphincter (AUS). Validated urologic health questionnaires were also used to capture patients' perceived urologic health. Statistical analysis included mean and standard deviation of the techniques for all scenarios and demographic data.

Results
There were 32 patients that met inclusion criteria, all of whom were in various stages of CaP care, with a mean age of 66.7 [SD 7.2]. The mean health state ratings from lowest to highest were as follows: binocular blindness (39.0 [22.2]), SUI (57.3 [22.7]), ED (65.0 [24.5]), osteoarthritis (72.0 [19.9]), and monocular blindness (75.0 [14.2]). The mean willingness to risk death during surgery for disease state cure from lowest to highest were as follows: osteoarthritis (19.3% [27.0]), ED (20.5% [25.0]), SUI (24.6% [27.9]), monocular blindness (29.3% [29.2]), and binocular blindness (46.3% [28.7]). The mean number of years (out of 20) one would give up for disease state cure from lowest to highest were as follows: ED (2.7 years [3.7]), osteoarthritis (2.9 years [4.7]), monocular blindness (3.8 years [6.3]), SUI (4.3 years [4.5]), and binocular blindness (4.9 years [3.9]). The mean percent of year income one would give up for disease stage cure from lowest to highest were as follows: osteoarthritis (27.4% [26.9]), ED (32.2% [30.7]), monocular blindness (40.6% [32.7]), SUI (41.8% [32.9]), and binocular blindness (59.0% [31.8]).

Conclusions
Conditions associated with CaP treatment, such as erectile dysfunction and stress incontinence, cause significant distress and impair quality of life in patients. This negative impact on quality of life is on average greater than other common, debilitating conditions such as monocular blindness and osteoarthritis. Consistent in each metric, SUI was, on average, viewed as a worse health state than ED as participants rated it worse, were willing to accept a higher risk of death, give up more years, and give up a larger percentage of annual income for disease state cure. More broadly, our results indicate that the burden of these conditions associated with CaP treatment are of similar magnitude as potentially debilitating conditions like monocular blindness and osteoarthritis. Future analyses will explore potential correlations between HSUV responses, prostate cancer treatments, and patient specific urologic health questionnaire responses to evaluate impact of those factors on perceptions of outcomes and resulting quality of life.

Samual Hatfield, M2G
Medical Student Research Conference, 2023
University of Iowa, Carver College of Medicine

Title:

Foamated Hydrogels act Synergistically with Immune Therapy as a Local Niche for Peritumoral Dendritic Cells

Abstract:

Polymer-based hydrogels offer potential for the localized delivery of therapeutics in treating solid-tumor cancers. When combined with the chemokine Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), these gels can recruit immune cells to the tumor microenvironment, enhancing immune-mediated anti-tumor activity. However, the current design of hydrogels is limited in its ability to engage synergistically with immune cells and host tissues.

Using an affordable and safe food-grade whipping syphon, we developed a method to introduce gas bubbles efficiently into the polymer matrix. This innovation transforms the hydrogels into a porous foam. These foamated hydrogels, when paired with GM-CSF, enable the recruited dendritic cells to migrate into the gel, allowing them to inhabit the peritumoral region for a more extended period in a localized manner.

In a bi-flank murine melanoma model, we observed that tumors treated with foamated hydrogels and radiation exhibited slower growth compared to a control group treated with radiation alone, especially when combined with anti-PD-1 (Programmed cell Death 1) immunotherapy. Moreover, this combination therapy improved overall survival rates by a measurable margin.

The outcomes suggest that foamated hydrogels, GM-CSF, and anti-PD-1 may work synergistically to slow tumor growth and improve survival. Future research is planned to explore different types of gel materials, as well as a range of tumor lines. We will also evaluate the cellular population within these hydrogels and more thoroughly evaluate the material properties of the gels.

By innovatively combining localized therapy with immune cell recruitment, this study offers a promising structural mechanism for enhancing both immune response and host-tissue integration, potentially laying the groundwork for future immune and cell therapy platforms.

The Impact of Systemic Immunosuppression on Cutaneous Wound Healing

Authors: Rachel M. Heinrich, Anthony M. Fleck, Jennifer H. Ong, Trenton Greif, Jennifer G. Powers, and Kelly N. Messingham

Background: Proper wound healing requires coordination of a complicated series of molecular and cellular events. If the phases of wound healing do not happen appropriately, healing can be delayed or incomplete, or exhibit decreased integrity or abnormal scarring. Impaired wound healing results in chronic wounds, which are associated with increased morbidity, mortality, and poorer quality of life that leads to a substantial socioeconomic burden upon healthcare systems. Clearly, then, there is a tremendous need to develop therapies that improve management strategies and health outcomes for patients with chronic wounds.

Immunosuppressive therapies have become increasingly common in clinical practice, but how they impact wound healing is an ongoing topic of debate. This study derives from previous research that aimed to determine the effects of immunomodulatory therapies on cutaneous wound healing and scarring in patients with non-melanoma skin cancers. The unpublished findings indicate that patients treated with immunosuppressive agents had improved wound healing and scarring outcomes; however, the cellular mechanisms of this have not been explored. This study sought to characterize the immunologic and inflammatory milieu in samples of wounded skin from these patients.

Hypothesis: Systemic anti-inflammatory biologic or immunosuppressive therapies will influence factors associated with inflammation and wound healing in skin.

Methods: Skin was collected from patients undergoing excision of non-melanoma skin cancer who were already on immunomodulatory anti-rejection medications post organ transplant, or "no therapy" controls (10/group) (IRB#201905800). Serial skin cryosections (6 μm) on glass slides were labeled with antibodies specific for cells and factors associated with cutaneous inflammation and wound healing, followed by fluorescently tagged secondary antibodies. Images were collected with confocal microscopy and the number of positive cells, % area stained, and/or co-staining were evaluated using NIH ImageJ. Differences were evaluated using non-parametric analyses with p value < 0.05. Trichrome and H&E staining of tissue sections were used to measure thickness of epidermal and dermal matrix and histologic identification of infiltrating cells.

Results: Four panels of markers were used to evaluate different aspects of wound healing: Inflammation and macrophages (CD68, TNF, IL-6, GM-CSF); scar formation (TGFβ1, PDGF, PDGFR α/β); angiogenesis (EN1, CD31, PDI); growth factors (EGF, FGF, ACE-2). At the time of excision, the skin of immunosuppressed patients exhibited decreased levels of GM-CSF and IL-6, consistent with decreased inflammation. Immunosuppressed patients also had increased levels of PDI, a protein that is critical for cell migration, which might facilitate orderly migration into the wound bed, although levels of EN1, which regulates the same pathway, did not appear different. Image analysis and staining quantitation is currently ongoing.

Conclusions: Based on our current analysis, we conclude that systemic immunosuppressants lead to a reduction of inflammation and impacts cellular migration in a way that may be of benefit for cutaneous wound healing.

Student: Jared J. Hill (M1)

Mentor: Charles Yeaman

Poster Title: RalGPS2 Activates RalA for Primary Ciliogenesis in Epithelial Cells

Introduction:

The cilium plays a vital role human health. Diseases with cilia production are implicated in diverse pathologies such as Polycystic Kidney Disease (PKD). While the ciliogenesis has been studied extensively in fibroblasts, the mechanism of cilia formation in renal epithelial cells is less understood. In Madin-Darby canine Kidney (MDCK) cells, it is known that the monomeric GTPase RalA and its downstream effector RalBP1 are required to form a cilia. Because of this, we chose to research the upstream effectors (RalGEFs) of RalA in the ciliogenesis pathway. Using CRISPR/Cas9, we knocked out each of the upstream RalA effector proteins and survey cells for any effects on ciliogenesis.

Methods:

MDCK cells were established in culture for individual knockout and RNA Seq was performed to discover all active GEF's in the MDCK epithelial cell line. CRISPER/Cas9 guided transfections were performed to knock out each individual GEF as well as GFP. Polyclonal pools of cells were fixed and labeled for acetylated tubulin to mark for cilia. MetaMorph v7.8 was used to quantify the percent cilia in each pool of knockouts relative to the number of nuclei. For any GEF responsible for ciliogenesis, knockout gene was re-transfected into the cell line and ciliogenesis was surveyed by immunofluorescence.

Results:

Acetylated tubulin labeling revealed a lack of cilia in the cells with RalGPS2 knocked out. MetaMorph analysis of the polyclonal pools found that the RalGPS2KO cells had significantly less cilia than any other knockout cell line. RalGPS2 Recovery demonstrated a significant increase in cilia. RalGPS2 labeling showed localization to the apical membrane and ciliogenic compartments.

Conclusion:

RalGPS2 is required GEF for upstream activation of RalA which causes ciliogenesis in epithelial cells. During cilia formation, RalGPS2 is localized to the apical membrane for spatial activation of ciliary proteins. The mechanism of cilia formation in kidney epithelial cells requires further study, however GP135 labeling reveals that RalGPS2 activation of RalA is required for a later stage of ciliogenesis which occurs after apical clearing.

The Acidity of Normal Saline Irrigation Impairs Chondrocyte Health by Promoting Oxidative Stress

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Disclosures: Arman Hlas (N), Venkateswaran Ganesh (N), Jaison Marks (N), Joseph Buckwalter (N), Kyle Duchman (N), Kyungsup Shin (N), James Martin (N), Dongrim Seol (N)

INTRODUCTION: For decades, surgeons have utilized 0.9% normal saline (NS) for joint irrigation to improve visualization during arthroscopic procedures. This continues despite mounting evidence that NS exposure impairs chondrocyte metabolism and compromises articular cartilage function. NS differs from synovial fluid in terms of its low pH, hypotonicity, and lack of glucose, any of which could contribute to its toxicity. While this indicates a need for a more biocompatible joint irrigant, it is unclear how this can be achieved without better knowledge of the mechanisms underlying NS toxicity. The primary goal of this study was to define the mechanism of NS toxicity in an effort to develop a practical intervention that can be rapidly and widely adopted for clinical use. We hypothesized oxidative stress induced by low pH is the dominant factor driving NS toxicity and that buffering NS to increase its pH would help mitigate these effects.

METHODS: Bovine stifle joints were procured from a local abattoir for isolation of primary bovine chondrocytes and synoviocytes. Monolayer and 3D agarose cultures were used to investigate the effects of irrigants on cell viability, morphology, and oxidant production using fluorescent probes and confocal microscopy. Sterilized 0.9% NS and culture media served as a control for all experiments, and 25 mM N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES), a zwitterionic buffering agent, was supplemented to NS to determine the effects of pH regulation. Cell viability was assessed by incubating primary bovine chondrocytes in culture media and normal saline for 3 hours with subsequent staining with CellTiter 96 reagent and quantification using a microplate reader. Changes in cellular morphology were verified by phalloidin immunofluorescence staining and confocal microscopy. Oxidant production was assessed by co-staining samples with Calcein AM and dihydroethidium (DHE) to visualize live cells and reactive oxygen species (ROS) production respectively under confocal microscopy. Metabolomic analysis was completed on treated samples using high-resolution mass spectrometry following gas and liquid chromatography. All quantified data was normalized to culture media control. Data was analyzed by one-way ANOVA with the Tukey post-hoc test using SPSS Statistics. Statistical significance was set at $p < 0.05$.

RESULTS: Cell viability of NS at 3 hours was 43.5 ± 13.9% ($p < 0.001$) compared to control. This cytotoxicity was validated by morphological changes, with severe cytoskeletal damage resulting in dramatic cell shrinkage and detachment in chondrocytes incubated in NS. Chondrocytes treated with NS had increased production of ROS as imaged by DHE staining (Figure 1). The levels of ROS after 3 hour incubation were approximately 500-fold ($p = 0.03$) and 2.4-fold ($p < 0.001$, Figure 1) higher than control in both monolayer and 3D agarose culture systems, respectively. Supplementation of 25 mM HEPES in 0.9% NS significantly reduced cellular damage characterized by phalloidin staining. The addition of HEPES significantly reduced ROS levels in both monolayer culture ($p = 0.033$) and 3D agarose culture ($p = 0.012$, Figure 1). Bovine synoviocytes exposed to NS also demonstrated a similar trend of ROS overproduction with a 3-fold ($p = 0.002$) increase compared to control with HEPES supplementation negating this deleterious effect ($p < 0.001$). Exposure to NS caused disruption of glycolysis, pentose phosphate and tricarboxylic acid pathways and buffering with HEPES helped return metabolite levels to near control levels (Table 1).

DISCUSSION: In the present study, NS exposure induced ROS production in chondrocytes and synoviocytes in addition to cell shrinkage, detachment, and death. Metabolomic analysis clearly showed that NS exposure profoundly disrupted metabolic pathways related to energy production, intracellular signaling, and antioxidant defenses. The addition of HEPES to NS significantly reduced ROS production and cytotoxicity and restored metabolic function to near control levels, supporting the hypothesis that the sub-physiologic pH of NS is at least partly to blame for its negative effects on chondrocytes. This harmful effect, in conjunction with other forms of injury that can occur during arthroscopy including iatrogenic injury and the loss of lubricin, a critical boundary lubricant, from the articular surface could lead to significant injury to chondrocytes and synovium in an already damaged joint. With arthroscopy used increasingly in young and healthy patient populations, the cumulative effects of this damage may be difficult to quantify in the immediate postoperative period; however, these adverse effects may contribute to delayed recovery or increase the risk of osteoarthritis and potential arthroplasty in patients who have previously undergone arthroscopy.

SIGNIFICANCE/CLINICAL RELEVANCE: While NS remains a commonly utilized irrigation solution in arthroscopic surgery, our data suggests that exposure to unbuffered NS profoundly disrupts articular cartilage and synovial cell function which can be reversed through the addition of HEPES, a readily available biologic buffer.

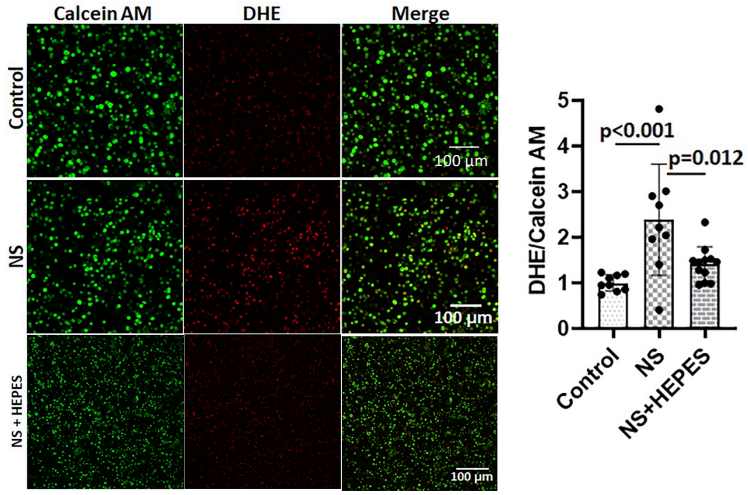

Figure 1: Representative confocal images of DHE and Calcein AM in 3D agarose culture after 3 hours (left) and quantified DHE/Calcein AM ratios normalized by control group (culture media) (n = 9-12, right).

	NS *versus* Control		NS + HEPES *versus* Control	
Metabolites (up)	**Fold change**	**p-value**	**Fold change**	**p-value**
Glucose 6-phosphate	70.3	5.9E-09	23.4	1.5E-04
Ribose 5-phosphate	34.3	5.8E-09	6.8	1.2E-02
Fructose 6-phosphate	7.5	5.9E-09	2.8	7.6E-04
D-Ribulose 5-phosphate	4.2	5.8E-09	2.0	1.6E-05
Adenosine monophosphate (AMP)	2.3	5.8E-09	0.8	9.1E-03
Metabolites (down)	**Fold change**	**p-value**	**Fold change**	**p-value**
Reduced nicotinamide adenine dinucleotide phosphate (NADPH)	-31.1	6.6E-09	-0.8	7.2E-04
Alpha-Ketoglutarate (KG)	-22.0	5.8E-09	-15.5	5.8E-09
Alpha-Ketoisovalerate (KIV)	-12.4	6.1E-09	-4.8	8.3E-09
Cytidine triphosphate (CTP)	-11.8	5.8E-09	-1.4	5.7E-06
Nicotinamide adenine dinucleotide + hydrogen (NADH)	-9.6	1.2E-07	-0.8	7.0E-03
Lactate	-7.2	5.8E-09	-3.3	5.8E-09
Oxidized glutathione (GSSG)	-4.8	7.9E-08	-1.7	1.4E-04

Table 1: List of metabolites showing ≥ 2-fold changes between control and 0.9% normal saline (NS). Chondrocytes were treated with each irrigation solution for 30 minutes (n = 6). Positive fold change (up): NS or NS + HEPES > control, negative values change (down): NS or NS + HEPES < control.

Title: Assessing the effects of CDK4/6 and MEK1/2 inhibition in Undifferentiated Pleomorphic Sarcoma

Name: Jason Hristopoulos[1]
Mentor: Rebecca Dodd, PhD[2]
Collaborators: Gavin McGivney[2,3,4], Akshaya Warrier[1,2,3], Alexa Sheehan[2,5]
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Introduction: Undifferentiated pleomorphic sarcoma (UPS) is a rare type of soft tissue sarcoma that lacks the histological markers present in other sarcomas. Nonetheless, UPS shares similar features with other sarcomas, such as malignant peripheral nerve sheath tumors (MPNST). These common features include a strong dependency on the RAS/MAPK pathway and activation of CDK4/6, both of which appear to be promising therapeutic targets in MPNST.

Hypothesis: Given the similarities between MPNST and UPS, we aimed to evaluate the *in vitro* efficacy of palbociclib, a CDK4/6 inhibitor, and mirdametinib, a MEK1/2 inhibitor, in a murine UPS cell line. We also sought to assess the potential synergy between palbociclib and mirdametinib in combination therapy.

Methods: Murine UPS cells expressing oncogenic KRAS and loss of p53 were derived from primary tumors of LSL-Kras ^{G12D}; p53^{LoxP} (KP) mice following injection of adenovirus-Cre into the gastrocnemius muscle. These cells were treated *in vitro* with increasing concentrations of palbociclib, mirdametinib, or combination therapy for 48 hours and assessed for cell viability.

Results: Palbociclib reduced *in vitro* cell viability in a dose dependent manner, consistent with its known cytotoxic effects. Conversely, the effects of mirdametinib were relatively unaffected by increasing the drug concentration, indicating an initial cytostatic effect. Combined palbociclib and mirdametinib treatment significantly reduced *in vitro* cell viability in an additive, but not synergistic, manner compared to single drug treatments.

Conclusions: Murine UPS cells appear to be sensitive to single-agent *in vitro* palbociclib but not mirdametinib treatment, though this effect is potentiated in combination therapy. This suggests that concurrent CDK4/6 and MEK1/2 inhibition might be an effective treatment for UPS, however future studies are still needed to evaluate the *in vivo* effects of these treatment.

Poster #1: Preventing Skin Disease through Screening and Education at Primary Schools in Bagamoyo, Tanzania

Authors: Joshua Cheek, Erica Hsu, Katherine McDonald, Gasper Mmbaga, Omary Juma, Jane Mcharo, Stephen Humphrey, Karolyn Wanat.

Introduction:

Worldwide, skin diseases are the fourth leading cause of nonfatal disease burden, and they often negatively impact quality of life[4]. In Tanzania, the prevalence of skin diseases is as high as 35% in rural areas, with transmissible diseases making up 79% of all skin diseases and disproportionately affecting children[1,3]. It has been reported that 55% of primary school children have at least one skin disease[2]. The most common skin diseases in rural Tanzania include tinea capitis, tinea corporis, scabies, acne, and eczema, some of which are preventable through good hygiene[3].

Hypothesis/Purpose:

This study aimed to determine the most prevalent skin diseases in primary schools. This data was then used to provide relevant education on prevention practices to students and school administration.

Methods:

Three local primary schools were visited to screen students for skin diseases (Kongo Primary School, Miembe Saba Primary School, and Kiromo Primary School). Teachers at each school pre-selected students with skin conditions to participate in screening, and a team of 1-2 physicians from Bagamoyo District Hospital and four medical students evaluated, diagnosed, and constructed a treatment plan for each primary student. Skin diseases observed were then placed into the following categories: fungal infections, bacterial infections, atopic dermatitis, scabies, and other. Based on our findings, we developed targeted educational materials for primary school students.

Findings/Results:

Among the 494 primary school students that were screened for skin diseases, there was a total of 587 skin disease diagnoses. The majority (85%) of skin diseases were diagnosed as fungal, while bacterial infections were the second most prevalent (8%). Other diagnoses included scabies (1%) and other skin diseases (6%). Based on this, we focused our educational outreach on five main methods of prevention: washing hands with soap, not sharing clothes or towels with others, washing clothing often, washing hands after touching animals, and getting medical help right away.

Conclusion/Overall significance/Broader perspective:

The data collected from primary schools provide a unique understanding of the most common skin diseases in school-age children in Bagamoyo. Our results were disseminated to local health care providers and used to provide health education to students to enhance intervention, treatment, and prevention of these diseases in the future.

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Understanding the relationship between Bladder and Bowel Dysfunction and Attention Deficit/Hyperactivity Disorder

Amy Huang, Laura Fuller, Angelena Edwards

Pediatric patients with bladder bowel dysfunction (BBD) experiencing lower urinary tract symptoms like urinary urgency, frequency, incontinence, dysuria, recurrent non-febrile urinary tract infections, delayed toilet training, constipation or encopresis, nocturnal enuresis (NE) may also have comorbid attention-deficit/hyperactivity disorder (ADHD). A previous study showed lower urinary tract dysfunction and psychiatric disorders co-exist at a rate of 29.4%, with ADHD being the most common [1]. In fact, previous work has already demonstrated ADHD and incontinence co-occur at a higher rate than chance, as children with ADHD were 4.5x more likely to have urinary incontinence and 2.5x more likely to have NE than their matched controls [2]. The literature regarding the management of ADHD on BBD treatment is limited. Prior study cohorts have only included ADHD patients receiving pharmacological treatment for their ADHD at the time of evaluation and treatment of their urinary incontinence [3]. Resolution of enuresis after starting a stimulant medication for ADHD has also been shown in adolescent patients, supporting the need to understand the interplay between continence and ADHD for this patient population [4].

Our study aims to compare BBD patients with comorbid ADHD receiving medical treatment–a stimulant medication, non-stimulant medication, or a combination of the two, and patients not receiving medical treatment for their ADHD. Our hypothesis is pediatric urology patients with comorbid ADHD receiving medical treatment show faster improvements of their symptoms and achieve earlier resolution than patients with comorbid ADHD who are not receiving treatment.

A retrospective chart review was conducted. One hundred sixty patients met the inclusion criteria with a qualifying BBD chief complaint, at least one follow-up visit, ages 5-18, and received an ADHD diagnosis during their treatment with pediatric urology providers (outpatient consultation with pediatric urology or seen in a multidisciplinary clinic with the assistance of a psychiatric provider alongside a urology provider) between 1/1/2015 and 12/30/2022. All patients filled out a validated Iowa BBD questionnaire at their visits. Data was entered into REDCap and analyzed with R Studio.

Patients with isolated nocturnal enuresis (n=22) were analyzed separately due to being a distinct subset of patients. There were 17 patients in the medical therapy group with an ADHD diagnosis at their initial visit and four in the no medical therapy group. The mean age was 11.21 years, 11.65 years in the medical therapy group, and 10.71 years in the no medical therapy group. The average BBD questionnaire score at the initial visit in both groups was 18.25. Upon follow-up, the average BBD score for medical therapy was 12.77 and 16.75 for no medical therapy ($t=-0.725$, $p=0.504$). Subsequent 2nd follow-up scores were 9.5 for medical therapy and 15 for no medical therapy. The 3rd follow-up score was 12.5 for medical therapy. No patients in the no medical therapy group had a 3rd follow-up visit. The sample was not large enough for the 2nd and 3rd follow-ups to conduct a t-test.

All other chief complaints were analyzed together under the umbrella of being diagnosed as BBD (n=138). There were 83 patients in the medical therapy group with an ADHD diagnosis at their initial visit and 25 in the no medical therapy group. The mean age was 8.94 years, 9.50 years in the medical therapy group, and 10.09 in the no medical therapy group. The average BBD questionnaire score at initial visit was 28.16 in the medical therapy group and 28.77 in the no medical therapy group. Upon follow-up, the average BBD score for medical therapy was 24.87 and 22.14 for no medical therapy. 2nd follow-up scores were 25.47 for medical therapy and 21.67 for no medical therapy. 3rd follow-up scores were 22.9 for medical therapy and 22.71 for no medical therapy. There were no statistically significant differences between the medical group and no meds group at any of the visits (Initial visit $t=-0.175$, $p=0.862$; 1st follow-up $t=1.053$, $p=0.295$; 2nd follow-up $t=0.776$, $p=0.449$; 3rd follow-up $t=0.048$, $p=0.962$).

As of 2019, 9.8% of children had been diagnosed with ADHD [5]. In addition, 20-25% of children with ADHD have urinary incontinence, and 20% of children with encopresis–involuntary/voluntary passage of stool in an inappropriate place, and enuresis have ADHD [6]. These patients are routinely evaluated in pediatric urology clinic, and prior studies in the medical literature excluded patients with ADHD that are not receiving medical therapy to manage their ADHD. This can be a sizeable portion of patients presenting to pediatric urology. Therefore, we found it important to study this patient population, showing their experience is similar to other children that received medical therapy for their ADHD. Our study did not find a statistical difference between children on medical therapy vs. no medical therapy for their ADHD when using a validated questionnaire to determine objective improvement. Our study is the first to our knowledge in the medical literature to include patients with a diagnosis of ADHD who were not on medical therapy.

Title: Development of Clinical Study: RP1 in Combination with PD1 Blockade in Patients with Solid Tumors
Student: Brianna Iverson
Mentor: Dr. Mohammad Milhem

Metastatic melanoma is a disease of high mortality with a five-year survival between 32%-71% depending on if it is regional or distant metastasis**.** Immunotherapy has become the standard of treatment in the past decade, especially immune checkpoint inhibitors (anti-PD1, anti-CTL4, and anti-LAG-3). Even with these therapeutic advances, over 50% of patients with cutaneous melanoma treated with single agent anti-PD1 drugs experience primary resistance. There is an **unmet need** for the treatment of relapsed and refractory to PD-1 checkpoint blockade metastatic melanoma.

RP1 is a HSV-1 oncolytic virus, with a potency that is 30x of T-VEC, that selectively targets and infects tumor cells. Oncolytic viruses, including RP1, work mechanistically by selective lysis of tumor cells, induction of local and systemic immune responses, and the reversal of local immunosuppression. These mechanisms make RP1 uniquely positioned to have the potential to reverse the common mechanisms of anti-PD1 resistance.

In treatment of failed anti-PD1 metastatic melanoma with biweekly injections of RP1 and nivolumab the objective response rate (ORR) was 36% in 75 patients, including a complete response rate of 20%[10]. These results demonstrate that RP1 in conjunction with anti-PD1 therapy shows clinically meaningful responses for patients with relapsed and refractory metastatic melanoma. The focus of this summer research fellowship was the **proposal of a clinical trial** to investigate an accelerated dosage schedule to determine if we can further improve the response amongst patients with relapsed and refractory metastatic melanoma.

Our **hypotheses/anticipated results:**
1) weekly injections of RP1 in conjunction with anti-PD1 will be well tolerated amongst patients with relapsed and refractory metastatic melanoma
2) there will be an objective response rate greater than 36% in treatment of patients with relapsed and refractory metastatic melanoma with weekly injections of RP1 in conjunction with anti-PD1
3) there will be a complete response rate greater than 20% in treatment of patients with relapsed and refractory metastatic melanoma with weekly injections of RP1 in conjunction with anti-PD1.

We have submitted a letter of intent to Replimmune to receive funding and are currently working on protocol development.

Development of an Automated EEG Analysis Algorithm to Assess the Efficacy of Naltrexone in the Prevention of Epilepsy

Kyle Jackson, Saul Rodriguez, Grant Tiarks, Angela Wong, Sammy Santiago, Alexander G. Bassuk

Background: Traumatic brain injuries (TBIs) are well-known to cause reduced cognitive capacity, epilepsy, and significant functional impairment. TBIs trigger mechanisms that cause neuroinflammation, glial cell activation, neuronal network remodeling, and post-translational synaptic protein modification that result in cognitive and functional deficits. Sustained disruption of normal homeostasis can ultimately result in anxiety, dementia, and post-traumatic epilepsy (PTE), with PTE developing in greater than 50% of severe TBI cases. While many anti-epileptic drugs are currently available for the treatment of epilepsy, there is minimal evidence suggesting that these medications prevent the changes observed in PTE. Given the substantial burden that these injuries pose to affected individuals, we sought to evaluate the effectiveness of Naltrexone in the prevention of epileptic activity. To simplify the cumbersome process of manual electroencephalogram (EEG) analysis, an automated algorithm was developed to rapidly process large volumes of EEG readings and remove the inherent bias associated with manual, visual-based analysis.

Methods: In the TBI model, four-week-old C57BL/6J mice were subject to diffuse brain injury using free-fall weight drop. After EEG electrodes and telemetry devices were placed, a subconvulsive dose of pentylenetetrazol (PTZ) was administered followed by Naltrexone or saline control. Mice were given two doses of Naltrexone or saline for 3 days, followed by a single dose for four more days. All mice were continuously video EEG (vEEG) recorded for 7 days and intermittently thereafter for 3 months until euthanasia. In the pilocarpine-induced epilepsy model, six-week-old C57BL/6J mice first underwent EEG electrode and telemetry device implantation. Methylscopolamine was administered followed by pilocarpine, a medication known to cause epileptic activity similar to temporal lobe epilepsy in humans. After behavior analysis for 90 minutes, the mice were given diazepam followed by Naltrexone or control as per the same protocol in the TBI model. The mice were then observed for 3 months on vEEG before euthanasia.

Results: Analysis of the vEEG data from our TBI model showed significant reduction in the number of electrographic events, which included electrographic seizures and interictal activity, in mice treated with Naltrexone following traumatic brain injury. Further, all mice treated with Naltrexone did not develop PTE during the 3-month observation period, whereas 71% of the control animals went on to develop PTE. In the pilocarpine-induced epilepsy model, there was no significant difference in the number of recorded electrographic events observed for the animals that received naltrexone vs control. Additionally, there was no protective benefit from Naltrexone at the end of 3 months compared to controls.

Conclusions: Administration of Naltrexone following traumatic brain injury was shown to significantly reduce electrographic activity and prevent the development of PTE in treated animals. These findings likely reflect the anti-inflammatory properties of Naltrexone which help reduce the neuroinflammation, glial cell activation, and neuronal remodeling that occurs following TBI. No significant changes in electrographic events or the development of epilepsy were observed in the pilocarpine model. We conclude this is likely due to the absence of inflammation present in the CNS tissue of the pilocarpine-model animals versus those of the TBI-model animals which demonstrated significant inflammation. Additionally, an observation period greater than 3 months may be necessary to observe the true effects of Naltrexone in both models.

The Impact of Mental Readiness on the Return to Athletic Performance Following Hip Preservation Surgery

Mentee: Olivia Jenks
Mentors: Robert Westermann & Michael Willey
Collaborator: Jacob Henrichsen

Introduction: Athletes frequently face intra-articular hip pathologies necessitating hip preservation surgery, including hip arthroscopy, periacetabular osteotomy (PAO), and/or derotational femoral osteotomy (DFO). While previous research has shown promising return-to-sport rates post-surgery, the role of an athlete's mental readiness in this process remains underexplored. The purpose of this prospective cohort study was to assess the impact of mental health factors on athletes' recovery and their ability to return to sport following hip preservation surgery.

Methods: We enrolled 71 athletes from 2020-2023 who wanted to return to play following hip preservation surgery. Patient-reported outcomes including the Hip Return-to-Sport Index (hip-RSI), Hip Outcome Score - Sport Subscale (HOS-SSS), and perceived function were collected preoperatively, 3-months post-operatively, and 6-months post-operatively. Statistical analyses were performed using Mann-Whitney U and chi-squared tests ($p<0.05$).

Results: Athletes who successfully resumed their primary sport within the 6 month postoperative period exhibited higher hip-RSI scores (74.5/100 vs 57.1/100, $p=0.002$) and reported better function (8.5/10 vs 7.4/10, $p=0.041$) compared to those who did not. Patients who underwent hip arthroscopy alone reported higher hip-RSI scores than with concomitant PAO or DFO procedures (72.3/100 vs 55.7/100, $p=0.013$).

Conclusion: Our study underscores the significance of an athlete's confidence in their hip in predicting a successful return to sport within 6 months following hip preservation surgery. These findings have practical implications for clinicians and sports professionals involved in the rehabilitation process, highlighting the importance of addressing mental readiness as a key aspect of recovery.

Keywords: Athlete, hip preservation surgery, mental health, Hip Return to Sport Index, rehabilitation, patient-reported outcomes.

A Retrospective Review of Hormonal Contraceptive Use in Young Women Undergoing ACL Surgery

Student: Gretchen Jones, M2
Mentors: Dr. Kyle Duchman MD, Dr. Robert Westermann MD

Background: Anterior cruciate ligament (ACL) tears are a common sports injury, typically requiring surgery for predictable return-to-play. However, due to a multitude of factors, some athletes do not return to sport after ACL injury. ACL injury is particularly common in females, with reported rates two to nine times greater in women compared to men. In addition to known risk factors, such as increased Q angle and decreased hamstring strength in women, the female menstrual cycle hormones estrogen, progesterone, and relaxin may contribute to this disparity. The ACL in menstruating women undergoes cyclic structural degeneration in response to menstrual hormone exposure. During the menstrual cycle, an initial peak of estrogen increases expression of relaxin receptors (RXFPs) and synthesis of the proinflammatory matrix metalloproteinases (MMPs). The subsequent menstrual cycle peak of progesterone indicates formation of the corpus luteum, the main site of relaxin synthesis. Because of this, the peptide hormone relaxin is last to peak in the cycle. Relaxin binds the receptors and activates the MMPs; critically MMPs 1, 2, 3, and 9—enzymes more commonly known as collagenases (1, 3) and gelatinases (2, 9). Together, these enzymes decrease collagen quantity and quality around receptor sites. The pivotal factor driving concern with this cascade is the multiple studies showing dense, uniform presence of relaxin receptors on female, but not male, ACLs. Hormonal contraceptives alter the levels of estrogen, progesterone, and relaxin in serum; reducing levels of relaxin is one method by which hormonal contraceptives may exhibit a protective effect against ACL injury. Ovulation is known to be inhibited when using combined hormonal oral contraceptives by suppressing peak levels of estrogen and progesterone during the menstrual cycle. Inhibiting ovulation inhibits the formation of a corpus luteum and production of relaxin.

Purpose: As the impact of hormonal contraceptives on ACL injury is debated in literature, we aimed to evaluate the prevalence of hormonal contraceptive use in a group of women surgically treated for ACL injury at University of Iowa Hospitals and Clinics (UIHC) to provide foundation for future research.

Methods: We retrospectively reviewed a prospectively collected ACL database, identifying female patients ages 15 – 29 who had undergone ACL reconstruction at UIHC between February 2013 and May 2023. An initial cohort of 709 patients was identified and then inclusion and exclusion criteria were applied to further refine the cohort, yielding a total of 500 patients. Chronic ACL injuries, ACL injuries due to motor vehicle accidents, and revision ACL reconstruction procedures were excluded from the study. Data collected included laterality, type of hormonal contraceptive, reconciled list of medications at initial visit, mechanism of injury, type of graft used, concomitant procedures performed, and history of previous knee injury. Types of hormonal contraceptives were categorized as oral contraceptive pills (OCPs), intrauterine devices (IUDs), and contraceptive implants. Prevalence of hormonal contraceptive usage in women with ACL injuries was calculated in two separate age cohorts 15-20 and 20-29 and compared to the national rate of hormonal contraceptive use.

Results: The two distinct age cohorts, 15-20 and 20-29 years of displayed hormonal contraceptive use prevalence of 37.7%, and 48.5%, respectively. According to the latest Centers for Disease Control (CDC) report, which examined the contraceptive status of women in the United States based on a 2017-2019 national survey, the hormonal contraceptive prevalence rates for the same age groups were 25.3% and 37.3%, respectively.

Conclusion: The prevalence of hormonal contraceptive use was higher in our cohort of patients who underwent ACL reconstruction at UIHC than the national prevalence of hormonal contraceptive use. Given our initial hypothesis proposing a potential protective effect of hormonal contraceptives against ACL injuries, we anticipated observing a lower prevalence compared to the national average. Exploring additional variables like geographical location, religious beliefs, athletic involvement, and higher educational attainment could prove advantageous in understanding the reasons behind the elevated usage of hormonal contraceptives within this study's cohort. Future steps include conducting a longitudinal study over a group of women, potentially an Iowa sports team, which would allow a more comparable control group.

Title: ELISpot Optimization for Sepsis Immunophenotyping

Authors: Andreas Kantartzis, Mahil Rao, Vladimir Badovinac

BACKGROUND: Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. In the United States, sepsis affects approximately 1.7 million adults annually, with a mortality rate of 1 in 5 individuals. Alarmingly, over 40% of sepsis survivors are dead within a year, largely attributed to persistent immunoparalysis; a state characterized by a dysfunctional innate and adaptive immune system. This immunoparalysis leads to a heightened risk of viral reactivation (50%) and secondary infections in ICU settings (15%). Thus, the imperative to immunophenotype these patients for treatment guidance, optimal discharge timing, and reinfection risk assessment is evident. The enzyme-linked immunosorbent spot (ELISpot) is a functional assay that can quantitatively measure ex-vivo cytokine-producing cells and their secretion levels under various stimulation conditions. IFN-γ, primarily released by T cells during infection, serves as a distinctive marker of T cell exhaustion. Consequently, the utilization of ELISpot to quantify IFN-γ levels offers a means to characterize the adaptive immune system's functionality and perform immunophenotyping of septic patients. Previous research has already displayed IFN-γ ELISpot's potential to predict fatality among septic survivors. Presently, the University of Iowa is participating in ongoing human clinical trials (SPIES) that incorporate the use of ELISpot in sepsis survivors. However, patient heterogeneity and significant variability in the results of ELISpot have called for a need to refine the assay in this clinical context. Consequently, this study aims to optimize the human sepsis IFN-γ ELISpot assay through murine models.

METHODS: The first experiment aimed to elucidate the response to sepsis and determine the optimal stimulant concentration. Six mice underwent cecal ligation and puncture (CLP), which induces sepsis, while three mice received sham surgery. Three CLP mice were sacrificed at day 1, with another three at days 5 or 7. Splenocytes were isolated, plated 400,000 cells per well, and varying CD3/28 stimulant concentrations (51.2, 128, 320, 800, 2000, 5000) were used. The second experiment aimed to identify the ideal stimulation time and determine the appropriate number of cells to plate per well. 200K, 400K, 800K, or 1600K splenocytes were plated and were stimulated for either 4h or 22h. BL/6 WT mice were used for both experiments and IFN-γ production was determined by ELISpot.

RESULTS: A two-fold reduction in spot count (IFN-γ producing cells) was observed one day post-CLP, subsequently recovering to surpass sham surgery levels by days 5 or 7 post-CLP. Optimal CD3/28 stimulant concentrations were identified as 51.2-320 µg/mL CD3 and 512-3200 µg/mL CD28. The second experiment revealed that a 4h incubation exhibited fewer spots and reduced variability compared to the 22h incubation. Moreover, improved resolution resulted from using fewer cells. 800K cells was the maximum number of cells per well for a 4h incubation and 400K was the maximum for 22h.

CONCLUSION: This study's primary objective was to optimize the human sepsis IFN-γ ELISpot assay through murine models. Contrasting with the SPIES human clinical trial protocol, which employs a high CD3/28 stimulation concentration of 5000µg/mL of CD3 and 50000µg/mL of CD28, our findings suggest that lower stimulant conditions of 320 and 3200 respectively can better elucidate differences between patient responses. Additionally, we observed that a 4-hour incubation improves resolution and decreases variability. Thus, the 22-hour incubation listed in the SPIES protocol may need to be reconsidered. Although an overnight incubation might align with clinical convenience, a 4-hour incubation could mitigate variability in patient samples and expedite turnaround time. Given the urgency of sepsis management, this approach holds promise for more effective immunophenotyping and timely interventions.

Title: Characterization of Parental Stress Levels in the NICU

Authors: Rekha Karuparthy MSW, BA, Allison Momany PhD, Paige Nelson MA, Ece Demir-Lira PhD, John Dagle MD,PhD

Background: The Neonatal Intensive Care Unit (NICU) is a stressful and emotional experience for many parents. It has been shown that parents in the NICU are at a higher risk for developing depression, anxiety, and especially, post-traumatic stress disorder. Currently, mood is assessed at Iowa's NICU through the GAD-7 and PHQ-9, which is necessary for providers to screen anxiety and depression symptoms. However, there has not been a gauge of parent stress levels in relation to the NICU environment. By administrating the Parental Stressor Scale:NICU (PSS:NICU), a 46-questionnaire divided into four sections—sights and sounds, baby looks and behaves, relationships and parental role, and staff behaviors and communication—this study is aimed to further characterize parental stress, provide a potential new tool that captures mood symptoms manifested in a NICU environment, and inform potential strategies to address the emotional health of caregivers.

Objective: Characterize parental stress for parents with an infant hospitalized in a Level IV NICU and examine the relation between the PSS:NICU, PHQ-9, and GAD-7 in a population who are at risk for developing mood, anxiety, and stress-related disorders due to an infant being hospitalized in the NICU.

Design/Methods: This study collected quantitative and qualitative data from NICU parents through the current IRB approved study. Parental consent was obtained when the infant was medically stable and preparing for discharge from the NICU. Parents completed the PHQ-9, GAD-7, and PSS:NICU prior to discharge. The PHQ-9 and GAD-7 are evidence-based screening questionnaires for depression and anxiety symptoms respectively. Both screens utilize a Likert scale for the severity of mood/anxiety symptoms: 0=not at all, 1=several days, 2=more than half the days, 3=nearly every day. The PSS:NICU is a measure of parental stress related specifically to the NICU environment. Similarly, the PSS:NICU uses a Likert scale: 1=not at all stressful, 2=a little stressful, 3=moderately stressful, 4=very stressful, 5=extremely stressful. However, 18 participants did not complete the Staff Behavior and Communication section, so this section was excluded from the PSS:NICU total score. Individual interviews were also conducted with 8 parents to learn more about their responses to the PSS:NICU and additional stressors that were experienced throughout the NICU admission. Statistical analyses were completed in SPSS 29 for a total of 35 participants. Pearson correlations were conducted to examine the relationships between the PSS:NICU, PHQ-9, and GAD-7. Additionally, correlations were analyzed between scoring and infant gestation age. For interviews, common themes were identified from parental responses.

Results: The PSS:NICU total score was positively correlated with PHQ-9 total score ($r=0.684$, $p=<0.001$) and GAD-7 total score ($r=0.505$, $p=0.004$). Out of the four subscales on the PSS:NICU, Staff Behavior and Communication has the strongest correlation with both the PHQ-9 ($r=0.669$, $p=0.003$) and the GAD-7 ($r=0.562$, $p=0.019$). Interestingly, none of the questionnaire total scores or PSS:NICU subscale scores were correlated with infant gestational age at birth. Qualitative data from individual interviews elucidated common themes for each subscale. *Sights and Sounds:* Several parents reported stress related to watching their infant's vitals on the monitor and neighboring infants' vitals shown on their monitor that their nurse was caring for collectively. *Baby Looks and Behaves:* Numerous parents indicated distress related to fear of handling their infant due to small size and uncertainty about how to navigate complex medical equipment. *Parental Role and Relationships:* Most parents discussed feeling a loss of parental role in regards to feeling the need to ask for permission to hold their baby, being deemed a visitor in the NICU, feeling they do not know what is best for their infant, and a generally less independence. *Staff Communication and Behaviors:* Each parent identified nursing staff as a critical role in their experience. Consistency in nursing was a key element of comfort and ease of stress for parents. Communicating with nursing staff for updates and discussing infant preferences for cares was important for parents.

Conclusion: The PSS:NICU is a questionnaire that is moderately positively correlated with common mood and anxiety symptoms screening tools—PHQ-9 and GAD-7. The PSS:NICU could be implemented as a possible screening tool to capture specific stressors felt by NICU parents in order to better address mental health symptoms in a personalized manner and empower parents during their NICU admission.

Proximal release of the long head of the biceps tension in repair of chronic distal biceps rupture, a feasibility study

Authors: Kevin Kato, James Nepola MD

Background: Chronic rupture of the distal biceps tendon is an increasingly common injury occurring mostly in working aged men. Individuals who sustain a chronic distal biceps tendon rupture injury show a considerable decline in function, including loss in supination strength, loss in flexion strength, and loss in sustained grip strength. There are two treatments for these injuries: a non-surgical approach, accepting the deformity and weakness, and surgical repair which may be complicated by a retracted tendon which often requires intercalary tendon grafting with unpredictable outcomes. Historically, patients with rupture of the proximal long head of the biceps tendon will show a “Popeyes” deformity, where the muscle belly budges distally down the arm suggesting that there might be “slack” in the long head of the biceps which could be helpful in achieving direct distal repairs in delayed circumstances. These injuries often recover successfully without deficit. There is currently no research measuring the excursion created from release of the proximal long head of the biceps tendon, and if it would allow enough “slack” to re-fix a chronically ruptured distal biceps tendon back to the radial tuberosity. This approach to repair has never been described in the literature.

Aim: This study aims to measure the amount of excursion available to a ruptured distal biceps tendon from a proximally tenotomized long head of the biceps tendon. Secondarily, the study examines possible anatomic tethering points affecting further excursion, as well observing the effects on the neurovasculature associated with distal translation of the myotendinous unit.

Methods: Cadaver specimens were obtained from the shoulder through the distal forearm. The thawed specimens were then dissected to expose the distal biceps tendon and the proximal long head of the biceps tendon. The tendons were then both tenotomized and the site at which the tendon was cut was marked. The distal biceps tendon was then pulled until it was unable to move further, and the distance was measured. The specimen was then further dissected to identify the tether points preventing further excursion and for the effects on the neurovasculature.

Results: 11 specimens were obtained and dissected. With a tenotomy of the distal biceps tendon and the long head of the biceps, there was an average added excursion of 3.17cm. There were two main attachment points preventing further excursion, the long head of the biceps tendon fascial attachments in the bicipital groove, and the short head of the biceps tendon in its attachment to the coracoid process. Fully clearing out the long head of the biceps tendon from the bicipital groove added an average extra .52cm of excursion on average. Cutting the short head tendon from the coracoid process added an extra .77cm of excursion on average. Visually, the two main attachment points prevented any excessive strain on the neurovasculature of the biceps. There was little visual strain on the musculocutaneous nerve branches innervating the biceps until 4cm of excursion, with obvious tension seen on the nerve only after both main attachment points were released.

Conclusion: Preliminary results demonstrate that repair of chronic distal biceps ruptures by tenotomizing the long head of the biceps tendon may provide enough excursion to be a reasonable surgical adjunct permitting direct repair and avoiding the need for intercalary grafting. However, more analysis must be completed to identify how the results may differ for a real patient with chronically ruptured biceps in contrast to the cadaver specimens used.

Title: Changes in rat ultrasonic vocalizations following lesion of amygdala, insula, and anterior cingulate cortex.

Student: Aditi Katwala, BS;

Mentor: Matthew R. Hoffman, MD, PhD

Collaborators: Brian Mostaert, BS; Linder Wendt, MS; Emma Thayer, BS; Matthew R. Hoffman, MD, PhD; Martin Cassell, PhD; Doug Van Daele, MD

ABSTRACT

Background: There are several important brain regions that play a role in speech production. These primary areas include laryngeal motor cortex, premotor cortex, supplementary motor area, and portions of the cerebellum, but secondary areas such as the amygdala, insula, and anterior cingulate cortex (ACC) also contribute to voice. Rodents are an excellent model to study the connection between subcortical structures and voice because they communicate through ultrasonic vocalizations (USVs), which are divided into simple, harmonic and frequency modulated (FM) calls. We report on voice parameters following bilateral lesions on the rodent amygdala, insula, and ACC.

Purpose: The purpose of this project is to better understand how speech is generated by high level brain centers (cortical and subcortical regions), specifically the amygdala, insula, and ACC.

Methods: Male rats were divided into amygdala (n=2), insula (n=2), and ACC (n=2) cohorts. Animals served as their own controls. Call counts, frequency, duration, and bandwidth were measured before and after lesion. To elicit calls, one female rat in estrus was placed in the male's home cage and male was allowed to mount twice without ejaculation. The male was then separated from the female by a divider that was equipped with 2 ultrasonic microphones. Bilateral Ibotenic Acid Injections (BIAI) were performed on the male rats in one of the three subcortical structures. Calls were recorded for two weeks before lesion and two weeks after lesion.

Results: Total calls significantly declined in the amygdala ($p=0.033$), ACC ($p=0.003$), and insula groups ($p=0.015$). Harmonic calls decreased after amygdala lesions. Simple, harmonic, and FM calls decreased after lesions to the insula and ACC. There were no changes in call duration. The percentage of harmonic and FM calls decreased post lesion while the percentage of simple calls increased, indicating decreased call complexity.

Conclusions: Results from this small study suggest the amygdala, insula, and ACC are part of the neural pathways which control voice production. Disruptions in this system are associated with decreases in the amount and complexity of vocalizations. Further work should explore specific contributions each structure makes in speech.

Title: Tragal cartilage graft in transcanal endoscopic tympanoplasty in pediatric patients

Authors: Tanner Kempton, Zachary Fleishhacker, Wesley Schoo, Douglas M. Bennion, Sohit Paul Kanotra
Corresponding author: Douglas M. Bennion

Abstract

Background

The use of otoendoscopes has added a new dimension to the management of ear disease. Traditional approaches to tympanoplasty include postauricular, endaural and endomeatal, with use of an operating microscope for visualization. While large central or anterior perforations have often necessitated a post-auricular approach for tympanoplasty in pediatric ears, small central or posterior perforations are often amenable to a transcanal approach. With the addition of endoscopy, previously impractical perforations can now be addressed transcanal with graft material harvested via a small endomeatal incision over the tragal cartilage without the need for external incisions.

Objective

To describe the anatomical and audiological (functional) results of the use of transcanal endoscopic tympanoplasty using tragal cartilage for various tympanic membrane perforations in the pediatric population.

Materials and Methods

A retrospective case series of 15 pediatric patients (17 ears) who underwent tympanoplasty between January 2018 to December 2022 for repair of tympanic membrane perforations of various sizes and locations. An endoscopic transcanal approach was undertaken in all cases, with placement of tragal cartilage graft in underlay fashion. Success was defined as graft uptake with healed tympanic membrane at follow-up with hearing outcome as a secondary measure.

Results

Uptake and closure of the perforation was achieved in all but 1 case (94% successful closure). Air bone gap closure was achieved at an average of 12.0dB at 500Hz, 13.3dB at 1kHz, and 3.1dB at 2kHz. No serious adverse events were encountered.

Conclusion

Transcanal endoscopic tympanoplasty for pediatric tympanic membrane perforation using tragal cartilage gives excellent results with stable long term hearing outcomes.

Poster Abstract

Investigating learning-induced expression of Nr4A2 in the ventral tegmental area and dorsal hippocampus

Victor Kilonzo, Lucy Langmack, Utsav Mukherjee, Pravda Quinones, Emily Walsh, Ted Abel

Neuronal activity associated with learning is known to activate the cAMP-PKA-CREB signaling pathway in the hippocampus. This intracellular cascade of events is known to upregulate the expression of the Nr4A subfamily of transcription factors, implicated in memory consolidation. These learning-induced transcription factors display rapid and transient increases in expression in the hippocampus after behavior, categorizing them as immediate-early genes. Different members of the Nr4A subfamily play different roles in memory consolidation and show heterogeneous expression profiles. Nr4A2, a unique member of the Nr4A subfamily, exhibits restricted upregulation in the Cornu Ammonis (CA) subregions of the hippocampus shortly after learning, crucial for spatial and novel object recognition memory. Moreover, in the midbrain, Nr4A2 acts as a key regulator of dopaminergic neuron differentiation, maintenance, and survival. Despite its pivotal roles in hippocampal synaptic plasticity and midbrain dopaminergic neuron maintenance, the impact of learning and memory on Nr4A2 expression in both regions remains largely unexplored. In this study, we quantified the extent of Nr4A2 expression an hour after learning via the spatial object recognition task, in both the dorsal hippocampus and the ventral tegmental area. Our findings not only reveal upregulation of Nr4A2 in the dorsal hippocampus following learning but also demonstrate induced Nr4A2 expression in dopaminergic neurons within the ventral tegmental area. This study underscores the intricate interplay between memory processes and dopaminergic neuron regulation, setting the stage for future investigations into some of the dynamic molecular events that govern cognitive function and dopaminergic signaling.

Iterative Development and Evaluation of a Community-Based Health Education Program about Patient-Centered, Culturally Responsive Care for Post-Acute Sequelae of COVID-19

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Introduction: Post-acute sequelae of COVID-19 (PASC) are long-term symptoms that persist after an initial COVID-19 infection, including asymptomatic episodes. PASC is common, with up to 80% of individuals exhibiting persistent symptoms after COVID-19. Symptoms can be so severe and debilitating that PASC is now recognized under the Americans with Disabilities Act. Chronic pain is a frequent manifestation of PASC, which adds to an already substantial chronic pain burden in the United States and contributes to long-standing inequities in chronic pain care. Thus, it is necessary to consider the disproportionate impacts of PASC among marginalized groups and to effectively engage patients and communities in the development of PASC treatment models to ensure full and equitable access to care.

Purpose: The aim of the study was to develop a training module about culturally responsive, patient-centered care for PASC-related chronic pain for application in community and healthcare settings by integrating community-based participatory research into the process of medical curriculum development.

Methods: In this mixed-methods research project, educational content was based on initial qualitative interviews with non-academic community members in Iowa. These interviews assessed patients' views about culturally responsive care, patient-centered care, and PASC. The community input from initial interviews directly guided the composition of the training module. This input was then coupled with a focused review of salient literature and existing resources to augment the training module. To expand upon this foundation and gauge the potential value of the training module in both academic and community settings, focus groups and interviews were held to pilot the module among three separate groups—medical students from the Carver College of Medicine, healthcare providers from the University of Iowa Health Care, and the same community members who provided the original input. Participants completed brief quantitative surveys before and after the module was delivered. Qualitative and quantitative input from the focus groups was combined to iteratively improve the training module concerning its content and delivery.

Results: Participants included 5 community members who participated in initial and follow-up sessions before and after the module's development (100% retention between sessions), 17 medical students who participated in a session after a draft module was completed to provide input on its content and pedagogical approach, and 5 providers who participated in a session to provide broad input on the module's content, approach, and clinical context. The resulting module was a 30-minute case-based, interactive module. In quantitative surveys, participants indicated that they were prepared to work with patients of different cultural backgrounds (93%), were comfortable discussing pain with patients (89%), were aware of patient barriers to addressing PASC (100%), and were ready to recognize PASC symptoms (78%). Participants reported that the training deepened their understanding of PASC (96%) and that the training would be helpful to deliver in community, educational, and healthcare contexts (100%). Based on qualitative input, medical students and providers viewed the training positively, gained substantial knowledge about PASC, and appreciated that community input guided the material. Community members noted a substantially improved knowledge of PASC and felt that their input was appropriately reflected. Participants suggested that the training would be useful for community members, healthcare providers, and health professions students.

Conclusion and Significance: This study illustrates that combining community-based participatory research practices and medical student input represents a promising, adaptive approach to curriculum development focused on culturally responsive, patient-centered care.

Title: Impact of MIRO1 on Vascular Smooth Muscle Cell Proliferation

Authors: Tara Kortlever, Olha Koval Ph.D., Isabella Grumbach M.D. Ph.D.

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BACKGROUND: Excessive vascular smooth muscle cell (VSMC) proliferation has been implicated in the development of cardiovascular diseases. This process is dependent on mitochondrial energy production, driven in part by calcium (Ca^{2+}) transfer from the endoplasmic reticulum (ER) to the mitochondria. Ca^{2+} transfer occurs through protein complexes —MERCS (mitochondrial-ER contact sites). One of the proteins regulating MERCS formation is Mitochondrial Rho GTPase-1 (MIRO1). MIRO1 is a multifunctional protein which not only maintains MERCS formation, but also facilitates mitochondrial movement and Ca^{2+} transfer from the ER to the mitochondria. Mitochondrial Ca^{2+} plays a key role in the dephosphorylation and subsequent activation of pyruvate dehydrogenase (PDH), a mitochondrial matrix enzyme which supplies metabolites for adenosine triphosphate (ATP) synthesis.

Furthermore, a nonproliferating cell stays in G0 while a proliferating cell passes through multiple cell cycle phases—G1, S, G2, and M. Ca^{2+} levels steadily increase as cells transition from the G0 to G1/S phases, reaching a peak at the G1/S border. Recently we found knockout of MIRO1 in VSMCs reduced cell proliferation and cells appear to be stuck at the G1/S border. Lack of MERCS formation and proper Ca^{2+} transfer at the G1/S border during cell proliferation is suspected to play a role.

HYPOTHESIS: $MIRO1^{-/-}$ reduces proliferation of VSMCs due to a lack of MERCS formation.

METHODS: VSMCs were infected with adenovirus: split GFP-based contact site sensor (SPLICS) for MERCS, mtPericam (485/415 nm), and ATP sensor (ratiometric [GFP/RFP] protein) for Ca^{2+} and ATP analysis, respectively. Epifluorescent microscopy was used for cell imaging. Phosphorylated and total PDH protein levels were measured via Western Blot. Data were collected at two timepoints: starved/synchronized (G0 cell cycle phase/0 h) and 24 h post-starvation (G1/S phase/24 h).

RESULTS: $MIRO1^{-/-}$ VSMCs demonstrated a reduced proliferation rate compared to WT. With progression through the cell cycle, the number of contact sites in WT cells increased, but did not change in $MIRO1^{-/-}$ cells. Mitochondrial Ca^{2+} levels increased in WT but not $MIRO1^{-/-}$ cells as they progressed from G0 to G1/S. Subsequently, PDH phosphorylation decreased in WT cells but was unchanged in $MIRO1^{-/-}$ cells. ATP levels increased in WT cells from G0 to G1/S but remained the same in $MIRO1^{-/-}$.

CONCLUSION: $MIRO1^{-/-}$ results in decreased MERCS formation and impaired VSMC proliferation. Reduced MERCS formation was accompanied by decreased mitochondrial Ca^{2+}, suggesting MIRO1 plays a key role in the movement of Ca^{2+} during cell cycle progression. Potential impacts of MIRO1 expression in VSMCs in relation to vascular diseases should be investigated.

Multiplex PCR Urine Testing Compared to the Standard Urine Culture for Preoperative Screening in Elderly Urology Patients

Authors:
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Background: Prior to certain urologic procedures and surgeries, the American Urological Association (AUA) recommends testing for pathogens in the urinary tract followed by antibiotic prophylaxis if indicated. Testing is recommended for most procedures where the urothelium is or could be breached. Antibiotic prophylaxis is provided to reduce the risk of surgical site infections and preventable periprocedural infections. The current standard for preoperative urine testing is the standard urine culture (SUC), where a urine sample is inoculated onto growth media, incubated, then any growth is identified and undergoes susceptibility testing. Newer molecular testing is now available that is more sensitive in detecting potential uropathogens when compared to SUC. However, the clinical utility of these high-sensitive tests has yet to be determined.

Our study explores the use of one of these novel tests, multiplex polymerase chain reaction (mPCR), in the setting of detection of uropathogens prior to a urological procedure. mPCR refers to the use of PCR to amplify several different DNA sequences simultaneously using multiple primers. This allows for rapid identification of potential uropathogens, as well as identification of fastidious organisms that would not otherwise grow in a SUC. For the mPCR, we chose to use the Pathnostics Guidance UTI test which includes the urine mPCR, resistance gene detection by PCR, and pooled antibiotic susceptibility testing (P-AST).

Purpose: The purpose of our study is to determine the concordance in detecting bacteria in the urine in elderly urology patients between the Pathnostics Guidance UTI test and our hospital's laboratory SUC. Our study also seeks to identify the frequency of post-operative urinary tract infections in study patients.

Methods: This is a single-site study at the University of Iowa Hospitals and Clinics (UIHC) Urology Clinic involving patients aged 65 years or older planning to undergo a surgical urologic procedure where the surgeon would routinely obtain a pre-operative standard urine culture. Institutional Board Review approval was obtained (IRB number 202303593). Basic demographic and clinical data were collected via chart review for participants in the study. Once informed consent was obtained from eligible patients, a urine sample was sent for both SUC at UIHC and mPCR + P-AST completed by Pathnostics. A chart review was completed for each subject at six weeks post-procedure to evaluate for post-operative UTI. All data was stored in a secure REDCap database.

Results: Multiplex PCR was able to identify uropathogens in all cases identified by UIHC except for one. The one case involved an organism that was not tested for by the mPCR test, *Moraxella osloensis*.

For 40.6% (13/32) cases, UIHC SUC reported "mixed flora" or "multiple organisms." In all of these cases, mPCR was able to identify anywhere from one to five discrete organisms. In 3% (1/32) of cases, UIHC reported "no growth" while mPCR reported *E. coli*. In only one case did UIHC SUC identify a uropathogen: *Moraxella osloensis*, while mPCR did not.

Multiplex PCR identified *Actinobaculum schaalii* and *Aerococcus urinae*, while SUC did not detect these organisms, in 10 and 5 cases, respectively.

Thus far, six patients have developed post-operative symptomatic UTI within the six week post operative period. Of these, three had negative pre-operative SUC and negative mPCR. In one of the cases, the preoperative mPCR showed *A. schaalii* while the SUC was reported as "mixed urogenital flora," the post-operative urine culture showed *A. schaalii*.

Conclusions: Preliminary data showed that in a 100% of cases, where UIHC SUC reported "mixed growth," mPCR was able to identify specific uropathogens. In at least one of our cases, post-operative infection may have been prevented if the clinician had the mPCR data. In this particular clinic setting where urologists are routinely treating positive urine cultures even in the absence of symptoms, mPCR may play a role. More clinical data are needed to support changes in preoperative testing standards.

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The Clinical Usefulness of the iHOT Survey in the Evaluation of Hip Pain and Hip Preservation Surgery

Presenters: Andrew Lee, Olivia Jenk
Mentor: Dr. Robert Westermann, MD

Introduction:

The International Hip Outcome Tool (iHOT) is a self-administered questionnaire designed to evaluate hip functionality, activity resumption, and the likelihood of revision surgeries. The questionnaire uses a score ranging from 0-100, where 100 represents the absence of pain or functional loss. The iHOT scores have been found to have good reliability and validity and can detect meaningful changes in patients undergoing hip arthroscopy.

Purpose:

To determine whether iHOT scores can evaluate hip pain at initial presentation and surgical candidacy for hip preservation surgery.

Method:

This retrospective study examined 661 patients who sought medical attention for hip pain. Inclusion criteria encompassed an age of over 13 and the completion of the iHOT survey at the initial consultation. Demographic data (age, sex, BMI), the presence of intra-articular pain, iHOT scores, laterality, indications for hip preservation surgeries, and surgical history were documented. Subsequent comparisons of iHOT scores were conducted among the following groups: 1) Patients with intra-articular (true) versus extra-articular (false) hip pain, 2) Patients indicated for hip preservation surgery versus those not recommended for surgical intervention, 3) Primary surgery candidates versus patients requiring revision surgery. Statistical significance was evaluated using independent two-tailed T-tests or ANOVA ($p<0.05$).

Results:

No statistically significant difference was observed in mean iHOT scores between patients with extra-articular pain (33.2 ± 15.3) and those with intra-articular pain (29.5 ± 12.4) ($p=0.3995$). However, there was a significant difference in patients indicated for hip preservation surgery compared to those not indicated for any surgery; those indicated for surgery had lower mean iHOT scores (35.8 ± 17.6) than those not indicated (39.4 ± 20.7) ($p=0.0378$) and this difference remained significant even after adjusting for age ($p=0.0023$). Additionally, in the analysis of primary hip preservation surgery versus revision surgery, primary surgery candidates initially did not show a significant difference in mean iHOT scores (36.2 ± 20.2 vs. 33.4 ± 15.2, $p=0.0853$), but after adjusting for age, BMI, and sex, a significant difference emerged ($p=0.0252$), with primary surgery candidates having higher scores.

Conclusion:

Our findings suggest that the iHOT survey may not be specific enough to distinguish between intra-articular and extra-articular hip pain. However, the significant differences in iHOT scores between patients indicated and those not indicated for surgery, as well as primary and revision surgery candidates, suggest the potential utility of the iHOT as a surgical candidate assessment tool.

Regional Pulmonary V/Q Improvements with Sildenafil vs. Placebo in a Smoking Cessation Study Monitored via Multi-spectral CT

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Background: We hypothesize that the use of sildenafil combined with smoking cessation will decrease inflammation in the lung through restoration of perfusion by inhibiting hypoxic pulmonary vasoconstriction (HPV) in areas of smoking associated infiltrates. Previous studies using dual-energy computed tomography (DECT) have demonstrated that heterogeneity of pulmonary blood volume (PBV), a surrogate for perfusion, is significantly increased in emphysema susceptible smokers, and this heterogeneity is reduced with sildenafil. If the development of emphysema is due to failure to block HPV in regions of the lung injured by smoking, blocking the vasoconstriction with sildenafil may be a viable treatment option in patients that are identified early. We hypothesize that sildenafil administered during a smoking cessation program will serve to improve regional ventilation-perfusion matching ($\dot{V}/\dot{Q}$) by reducing the percent of lung falling at the high or low end of the $\dot{V}/\dot{Q}$ histogram.

Methods: Smokers (n=80) between the ages of 21 and 65 were randomized to 3x/day sildenafil or placebo. All subjects returned for four visits (baseline, 30-day, 60-day, and 90-day) to collect vitals, blood tests, questionnaire answers, pulmonary function tests. CT scans were obtained using standardized protocols on Siemens SOMATOM Force scanner (Erlangen, Germany). Non-contrast CT scans were obtained at total lung capacity (TLC) and residual volume (RV). Contrast-enhanced DECT scans on *days 0* and *90* included an additional scan with iodinated contrast. Contrast-enhanced DECT scans were obtained at functional residual capacity (FRC) and used for detecting vascular abnormalities and quantifying regional perfused blood volume. Regional ventilation-perfusion ratios ($\dot{V}/\dot{Q}$) were obtained using both in-house and scanner supported software to perform dual-energy material decomposition. In this method, high- and low-energy images are decomposed into an iodine attenuation component and a virtual non-contrast (VNC) component. The VNC image is used for registration and segmentation, whereas the iodine attenuation can be derived to result in blood volume in each voxel. We have shown previously that DECT-derived PBV measurement and lung perfusion quantification methodology is comparable with dynamic CT-based lung perfusion measurements. By image matching of the TLC image to the FRC virtual non-contrast image, we acquire estimates of regional volume change, an estimate of regional ventilation. Thereafter, each region of the lung was represented as a percent regional volume change relative to the whole lung volume change to assess % volume change or % ventilation ($\dot{V}$). By representing the same region by a value of PBV calculated to be a % total PBV ($\dot{Q}$), we assessed an index of regional $\dot{V}/\dot{Q}$. $\dot{V}/\dot{Q}$ histograms were assessed in terms of their mean, median, mode and V/Q High (>4) and V/Q Low (<1/4). A missing-at-random assumption waws made for nearly 50% missing data. This was accounted for via inverse probability weighting.

Results:
(S=Sildenafil, P=Placebo, Q=Quitters, NQ=non-quitters)

- S had a higher V/Q med. at 90 days compared to P, 95% CI (0.001, 0.034) (p=0.046).
- S-NQ had a higher V/Q med. at 90 days compared to P-NQ, 95% CI (0.012, 0.056). (p=0.008)
- S-NQ had a higher V/Q mode at 90 days compared to the P-NQ, 95% CI (0.032, 0.228), (p=0.024)
- P-Q trended to a higher V/Q_high at 90 days compared to S-Q, 95% CI (0.123, 4.670). (p=0.079)
- S-Q had a lower V/Q_high at 90 days compared to S-NQ, 95% CI (-4.330, -0.577). (p=0.038)
- S-Q had a lower V/Q_low at 90 days compared to S-NQ, 95% CI (-2.290, -0.274). (p=0.017)
- P-Q had a higher V/Q_low at 90 days compared to S-Q, 95% CI (0.186, 2.094). (p=0.046)

Conclusions: The study demonstrates that sildenafil promotes the matching of $\dot{V}/\dot{Q}$, the minimization of extremely low and high values of $\dot{V}/\dot{Q}$ within the over-all group and within groups who do or do not quit smoking over a 90-day period. In a separate report, we have demonstrated that taking sildenafil during a smoking cessation program increases the adherence to cessation over the 90 days, possibly because of the improved gas exchange which would accompany improved matching of $\dot{V}/\dot{Q}$. The data presented here supports the need for a larger clinical study.

Urine Copeptin and Preeclampsia in Rural and Urban Women

Emma Lewis MS4, Donna Santillan PhD, Mark Santillan MD PhD

Introduction: Preeclampsia is a disorder of pregnancy involving hypertension and end organ damage. Preeclampsia (preE) affects 2-7% of all pregnancies and is one of the leading causes of maternal/fetal morbidity and mortality worldwide. Preeclampsia results in morbidity and mortality for both mother and child during the pregnancy and long afterwards. Prior research has demonstrated increased secretion of arginine vasopressin (AVP) in preeclamptic pregnancies. In recent years, copeptin has been widely accepted as a stand-in for AVP given the short in vitro half-life of AVP. Prior research from Santillan, et al. has shown that elevated maternal plasma copeptin is significantly predictive of the development of preeclampsia as early as the 6th week of gestation. It remains unknown whether urine copeptin is also predictive of the clinical development of preeclampsia later in pregnancy.

Objective: We aim to investigate the relationship between urine copeptin prior to 20 weeks gestation and the development of preeclampsia. We also aim to investigate whether this relationship is affected by race and rurality as well as the covariates that affect this relationship.

Methods: This study was a retrospective case-control study utilizing data and samples provided through the University of Iowa Maternal Fetal Tissue Bank (MFTB). This study included 210 pregnant participants (158 control, non-preeclamptic women and 52 preeclamptic women) who received obstetric care at the University of Iowa and provided urine samples prior to 20 weeks gestation. Urine copeptin concentration was measured using an automated immunofluorescence assay. Total urine protein concentration was measured using a colorimetric assay and read in a spectrophotometer at 562 nm. Rurality was classified by RUCA scores based on patient ZIP code.

Results: There is no difference in urine copeptin/protein ratio (CPPR) between participants from various urban-rural classifications. CPPR prior to 20 weeks GA is significantly lower in preeclamptic pregnancies when compared with non-preeclamptic pregnancies (146.3 +/- 15.4 vs. 252.4 +/- 36.2, P= 0.008). The relationship between urine CPPR and preE is no longer significant when controlling for history of preE (OR 0.999, P=0.248). History of preE in a prior pregnancy is strongly associated with a lower urine CPPR (P=0.004). Other cardiovascular risk factors of BMI and gestational diabetes mellitus are not significantly associated with any change in urine CPPR.

Conclusion/Discussion: These data support the concept that lower urine copeptin concentration in early pregnancy is associated with the development of preeclampsia. Additionally, as there is no difference in CPPR with BMI, gestational diabetes mellitus, rurality, or race, this suggests that decreased urinary CPPR is related to physiologic changes rather than external factors and that the relationship between preeclampsia and urine CPPR is specific rather than a reflection of general cardiovascular risk. In the setting of high serum copeptin in preeclamptic women, low urinary excretion of copeptin suggests increased renal retention and decreased urinary excretion of copeptin. The mechanism underlying this is unclear but may reflect long-term renovascular changes of preeclampsia. More research is warranted to elucidate the actions of copeptin and the renovascular changes of preeclampsia.

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Title: IS FRAILTY DISCOURAGING SURGEONS FROM PERFORMING THORACOLUMBAR FUSION? A RETROSPECTIVE STUDY

Introduction: Trauma patients with thoracolumbar fractures (TLF) often face a long recovery needing rehabilitation. The Canadian Study of Health and Aging clinical frailty scale (CSHA-CFS) predicts poor outcomes in older trauma patients. We evaluated whether frailty could predict outcomes and guide management of the TLF population.

Methods: Adult trauma patients admitted from 2017 to 2021 who presented with TLF were included. Frailty was scored using the CSHA-CFS. Endpoints were in-hospital mortality, hospital length of stay, surgical management, complications, and discharge disposition. Multivariate analyses adjusting for demographics, pre-injury antithrombotic use, injury severity score, mechanism of injury, coexisting cervical and rib fractures, whether patients suffered a thoracic and/or lumbar fracture, and whether thoracolumbar (TL) fusion was performed to assess the association between frailty and our endpoints.

Results: Overall, 1456 patients were included; 1013 fit, 240 pre-frail, and 203 frail (Figure 1). Patient characteristics are presented in Table 1. Compared to fit patients, frail patients were less likely to undergo any form of surgery (OR=0.5 [0.32-0.77], p=0.002). Undergoing TL fusion was associated with decreased risk of mortality (OR=0.31 [0.11-0.85], p=0.024). Frailty was associated with increased risk of death (OR=2.46 [1.07-5.67], p=0.035) and pneumonia (OR=2.93 [1.32-6.54], p=0.008). Frailty was associated with discharging home with services (OR=2.98 [1.29-6.93], p=0.011), LTACH (OR=5.43 [1.75-16.86], p=0.003), or SNF (OR=4.89 [2.66-9.0]), p<0.001).

Conclusion: Frail patients had poor outcomes and required higher level of care at discharge, yet were less likely to undergo TL fusion, which was associated with decreased mortality risk. This suggests that frailty status should not discourage surgeons from performing spinal fusion procedures, but prospective studies are necessary for validation.

Race and Rurality as Risk Factors for Preterm Birth: Abbie Lund, M2,
Mentors: Mark Santillan, MD, David Bedell, MD, Barcey T Levy, PhD, MD

Introduction: Preterm birth (PTB) defined as prior to 37 weeks gestation occurs in 10.5% of births in the United States and 10.0% of those in Iowa. PTB is associated with short and long-term neonatal health complications including infection, decreased lung development and death, as well as later developing conditions such as autism and attention deficit hyperactivity disorder. Furthermore, maternal and neonatal healthcare cost of PTB is markedly increased. Despite the prevalence of PTB, the cause of spontaneous PTB is unknown. Other research has shown that sociodemographic factors are associated with an increased risk for PTB, including Black race, low educational level, tobacco use, decreased access to family planning, and many others. Recent data also demonstrates that location of residence and the related socioeconomic resources can also determine risk for PTB. Given that in Iowa rural patients have decreased access to obstetric care, we believe there may be more risk for PTB in rural environments than urban. **We hypothesize** that each of rural residence and minority race mothers will have a greater risk for spontaneous PTB than others.

Methods: We conducted a retrospective cohort study using the Intergenerational Health Knowledgebase (IHK, IRB 201902830) which houses and extracts all data from the electronic medical record at UIHC. Pregnancies with a current diagnosis of hypertension, diabetes, and cholestasis were excluded as common potential reasons for an indicated PTB, leaving a total of 17497 delivered pregnancies delivered from 5/2009 to 5/2023. Pertinent socioeconomic, demographic, medical diagnosis, and pregnancy outcome data was extracted from the IHK. Rural Urban Commuting Area (RUCA) codes of residence at the time of delivery were grouped into categories of RUCA=1-3 (Metropolitan), 4-6 (Micropolitan), 7-9 (Small Town), and 10 (Rural). Dependent variables for hypothesis testing and regression modeling were defined as PTB <37 weeks, <34 weeks, <32 weeks, <28 weeks, and <24 weeks. The U.S. Maternal Vulnerability Index (MVI) is a county-level open-source tool to identify maternal vulnerability to poor health outcomes based on 6 domains from national data sets in reproductive healthcare access, physical health, mental health/substance abuse, general healthcare, socioeconomic determinants, and physical environment. Each county is rated 0-100 where 100 indicates the highest vulnerability for poor health outcomes. Overall MVI scores were determined based on county of residence at the time of delivery. Chi-square, t-tests, a multiple logistic regression modeling were performed as appropriate with α=0.05.

Results: Overall, maternal age and racial distribution were *clinically* similar between PTB <37 weeks and full-term birth (FTB) groups. When comparing PTB vs. FTB, there were significantly higher MVI scores (14.2±0.3 vs. 10.6±0.1, p<0.001), rates of tobacco use (13.7 vs. 5.7%, p<0.001), obesity (35.5% vs. 32.3%, p=0.007), percentage of mothers who were gravida 1 status (33.8% vs. 30.2%, p=0.001), and Medicaid insurance (34.6% vs. 28.2%, p<0.001) in the PTB group. Multiple regression models were created to understand the effect of specific race category and RUCA code on the development of PTB at different gestational ages. Asian race was associated with a decreased risk (OR=0.59, p<0.001) and rural residence (RUCA=10) was associated with an increased risk of PTB <37 weeks (OR=1.31, p<0.001) even after controlling for maternal age, MVI, tobacco use, primigravida status, obesity, psychiatric drug use, baby gender, Medicaid insurance use, and depression or anxiety diagnoses. In models evaluating PTB <34 weeks, Hispanic or Latino (OR=0.53, p=0.040) and Asian (OR=0.46, p=0.015) race was associated with a decreased risk and rural residence (RUCA=10) was associated with an increased risk of PTB <34 weeks (OR 1.49, p=0.028) even after controlling for maternal age, MVI, tobacco use, primigravida status, obesity, psychiatric drug use, baby gender, Medicaid insurance use, and depression or anxiety diagnoses. When examining PTB <34 weeks, Black race (OR=1.43, p=0.036) was associated with an increased risk and Urban residence (RUCA<4) was associated with a decreased risk of PTB <34 weeks (OR 0.67, p<0.001) even after controlling for maternal age, MVI, tobacco use, primigravida status, obesity, psychiatric drug use, baby gender, Medicaid insurance use, and depression or anxiety diagnoses. Interestingly, individual race or location of residency had no significant association with PTB <24 weeks.

Discussion: These data support a clear association between race and location of residence in the development of PTB. In comparison to other races, Hispanic and Asian populations exhibit a lower risk of PTB where the Black population is associated with a higher risk of PTB consistent with current literature. While the effect may be due to smaller numbers in more rural areas, it appears that in models focused on the Black population, living in a more urban area in Iowa, is associated with a lower risk of PTB. The observation that race and rurality have no association with PTB <24 weeks may suggest that idiopathic PTB early in pregnancy may be due to an underlying physiologic process rather than sociodemographic factors. Further work in this area is necessary to evaluate this lower incidence, but significantly higher healthcare resources are needed to research this intensive level of PTB.

The prevalence of surgical intervention in symptomatic carpometacarpal bossing.

Authors: Kimia Maddahi, Ignacio Garcia Fleury, M.D.; Joseph A. Buckwalter V, M.D., PhD

Abstract

BACKGROUND Carpometacarpal bossing is an uncommon condition marked by a dorsal prominence usually near the base of the second and third metacarpals. It is often asymptomatic but can give rise to discomfort and pain. Once symptomatic, it can be treated either conservatively or surgically. The etiology of carpal bossing is poorly understood; However, some of the proposed hypotheses are genetics, history of injury due to trauma, or participating in sports or occupations that require repetitive hand movements. Previous studies suggest that a symptomatic carpometacarpal boss is more likely to develop on the dominant hand. Individuals affected by symptomatic carpometacarpal bossing are usually in their early 30s, but there have been case reports from individuals from 11 to 75 years old. Currently, carpal bossing is a poorly researched topic. Most studies available are either case reports or discuss the diagnosis and treatment of the carpal boss. There is limited literature available regarding the prevalence and outcome of each treatment, or the cause of this phenomenon. Thus, we aimed to investigate and compare the prevalence of surgical intervention and conservative treatment. Additionally, we hypothesized that carpometacarpal bossing is more prevalent in individuals who participate in athletic activities. Therefore, we sought to investigate whether athletes constitute a significant demographic among those with symptoms.

METHODS This study followed a retrospective chart analysis approach. We utilized the ICD-10 codes for carpometacarpal bossing to search for patients with the diagnosis on the University of Iowa Hospitals and Clinics Epic database from January 1, 2009, to December 31, 2022. Subsequently, patient records, including physician notes and available imaging were manually reviewed to confirm the diagnosis and collect data regarding demographics, treatments, and athletic activity.

RESULTS The study comprised 23 patients, including 16 males and 7 females. The mean age of the cohort was 31, with an age range spanning from 15 to 62 years. Regarding treatment, 5 patients (21.7%) did not receive treatment, 9 patients (39.1%) opted for conservative treatment, and 9 patients (39.1%) underwent surgical excision. In terms of carpal boss distribution, 12 patients (52%) exhibited a carpal boss in the right wrist, while 11 patients (48%) had it in the left wrist. The data was insufficient regarding hand dominance. Of note, 13 patients (57%) participated in an athletic activity such as golf, gymnastics, baseball, or basketball. Furthermore, 4 patients (17%) had an occupation or lifestyle that necessitated weight-bearing activity on the wrists.

CONCLUSION While the prevalence of surgical intervention and conservative treatment was equal in the patients who received treatment, it is noteworthy that among those who initially opted for surgery, a significant 66% had previously explored conservative treatments that ultimately yielded ineffective results. This inclination towards surgical intervention underscores its potential as a more definitive treatment option. Notably, only one patient underwent revision excision in this cohort, which is consistent with literature that has shown that over 90% of patients who undergo excision for carpal bossing achieve complete symptom relief with only one surgery. Furthermore, our study expands upon the current limited literature by revealing a potential correlation between carpal bossing and activities requiring repetitive wrist movements. The substantial prevalence of such activities among our patient cohort (74%) reinforces the hypothesis that repetitive hand motions may contribute to the development of this condition.

Unraveling Growth Variability in Renal Masses of Von Hippel-Lindau Patients: A Comprehensive Analysis of Kinetics and RNA Expression for Predictive Biomarker Discovery

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Introduction: Von Hippel-Lindau (VHL) disease is a rare genetic disorder that makes individuals susceptible to various tumors, including renal cell carcinoma (RCC), a malignant growth in the kidneys. RCC in VHL patients is characterized by unpredictable growth patterns, complicating the determination of the best intervention timing. This research project addresses a critical knowledge gap by exploring the discovery of a biomarker capable of predicting the rapid growth potential of VHL-related renal masses. Importantly, these masses within the same patient exhibit significant growth rate variations, necessitating a deeper understanding of the underlying mechanisms. Currently, the standard approach involves monitoring these masses until they reach a 3cm size threshold, which may result in unexpected and rapid tumor growth, elevating the risk of metastasis and the potential need for radical nephrectomy.

Purpose: We aim to establish a biomarker that can signal whether small renal masses associated with VHL-disease are predisposed to rapid growth kinetics, thus posing a greater risk metastatic disease and surgical complication. The identification of a biomarker signaling rapid growth potential could revolutionize patient care, enabling the removal of tumors at smaller sizes, thereby preserving renal function, and mitigating the risk of metastatic progression.

Methods: This study utilizes the Genito-Urologic Molecular Epidemiology Resource (GUMER) established at the Holden Comprehensive Cancer Center in Iowa. GUMER includes 15 von Hippel-Lindau (VHL) patients who have provided paraffin-embedded tissue samples post partial or radical nephrectomy. We analyzed radiographs during their course of treatment at UIHC (spanning from 2001 – 2023) and documented the size of each mass chronologically to complete growth curves for each mass. These factors were input into GraphPad Prism to generate kinetic curves. Comprehensive RNA expression analyses on resected tissue samples are being carried out to identify differentially expressed genes, comparing between fast and slow growing masses. Resected RCC tissues from patients without VHL-disease will be included as a control.

Results: A retrospective chart review of 15 patients who underwent partial or radical nephrectomy for VHL-associated RCC revealed a notable statistical difference in growth rates between rapidly and slowly progressing masses during the same observation period, even when comparing masses from the same patient. However, with regards to RNA expression analysis, the project is still in progress, and as of now, a definitive conclusion cannot be drawn.

Transgender Women on Estrogen Have a Lower Burden of Thrombotic Events Compared to Cisgender Men: A Nationwide Hospital-Based Survey

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Due to public recognition and acceptance, more transgender women are being prescribed gender-arming estrogen therapy. Traditionally, sexual dimorphism has been shown to play a signicant role in the pathophysiology of thrombotic phenomena. While genetic factors remain the key players in the divergent male and female phenotypes, limited information is available regarding the thrombo-vascular effects of estrogen therapy in transgender women. Furthermore, available data has been conicting with respect to vascular outcomes in this specic population. Therefore, more evidence is required to understand the long- term effects of gender-arming estrogen therapy. In the current study, we investigated the thrombotic outcomes of estrogen therapy in transgender women (male sex assigned at birth), in comparison to cisgender men and cisgender women.

We performed retrospective analyses using the TriNetX database that includes de-identied data for over 250 million patients across 76 certied healthcare organizations. We included all adults over the age of 18 years and excluded those with the presence of documented prothrombotic risk factors such as obesity, diabetes, hyperlipidemia, smoking, and cancer. Within the cohort of cisgender women, we excluded pregnancy and post-menopausal status. The thrombotic outcomes within the transgender cohort were recorded after the start of hormone replacement therapy. To account for thrombotic events, we used search terms such as acute myocardial infarction (MI), cerebral infarcts, pulmonary embolism (PE), and deep vein thrombosis (DVT).

We found 12,369 transgender women, 29,746,302 cisgender men, and 32,591,972 cisgender women that were eligible for our study. The transgender women had lower incidences of MI (0.14% vs. 0.38%, P<0.0001), cerebral infarcts (0.21% vs. 0.49%, P<0.0001), and DVT (0.33% vs. 0.47%, P<0.022) compared to cisgender men. The incidence of PE was comparable in both these groups (P=0.85). Furthermore, we observed that transgender women also experienced signicantly lower incidences of cerebral infarcts (0.21% vs. 0.42%, P=0.0003) and a moderately decreased incidence of MI (0.14% vs 0.22%, P=0.062) compared to cisgender women. The incidence of venous thrombosis was similar in these two groups.

Overall, we observed a paradoxical decrease in rates of thrombotic events, suggesting that estrogen may play a protective role against the development of acute MI, cerebral infarction, and DVT in transgender women. Further investigation is required to understand the downstream targets that offer these cardioprotective effects. Importantly, our data may provide clinicians with reassurance that traditional vascular risks associated with estrogen may be less pronounced in males.

Bispectral EEG to predict delirium after spine fracture in older adults

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Introduction:
Delirium is a common but often preventable complication after spine fracture. Delirium is associated with medical complications, prolonged skilled nursing facility admission, mortality, and a significant cost burden. If delirium is recognized, interventions can mitigate negative outcomes. However, delirium can be difficult to detect amidst shift changes and busy hospital workflows because delirium fluctuates and can present hypoactive symptoms such as drowsiness and inactivity. Bispectral electroencephalography (BSEEG) is an objective noninvasive point-of-care test that has the potential to fill this need for a screening tool to identify older adults at risk for delirium. However, BSEEG has not yet been validated for effectiveness in older patients with spine fractures.

Purpose: The aim of this study is to evaluate the effectiveness of BSEEG as a screening tool for delirium in older adults with spine fracture.

Method: Patients over 50 years old with spine fracture requiring immobilization in a brace were enrolled prospectively. Baseline demographics were recorded including age, sex, and Charlson Comorbidity Index, and baseline cognitive function was measured using the Mini-Mental State Examinations (MMSE). Delirium was assessed clinically using the 3-Minute Diagnostic Interview for Confusion Assessment Method (3D-CAM) administered after each BSEEG measurement and daily Delirium Observation Screening Score (DOSS). Morning and afternoon BSEEG measurements were collected for up to 6 days of hospital admission. A power spectral density value was compared to a previously established threshold in order to determine a binary prediction if the patient was experiencing delirium.

Results: 15 subjects currently enrolled in the study were analyzed. The subject demographics are as follows: 47% female, age 72.8 ± 11.8, and 100% white/non-Hispanic. 5/15 subjects (33%) experienced delirium. The following preliminary performance metrics were determined for the device: sensitivity = 0.4, specificity = 0.1, accuracy = 0.2, PPV = 0.18, and NPV=0.25.

Conclusion: Preliminary results (pending enrollment of approximately 45 more subjects) do not support the conclusion that BSEEG is an effective method of predicting delirium in older adults who have experienced a spine fracture requiring immobilization in a brace. Results are limited by a small sample size. Ongoing enrollment in the study is needed for sufficient power to draw further conclusions.

Prognostic Factors for Long Term Outcomes in Neovascular Age-Related Macular Degeneration

Collaborators: Thomas Martinez, Amy Wu, Mary McCormick, Chris Sinkey, Kai Wang, Elliott Sohn

Background: Age-Related Macular Degeneration (AMD) is the #1 cause of irreversible blindness in the western world with at least 150 million people affected globally. Vision loss occurs in those with the 'wet' neovascular form of AMD (nvAMD), for which intravitreal anti-vascular endothelial growth factor (VEGF) injections are the standard of care. Unfortunately, up to 50% of patients do not have a complete response to these injections and visual acuity (VA) can worsen despite monthly treatments. A small percentage respond well to these injections and are able to discontinue treatments indefinitely. This study aims to explore these poorly understood discrepancies in long-term outcomes by examining morphological and functional factors present within the initial months of presentation. We hypothesize that a patient's initial response to anti-VEGF injections will be able to predict long-term outcomes.

Methods: Data were collected from Epic charts on 274 eyes from 198 patients that received regular treatments at the University of Iowa for at least one year from 2009 to 2023. Patients were excluded if there was presence of comorbid disease impacting VA, use of study drugs, and history of pars plana vitrectomy or photodynamic therapy. Statistical analyses were performed on the remaining 216 eyes from 167 patients. Initial response to anti-VEGF was measured as change in VA from first injection to fourth injection. A fixed effects logistic regression was used to examine predictors for patients who could discontinue injections for at least 12 months including age, sex, BMI, smoking status, initial geographic atrophy or subretinal fibrosis, initial VA, and change in VA from initial to fourth injection. An additional fixed effects logistic regression analyzed the same predictors for disease recurrence. Fixed effects linear regressions were used to determine significance of these predictors for the following outcomes: VA at 2 years, final VA, interval at 2 years, and final interval.

Results: 65 eyes from 58 patients were able to discontinue injections. Of these, 39 eyes from 35 patients experienced recurrent nvAMD and restarted injections. Ability to discontinue injections was associated with worse VA at initial presentation with an odds ratio estimate of 4.9 ($p=0.045$, 95% CI: 1.02, 23.3). Disease recurrence was not significantly predicted by sex, age, BMI, or smoking history. Additionally, no significant associations were found for change in VA from initial to fourth injection and the following outcomes: VA at 2 years, final VA, interval at 2 years, final interval, discontinue status and disease recurrence. However, a higher age of onset at the initial visit predicted a longer treatment interval at 2 years with an estimate of 0.1 weeks per additional year of age ($p=0.02$). Similarly, worse VA at onset predicted a shorter treatment interval at 2 years with an estimated slope of -2.0 ($p=0.01$) weeks per 10-fold decrease in VA, holding all other factors constant.

Discussion: Approximately 1/3 of subjects with nvAMD had anti-VEGF injections discontinued but over half of these subjects restarted treatment. Older subjects and those with worse initial VA may sustain a longer treatment interval at 2 years but not at the final visit, which may be due to other factors contributing to treatment interval length, such as physician preference, patient compliance, and access to healthcare. Further analysis is needed to confirm the reason for discontinuing injections as initial VA is correlated with increased odds of discontinuing injections, while also predicting a shorter treatment interval. Analysis of additional factors such as genotype and fluid may also assist in predicting cessation of treatment and recurrence.

Title: Understanding Cancer Networks: Development, Goals, and Operations

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Background: A popular strategy to facilitate high-quality cancer care delivery at small, resource constrained community hospitals is the “cancer network” model, which extends the services and expertise of large, resource-rich cancer centers via hospital partnerships. Cancer networks have been established in several states, though the structure, activities, evaluation, and outcomes of these networks are not well documented. To address this gap, we initially conducted surveys to explore the goals, composition, resources, and evaluation methods of existing networks. Subsequently, we carried out follow-up interviews to add context and enhance our understanding of the complex environments in which these networks operate.

Purpose: This study aims to investigate the development, goals, and operation of cancer networks using qualitative methods.

Methods: We conducted semi-structured interviews with representatives from the cancer networks identified in our previous study, focusing on the network's history, implementation processes, survey responses, and future directions. Participants were recruited via email. Interviews were conducted on Zoom, audio-recorded, and transcribed. Four team members independently coded the transcriptions using template analysis; consensus on overarching themes was reached through group discussion.

Findings/Results: Of the 18 targeted networks, we completed interviews with 11, mainly represented by executive roles like program directors and medical administrators. The networks serve diverse states, representing 7 of the 9 U.S. geographic census divisions. Our findings reveal that cancer care networks are highly varied, catering to specific geographic, clinical, and financial contexts. Despite these differences, we found commonalities. Notably, the brand value of the parent institution often plays a crucial role in shaping the network's overall reputation. Another shared aspect is a commitment to enabling high-quality care at affiliate sites. A recurring theme across our findings is the networks' adaptability. They continually evolve to meet the ever-changing demands of healthcare and technological advancements. This adaptability extends to hub-affiliate relationships as well; despite the presence of overarching policies, we observed significant room for negotiation and customization to meet the needs of both the hub and its affiliates. Each network, irrespective of whether their primary focus is on enhancing the quality of care, expanding research opportunities, or leveraging their brand reputation, exhibits unique strengths and weaknesses that align with their specific objectives and stages of development.

Conclusion: Our study laid the foundation for describing the complex landscape of cancer care networks, which can serve as a guide for new or emerging networks. We identified significant diversity in network goals, structure, activities, strengths, and challenges. More research is needed to define the characteristics of successful networks and identify strategies for evaluating their impact on quality of care.

Return to Sport, Post-Operative Performance Testing, and Reinjury Rates Among Athletes Treated with Hamstring, Quadriceps, and Patellar Tendon Autograft ACL Reconstruction

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Background: Anterior Cruciate Ligament (ACL) tears are a common sporting injury and optimal graft choice is of concern for both patients and surgeons. Few comparative studies have evaluated return to sport and reinjury rates across graft types.

Purpose: To evaluate return to sport rates and reinjuries among hamstring tendon (HT), quadriceps tendon (QT), and patellar tendon (BPTB) ACL reconstructions.

Methods: Recreational and competitive athletes ages 13-24 from 2010-2022 that underwent primary or revision ACL reconstruction were included. There were 837 total athletes comprised of 341 HT, 358 BPTB, and 138 QT autografts, of which 729 were primary and 108 were revision surgeries. Return to sport (RTS) rates, RTS testing results, clearance time, and reinjury rates were collected. RTS testing data included isokinetic testing of quadricep and hamstring strength and functional movement screening.

A Kruskal-Wallis test was used to detect differences among continuous variables. A GLIMMIX procedure was completed for multivariate analysis to detect differences between groups after adjusting for age and activity level. Chi-square statistics and Fisher's exact test were used for categorical variables. Odds ratio, adjusted odds ratio, and 95% confidence intervals were provided by logistic regression. All statistical analyses were performed using SAS 9.4 (Cary, NC). Statistical significance was measured at $p<0.05$.

Results: The median ages were 18 for HT and BPTB and 17 for QT ($p= 0.0001$). Females comprised 50.73% of HT grafts, 42.86% of BPTB grafts, and 41.30% of QT grafts. Return to previous level of play was observed in 118/130 (90.77%) HT, 124/136 (91.18%) BPTB, and 39/52 (75.00%) of QT grafts ($p=0.0045$); BPTB remained statistically more likely to return to previous level of play than QT after adjusting for age and activity level. RTS testing was completed in 28/341 (8.21%) HT, 142/358 (39.66%) BPTB, and 80/138 (57.97%) QT grafts ($p<0.001$); after adjusting for age and activity level, the results remained significant. Median isokinetic quadriceps testing at 300 degrees per second was 92% for 26 HT athletes, 83% for 134 BPTB athletes, and 87% for 77 QT athletes ($p= 0.0006$); results remained significant following age and activity level adjustment. Median isokinetic hamstring testing at 60 degrees per second was 89% for 24 HT athletes, 101% for 135 BPTB athletes, and 100% for 79 QT athletes ($p=0.0007$); results remained significant after adjustment for age and activity level. The median single-leg hop ratio was 98% for 5 HT athletes, 85% for 12 BPTB athletes, and 96% for 14 QT athletes ($p=0.044$); after adjusting for age and activity level, results remained significant. Time to be cleared for RTS was 25.89 weeks for 179 HT athletes, 34.75 weeks for 186 BPTB athletes, and 35.74 weeks for 75 QT athletes ($p <0.0001$) with the results remaining statistically significant following adjustment for age and activity level. ACL retear rates were 12.02% for HT, 3.07% for BPTB, and 5.07% for QT ($p<0.0001$) with hamstring grafts remaining significantly more likely to suffer an ACL retear than BPTB grafts after adjusting for age and activity level.

Conclusions: After adjusting for age and activity level, BPTB ACL autografts demonstrated a lower reinjury risk when compared to HT autografts. When comparing QT and BPTB, return to sport testing 6-9 months post-op was superior in the QT group; however, BPTB patients were more likely to return to sport. This data can help influence surgeon and patient shared decision-making models in athletes with ACL injuries.

Efficacy of Intraoperative Intra-articular Morphine on Post-Operative Pain and Opioid Consumption Following Hip Arthroscopy

Steele McCulley, BS, Jace Lapierre, BS, Courtney Seffker, PA-C, Qiang An, MBBS, MSPH, Robert W. Westermann, MD

Background: The use of intraoperative intra-articular morphine has been suggested to lower postoperative pain scores and opioid use. We sought to evaluate the effectiveness of intra-articular morphine with 0.75% ropivacaine when compared to the use of ropivacaine alone.

Purpose: To determine the efficacy of intra-articular morphine on pain control, opioid consumption, and discharge times in the immediate postoperative period.

Methods: We retrospectively reviewed the charts of 100 patients who underwent hip arthroscopy with repair for femoroacetabular impingement (FAI) between 2021 to 2023. 50 patients who received 5 mg of intra-articular morphine injections intraoperatively were identified, as well as 50 patients who did not. Patients undergoing hip arthroscopy without repair, revision surgery, or combined hip arthroscopy and femoral osteotomy or periacetabular osteotomy were excluded. Demographics including age, sex, race, ethnicity, BMI, and tobacco use were recorded. Procedural factors included total operative time, traction time, and time to discharge. Pain scores were assessed using the Visual Analog Scale (VAS), and the initial Post-Anesthesia Care Unit (PACU) and final PACU scores were recorded. Total acute opioid use was recorded using morphine milligram equivalents (MME) used from post-operation to discharge. We used the Wilcoxon rank sum test and chi-square statistics on continuous and categorical variables, respectively. The statistically significant level was set as $p<0.05$.

Results: No significant differences were found between demographics, operative time and traction time, or discharge time. The median age of patients in the non-injection group was 29 (48% M, 52% F), and 24.5 (34% M, 66% F) in the injection group. Differences between the non-injection and injection group in postoperative VAS scores were insignificant, with the mean initial PACU VAS scores (4.6 ± 3.0 vs 5.4 ± 3.0) and mean final PACU VAS scores (3.5 ± 1.9 vs 3.7 ± 1.4) respectively. The postoperative MME consumption difference was also insignificant (16.3 ± 17.1 vs 17.5 ± 17.9).

Conclusions: Intraoperative intra-articular morphine injection with ropivacaine does not provide a significant reduction in acute postoperative pain scores or opioid use when compared to ropivacaine use alone. Further investigation into the efficacy of intra-articular morphine is warranted.

Title: Preventing Skin Disease through Screening and Education at Primary Schools in Bagamoyo, Tanzania

Authors: Joshua Cheek, Erica Hsu, Katherine McDonald, Gasper Mmbaga, Omary Juma, Jane Mcharo, Stephen Humphrey, Karolyn Wanat.

Introduction:
Worldwide, skin diseases are the fourth leading cause of nonfatal disease burden, and they often negatively impact quality of life[4]. In Tanzania, the prevalence of skin diseases is as high as 35% in rural areas, with transmissible diseases making up 79% of all skin diseases and disproportionately affecting children[1,3]. It has been reported that 55% of primary school children have at least one skin disease[2]. The most common skin diseases in rural Tanzania include tinea capitis, tinea corporis, scabies, acne, and eczema, many of which are preventable through good hygiene[3].

Hypothesis/Purpose:
This study aimed to determine the most prevalent skin diseases in primary schools. This data was then used to provide relevant education on prevention practices to students and school administration.

Methods:
Three local primary schools were visited to screen students for skin diseases (Kongo Primary School, Miembe Saba Primary School, and Kiromo Primary School). Teachers at each school pre-selected students with skin conditions to participate in screening, and a team of 1-2 physicians from Bagamoyo District Hospital and four medical students evaluated, diagnosed, and constructed a treatment plan for each primary student. Skin diseases observed were then placed into the following categories: fungal infections, bacterial infections, atopic dermatitis, scabies, and other. Based on our findings, we developed targeted educational materials for primary school students.

Findings/Results:
Among the 494 primary school students that were screened for skin diseases, there was a total of 587 skin disease diagnoses. The majority (85%) of skin diseases were diagnosed as fungal, while bacterial infections were the second most prevalent (8%). Other diagnoses included scabies (1%) and other skin diseases (6%). Based on this, we focused our educational outreach on five main methods of prevention: washing hands with soap, not sharing clothes or towels with others, washing clothing often, washing hands after touching animals, and getting medical help right away.

Conclusion/Overall significance/Broader perspective:
The data collected from primary schools provide a unique understanding of the most common skin diseases in school-age children in Bagamoyo. Our results were disseminated to local health care providers and used to provide health education to students to enhance intervention, treatment, and prevention of these diseases in the future.

Restoring Helminthic Regulation of Intestinal Inflammation by means of Augmentation of STAT6 Activity in Donor T Cells in Graft-versus-Host Disease

Presenter: Emory McManimon (CCOM Class of 2026)
Mentor: M. Nedim Ince, MD (CCOM and Iowa City Veterans Affairs Medical Center)
Collaborators: Xiaoqun Guan, PhD, Tyler Atagozli, Hope Fury

Background: Allogenic bone marrow transplant (BMT), or hematopoietic cell transplantation, is used to treat leukemia, myeloma and lymphoma. Donor T cells added back during BMT induce a graft-vs-tumor (GVT) effect, but these cells can also cause graft-vs-host disease (GVHD) by attacking the host's healthy tissues. GVHD can be lethal and devastating. The intestine is frequently affected by acute GVHD, and gut involvement is a bad prognostic indicator in clinical practice. Acute GVHD is a T helper-1 (Th1) inflammatory process, which is regulated by activation of the Th2 pathway. Importantly, STAT6 is a key transcription factor in the Th2 pathway. In the past, the Ince laboratory has demonstrated in mice that inducing Th2 pathway by helminth colonization activates donor T cell Th2 pathway, regulates gut GVHD and promotes survival (Li et al. *J Immunol 2015, 194:1011*). During my 10-week rotation in the Ince laboratory, I tested the hypothesis of whether activation of the donor T cell STAT6 pathway by genetic over-expression of a constitutively active STAT6 regulates gut GVHD and restores helminthic immune regulation. Regulation of GVHD-associated colitis and ileitis were addressed in these studies.

Methods: GVHD was induced by transfer of donor T cells and T cell-depleted bone marrow (TCD-BM) cells from mice of the $H2^b$ MHC haplotype into irradiated BALB/c wild-type (MHC type: $H2^d$) recipients. Myeloablation was done using total body irradiation (TBI). Whereas TCD-BM cells originated from C57BL/6 wild-type mice ($H2^b$), donor T cells were selected from mice whose T cells overexpress a constitutively active form of STAT6 (STAT6VT mice or VT+; Bruns et al. *J Immunol 2003, 170:3478*) or their wild-type counterparts (VT-) (All donor strains $H2^b$). In addition, BMT was performed with helminth-infected BALB/c recipients after TBI and by transfer of WT TCD-BM and splenic T cells from C57BL/6 mice. Mice were analyzed 6 days after BMT. Colon and ileum were analyzed for GVHD-associated colitis using criteria graded on the degree of inflammation, crypt apoptosis, and ulceration involved (Kaplan et al. *J Immunol 2004, 173:5467*). In addition, spleen and mesenteric lymph node (MLN) cells were analyzed by flow cytometry for cell composition. Differences between groups were assessed by Student's t-test.

Learned techniques during the 10 weeks:

- Inducing and assessment of GVHD (performed with other lab members)
- Histopathological analysis of GVHD-colitis and GVHD-ileitis
- Spleen cell and MLN cell isolation
- Multicolor flowcytometry

Results: The colons of BMT recipients of VT- T cell donors displayed more severe colitis compared to colons of recipients of VT+ donors (6.3±1.1 (N (number of samples):10 vs 2.3±0.99 (N:8), $p<0.0001$), similar to regulation of GVHD-colitis after helminth infection (Li et al. *J Immunol 2015, 194:1011*). The ilea of BMT recipients of VT- mice T cell donors displayed more severe colitis compared to ileums of VT+ donors (7.2±1.2 (N:5) vs 1.8±0.98 (N:5), $p<0.0001$); this difference was more prominent than regulation of ileitis after helminth infection (Ince et al. *J Immunol 2009, 39:1870*). The regulation of colitis was associated with induction of $Foxp3^+$ regulatory T cells (Tregs) (4.39±1.98% in VT+ (N=7) vs 2.29±0.45% in VT- (N=7) splenic donor T cells ($p<0.05$); (13.91±5.49% in VT+ (N=4) vs 0.54±0.09% in VT- (N=5) MLN donor T cells ($p<0.001$)). (Other experiments in our laboratory by Guan, Fury, Atagozli, Shao, McManimon and other collaborators have shown that VT+ donor T cells also promote graft-versus-tumor effect (manuscript in preparation))

Conclusions/discussion: Constituently activating STAT6 in mice with GVHD (VT+ mice) helps to protect from inflammatory conditions due to Th2-mediated Th1 pathway regulation, as seen in the histopathology analysis of the colon and ileum. Genetic induction of donor T cell Th2 pathway can restore helminthic regulation of GVHD-colitis without using parasites. This same strategy can also prevent tumor recurrence.

Title: *Examining the utility of thermal imaging in trauma resuscitations*

Authors: Stephanie A. Meza, BS; Elizabeth A. Fuchsen, MSN, RN; Hayden L. Smith, PhD; Jonathan R. Hurdelbrink, PhD; Kaylee A. Dockter, MD; Carlos A. Pelaez**,** MD

Introduction: Video recordings have been used in trauma room quality assurance (QA) processes since 1988. In recent years, approximately 30% of level 1 and level 2 trauma centers in the United States have reported using video technology in resuscitation reviews. These applications have yielded benefits in error detection. However, there is limited research on the use of infrared thermal imaging in conjunction with real-time videos in the trauma room setting. The study purpose was to explore the potential value of a thermal camera system in the trauma resuscitation bay. The hypotheses were that thermal imaging has clinical usefulness and when combined with standard video taken concurrently, it also has quality improvement usefulness.

Methods: In a 10-week retrospective review at a Midwestern level I trauma center the thermal video recordings from MOBOTIX M16TB-R wall-mounted cameras in two trauma bays were analyzed. Milestone XProtect Smart Client facilitated real-time monitoring, recording, and video footage analysis. HIPAA-compliant authorization was ensured, and Institutional Review Board approval obtained. Eligible cases included level I and II trauma activations of all patient ages. Patterns associated with specific injuries, physiological states, or resuscitative interventions and scenarios were identified through initial medical student and secondary Trauma Medical Director reviews.

Results: During the 10-week review, 135 pediatric and adult trauma resuscitations were recorded, 50% level I and 50% level II trauma activations. Out of the 135 activations, 30 had non-useable thermal videos due to an obstructed view (n=22), not recorded (n=4), or other factors (n=4). Of the remaining 105 videos, 25 patients had patterns of interest related to: temperature/thermal control (n=8); tourniquets (n=5); shock (n=5); soft tissue injury (n=3); and others (n=4). Thirty-seven of all cases were identified as over triaged per Cribari Matrix Method with an additional 6 still requiring full injury coding due to hospitalization or pending autopsy results. Additional general patient characteristics included: 39 patients arrived by helicopter; primary mechanisms of injury were motor vehicle collisions (n=81), falls (n=19), and assaults (n=9); median age 41 years; and 20 patients died**.**

In temperature control videos, blankets and transport ventilators showed limited effectiveness on thermal imaging, while high flow nasal cannula and infusion pumps appeared to be more effective in rewarming patients. Effective tourniquet placement was confirmed in 1 out of 5 cases, with a notable improper application detected in a patient arriving 40 minutes post-tourniquet placement and with venous congestion misinterpreted as limb ischemia. Shock was documented in 10 patients with 5 visually presenting with "blotchy" thermal characteristics. Soft tissue injury cases exhibited cooler areas with reduced blood flow. Examples included devascularized tissue after a motorcycle crash and a tense leg hematoma leading to skin necrosis. Two other interesting findings included hemorrhage noted after chest tube placement and cold feet with normal vascular flow.

Conclusion: Thermal imaging in the trauma room has the potential to enhance quality improvement processes and demonstrates potential as a valuable tool for trauma surgeons, offering real-time insights for clinical decision-making in certain cases. Despite the benefits, implementation challenges include cost, patient privacy, compliance with the video recording process, and time needed to review thermal images. Nonetheless, the presented findings contribute to the growing evidence supporting the utility of thermal imaging in clinical settings, encouraging further exploration and adoption of this technology to improve patient care and outcomes.

Associations Between Vitamin D and Pediatric Celiac Disease Presentation

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Introduction: Celiac disease (CD) is a chronic autoimmune enteropathy elicited by the ingestion of gluten in genetically susceptible individuals. CD can develop at any age, but most patients present before age 10, often with a wide range of possible gastrointestinal or extraintestinal symptoms. Micronutrient insufficiencies and deficiencies are also common in patients with CD, and vitamin D, while well-known to be an important regulator of bone health, is also linked to autoimmunity as a regulator of autoimmune processes and intestinal permeability. Consequently, some have postulated that vitamin D status may play a role in CD development and management in children.

Purpose: The possible association between vitamin D status and CD is a relatively unresearched topic, and the existing literature is often contradictory. Given vitamin D's potential immunomodulatory role in CD, it is important to establish consistent conclusions to help inform clinicians about the value of monitoring vitamin D in CD diagnosis and management. Therefore, this study aimed to add to the literature by establishing a repository of pediatric CD patients to investigate the prevalence of vitamin D insufficiency and determine if vitamin D status was associated with markers of disease severity at diagnosis.

Methods: 450 pediatric patients at the University of Iowa Hospitals and Clinics with a positive CD diagnosis were identified, and 151 were ultimately included in our study. Clinic visit dates spanned September 2008 to April 2023. Inclusion criteria included age 0-18 years, CD diagnosis by a pediatric GI physician, and vitamin D recorded at diagnosis. Lab values considered to be at diagnosis included up to 3 months prior and 1 month after the date of diagnosis. A retrospective chart review was performed for all patients meeting inclusion criteria, and data including demographics, symptoms, past medical history, family history, growth parameters, labs (serum tissue transglutaminase IgA [tTg-IgA] and 25-hydroxy vitamin D), the season labs were tested, multivitamin and vitamin D supplementation, and endoscopy visual and histopathology findings were recorded. Statistical analysis was performed using SAS 9.4.

Results: 48% (72/151) of patients were vitamin D insufficient (<30 ng/mL) at diagnosis. Those who were vitamin D insufficient at diagnosis were significantly less likely than those sufficient in vitamin D to have a family history of CD and more likely to have a higher body mass index (BMI) Z-score. Patients who were vitamin D insufficient were also more likely than those sufficient to have had their vitamin D testing done in winter/spring. The average age, type of symptom presentation (gastrointestinal or extraintestinal), and percent of patients over 10 times the upper limit of normal for serum tTg-IgA levels were not significantly different. Vitamin D supplementation was rarely noted and also not significantly different.

Discussion and Conclusions: Our study is the second largest cohort of pediatric CD patients used to study vitamin D and CD associations to date, and our findings showed that vitamin D insufficiency is common in pediatric CD, with nearly half of the patients tested at diagnosis being insufficient. Without a healthy control cohort, it is difficult to conclude whether this vitamin inadequacy might be more common among children with CD than in healthy children. However, recent nationally representative data from the CDC suggests vitamin D insufficiency may actually be even more prevalent among the general U.S. pediatric population. Nonetheless, there was still a high prevalence of vitamin D insufficiency among our cohort of children with CD, and our results related to BMI suggest that vitamin D status does not necessarily go hand-in-hand with signs of generalized malnutrition. Therefore, clinicians should still consider testing serum levels in all CD patients at diagnosis to enable early intervention if necessary.

Development and Assessment of a Systematic Educational Intervention to Improve Knowledge of Disease and Quality of Life by Cutaneous Lymphoma Patients

William Moody, BS; Sarah Bell, MS; Eric Mou, MD; Vincent Liu, MD

Background: Cutaneous T-cell lymphomas (CTCL) are a diverse group of diseases representing a subset of non-Hodgkin lymphomas. Frequently limited to the skin in early-stage disease, CTCL uniquely often manifests an indolent disease course, effectively rendering it a chronic disease. Accordingly, management often revolves around symptom management and improving quality of life (QOL). Previous research has reported that CTCL patients often do not understand their disease well. Patients report that few accessible resources are available in print or online, and lack of awareness and understanding was a central theme reported, indicating the pervasive effects the disease can have on QOL. The focus of this investigation is the design and delivery of educational materials in verbal and written formats to understand whether an educational intervention could improve patient QOL, understanding, and satisfaction.

Methods: We developed "Managing Cutaneous T-cell Lymphoma: A Patient's Guide" (MCTCLPG), containing comprehensive information on symptom management, diet, finances, and disease specifics for mycosis fungoides (MF) or Sezary syndrome (SS). Notably, the guide featured a structured conversation covering diagnosis, disease progression, and treatment options, addressing the need for patients to communicate their condition to loved ones. The guide's efficacy was enhanced through iterative evaluation using the Patient Education Materials Assessment Tool (PEMAT) and the Flesch-Kincaid Reading Ease Formula (FKREF), focusing on understandability, actionability, and readability. Patients were enrolled after clinic visits and surveyed to assess health literacy, patient satisfaction, illness perception, self-efficacy, and QOL. Educational counseling and teach-back methods were conducted based on the guide. Follow-up surveys, mirroring initial assessments, were administered four weeks later. Statistical analysis employed linear mixed effects regression models with a spatial power correlation structure.

Results: The MCTCLPG's PEMAT Understandability score increased from 76% to 94%, and its Actionability score rose from 66% to 83% (5/6). The Flesch-Kincaid reading grade level improved from 9.3 to 7.7, and the FKREF improved from 50.4 to 60.1. Currently, 16 patients diagnosed with CTCL (15 MF, 1 SS; 10 early-stage, 6 late-stage) are enrolled; 10 patients have received 4-week follow-up surveys, with 8 completing all. 100% of patients found the educational session useful, and 75% used the material at least once post-visit. Notably, Skindex-16 Emotion scores significantly improved. Skindex-16 Functionality and Symptom scores and MF/SS CTCL QOL scores improved. There was a slight improvement in self-reported disease understanding and illness perception scores. Patient satisfaction and self-efficacy, though high overall, exhibited a slight decline.

Conclusion: While ongoing, this study highlights the successful development and implementation of a patient-centered educational intervention for CTCL. This intervention shows promise for improved patient understanding, emotional well-being, and symptom management, indicating the potential to enhance the overall QOL for CTCL patients. Refinement of the educational approach and identification of the highest-yield patient population will be examined to improve overall patient outcomes.

Diabetic Cardiomyopathy:
Sodium-Dependent Glucose Transporter 1 in Cardiac Mitochondrial Dysfunction

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Introduction: Diabetic cardiomyopathy encompasses abnormal myocardial changes among patients with diabetes mellitus, independent of cardiac risk factors such as hypertension and coronary artery disease. This disease is initially characterized by cardiac remodeling and dysfunction that can lead to clinical heart failure. In the general population, diabetic cardiomyopathy has a prevalence of 1.1% and has a high rate of morbidity and mortality. The pathophysiology underlying diabetic cardiomyopathy is poorly understood, though it has been found to be associated with abnormalities in glucose transport. Previous work in the Ahmad lab has shown that sodium-dependent glucose transporter 1 (SGLT1), one family of glucose transporters, is expressed in cardiomyocytes and that its expression is upregulated in the development of inherited and acquired forms of heart failure, including diabetic cardiomyopathy. The Ahmad lab has additionally shown that SGLT1-knockout mice exhibit diminished or reversed mitochondrial dysfunction. Further investigation is necessary to fully understand the mechanisms underlying the role of SGLT1 in cardiac mitochondrial dysfunction.

Aims and Hypothesis: There were two main aims of this study: (1) to investigate the effects of SGLT1 knockout on cardiac structure and systolic and diastolic function among mice with diet-induced obesity and (2) to investigate the mechanisms through which SGLT1 contributes to cardiac mitochondrial dysfunction among mice with diet-induced obesity. We hypothesized that among mouse models with type 2 diabetes and diet-induced obesity, reduced SGLT1 expression attenuates or reverses cardiac dysfunction and increases mitochondrial biogenesis through expression of the proteins PGC-1α, NRF-1, and TFAM.

Methods: As part of original methodology, comparison of cardiac function and mitochondrial dysfunction was to be conducted among floxed SGLT1 mice with tamoxifen-inducible cardiomyocyte-specific Cre and control mice exposed to a high fat/high sucrose diet. In vivo echocardiography was to be used to assess for wall thicknesses, chamber sizes, and systolic and diastolic function; histopathology was to be used to assess for myofiber hypertrophy. To assess for mitochondrial biogenesis, expression of PGC-1α, NRF-1, and TFAM was to be examined using immunoblot. However, in contrast to previous experiments, PCR and Western blot testing showed inadequate cardiac knockout of the SGLT1 protein among SGLT1-knockout mice previously injected with tamoxifen. Injection of old and new tamoxifen was instead performed among control-fed and high fat/high sucrose diet SGLT1-knockout mice; subsequent PCR and Western blot testing was performed.

Results: If the original methodology had been implemented, it was expected that there would be an improvement of diabetic cardiomyopathy and increased pathway activation in mitochondrial function. It was expected that high fat/high sucrose diet SGLT1-knockout mice would experience decreased cardiac hypertrophy, fibrosis, systolic dysfunction, and diastolic dysfunction. Furthermore, it was expected that expression of the PGC-1α/NRF-1/TFAM pathway would be upregulated among high fat/high sucrose diet SGLT1-knockout mice, indicative of mitochondrial biogenesis. In testing for SGLT1 expression, our findings currently indicate that both old and new tamoxifen generates a partial knockout of the protein among high fat/high sucrose diet SGLT1-knockout mice; the underlying basis for this partial knockout is currently being investigated by the Ahmad lab.

Discussion: Testing is currently in progress to investigate the partial knockout generated in the current mouse model. Possibilities include that the tamoxifen being injected is partially effective, non-cardiomyocyte cells such as endothelial cells in the heart may be expressing SGLT1, and that truncated but non-functional protein is instead being recognized in Western blot testing. Once complete knockout of SGLT1 is confirmed, the original methodology can be implemented to investigate for cardiac mitochondrial dysfunction. Inhibition of SGLT1 has important potential implications as a therapeutic target in the treatment of diabetic cardiomyopathy and heart failure.

Triggering Receptor Expressed on Myeloid Cells-1 (TREM-1) Restricts Allergic Airway Inflammation by Promoting Eosinophil Apoptosis

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Introduction: Asthma affects 8% of individuals living in the United States and standard treatment is often refractory for patients with severe asthma. As such, there is a critical need to elucidate the mechanisms driving allergic asthma pathology to develop better therapeutic targets. We tested the hypothesis that Triggering Receptor Expressed on Myeloid cells-1 (TREM-1) inhibits allergic airway inflammation (AAI) by altering eosinophil apoptosis.

Methods: We developed a model of AAI using ovalbumin (ova) in TREM-$1^{-/-}$ mice. Briefly, WT and TREM-$1^{-/-}$ mice were sensitized to ova/alum 20µg/4mg by intraperitoneal administration then challenged with 1% aerosolized ova. Disease severity was assessed using bronchoalveolar lavage and lung digestion, flow cytometry, and cytokine quantification by ELISA.

Results: TREM-$1^{-/-}$ mice developed less severe type 2 lung inflammation demonstrated by fewer airway eosinophils ($6.1x10^5 \pm 6.9x10^4$ vs. WT: $8.7x10^5 \pm 8.3x10^4$ numbers/mL), lung tissue eosinophils ($2.9x10^6 \pm 1.9x10^5$ vs. WT: $4.0x10^6 \pm 2.9x10^5$ numbers/100mg tissue), and decreased concentrations of IL-4 (62.5 ± 18.8 vs. WT: 165.9 ± 33.9 pg/mL) and IL-5 (239.0 ± 61.8 vs. WT: 493.5 ± 71.6 pg/mL) as compared to WT mice. When flow cytometry was performed, we unexpectedly identified TREM-1^+ eosinophils. These cells were then FACS sorted SSC^{hi} $CD45^+$ $CD11b^+$ $Ly6G^{lo/int}$ $CD11c^{lo/int}$ Siglec-F^+ TREM-1^+ and the eosinophil identity was confirmed by morphologic analysis. Interestingly, we found that tissue-resident eosinophils do not express TREM-1 in the lung or other tissues (small intestine lamina propria and intraepithelium, uterus, and thymus) at homeostasis. To investigate the role of TREM-1 expression by eosinophils, we generated an eosinophil specific TREM-1 deficient mouse using $Epx^{wt/cre}Trem1^{fl/fl}$. We found that $Epx^{wt/cre}Trem1^{fl/fl}$ mice developed more severe disease as demonstrated by higher concentrations of IL-5 in the airway (121.3 ± 12.5 vs 84.2 ± 10.0 pg/mL) and more eosinophils in the lung tissue ($2.5x10^6 \pm 3.0x10^5$ vs. $1.5x10^6 \pm 2.7x10^5$ number/100mg tissue) as compared to $Epx^{wt/cre}Trem1^{wt/wt}$ mice during AAI. These data suggest that TREM-1 expression is upregulated by eosinophils in response to inflammation and functions to paradoxically restrict AAI. Next, we examined whether TREM-1 alters apoptosis in WT eosinophils. $Epx^{wt/cre}Trem1^{fl/fl}$ eosinophils underwent less apoptosis (3.7 ± 0.3 vs. WT: 6.9 ± 1.1 % Annexin V^+ $Helix^-$) but had increased Caspase-1 (9.0 ± 0.8 vs WT: 5.7 ± 0.2 % Caspase-1^+) as compared to WT eosinophils, suggesting that TREM-1 drives non-inflammatory eosinophil cell death (apoptosis) to restrict disease progression ($p<0.05$ for all).

Conclusions: (1) Globally, TREM-1 promotes type 2 lung inflammation. (2) Eosinophils express TREM-1 during inflammation to paradoxically restrict AAI. (3) TREM-1 promotes apoptosis by eosinophils *in vivo* and *in vitro* to restrict disease severity in AAI.

A-priori prediction of negative V/Q scans in pulmonary hypertension

Student: Catherine Nugent

Mentor: Michael M. Graham, PhD, MD. Professor of Radiology – Division of Nuclear Medicine

Collaborators: Scott B. Graham BS, BSE, and Brian B. Graham, MS, MD

Introduction: Chronic thromboembolic pulmonary hypertension (CTEPH) is caused by unresolved emboli in the pulmonary arteries, leading to obstruction and vascular remodeling. When untreated, CTEPH may lead to progressive right heart failure and death. It is one of the few types of pulmonary hypertension (PH) that is treatable (with anticoagulation), which justifies efforts to make the diagnosis. The most accurate test for pulmonary emboli (PE) is the Single Photon Emission Computed Tomography (SPECT) ventilation-perfusion (V/Q) study, which shows the distribution of ventilation and perfusion in the lung. PE, either acute or chronic, appear as focal areas of absent perfusion with normal ventilation. About 80% of these studies are negative, and in retrospect were unnecessary. Our goal in this study was to determine if we can accurately predict at least a fraction of the negative studies a-priori, thus reducing the number of unnecessary studies without any negative impact on patient management. The problem is challenging due to the nonspecific symptoms of PE such as dyspnea and fatigue. The approach we pursued was to determine a large number of clinical characteristics from the electronic medical records of patients with SPECT V/Q studies and tried to predict the outcome of the SPECT V/Q study with a Machine Learning (ML) classifier. ML classifiers are algorithms that interpret relationships between input and output values and learn to apply these interpretations to predict outcomes.

Purpose: The purpose of this project is to determine if an ML classifier could be trained, utilizing previous patient characteristics and outcomes, to predict the result of a V/Q scan and thus predict the CTEPH status of a patient.

Method: A retrospective chart review was performed on 130 patients that underwent V/Q scintigraphy from 2010-2021 and resulted in a positive outcome. An equal number of age-matched controls within the same time frame were also reviewed. Relevant clinical characteristics that may have impacted the result of the V/Q scan were identified and assigned numerical values. Our initial approach was to use the classification methods from the Kaggle Competition to predict the survivors of the Titanic. Our problem is analogous, in that there is a miscellany of available data, including many features that are either yes or no. We tested 19 different ML models, primarily by evaluating the area under the curve (AUC) for the receiver operating characteristic (ROC) curves to maximize high-confidence predictions for negative outcomes. The primary measures of excellence were the AUC and the percent true negatives (TN) identified at the 5% false positive (FP) threshold. After examining model output, we opted to manually construct a decision tree to highlight identified clusters of patients with negative outcomes for transparency and ease of use.

Results: Of the 19 different ML algorithms tested, the SVC (Support Vector Classifier) performed the best. It achieved an AUC 0f 0.70 and 35% TNs at the 5% FP threshold. The simplified manual classifier (which uses 9 input parameters) had an AUC of 0.79 and 51% TNs at the 5% FP threshold. The simplified manual method was implemented in an Excel spreadsheet that makes it easy for potential clinical use.

Conclusion: The utilization of ML classifiers in predicting V/Q scan outcomes for PH patients is a promising approach that has the potential to significantly reduce the number of negative V/Q studies for CTEPH. The Excel spreadsheet requires entry of 9 clinical parameters and outputs a probability that the test will be positive or negative. If the probability is less than 5%, it might be appropriate to not do the study since the false positive rate is likely to be higher than the true positive rate. Because this is a preliminary analysis with a limited number of patients, it would be inappropriate to start using it clinically, but it should be tested prospectively and may prove to be a useful clinical tool.

Intravesical Device for Non-Muscle Invasive Bladder Cancer

Presenter: Ikenna Nwosu, MS
Mentor: James Byrne, MD, PhD
Collaborators: Emily Witt, Ashley Rhodes, Aaron Smith
Departments of Radiation Oncology, Urology, and Biomedical Engineering
University of Iowa Carver College of Medicine

Background

Bladder cancer is the sixth most common cancer type in the US, with more than 70% of these cases presenting with non-muscle invasive bladder cancer (NMBIC). NMIBC poses significant risk of recurrence and progression. Intravesical bacillus Calmette-Guerin (BCG) is currently recommended as the standard-of-care adjuvant therapy following complete transurethral resection of bladder tumor. Shortage and suboptimal efficacy of BCG therapy for NMIBC has prompted the investigation into other alternative local therapies, such as the successful gemcitabine and docetaxel (Gem/Doce) drug regimen pioneered at the University of Iowa. Unfortunately, this protocol requires a 2-hour intravesical delivery of gemcitabine and subsequent drainage, followed by an approx. 6-hour intravesical delivery of docetaxel.

Purpose

Our purpose was to overcome the clinical investment of the Gem/Doce therapy by creating an intravesical docetaxel-loaded device administered during the initial gemcitabine rinse. The device was designed to locally deliver docetaxel at therapeutic levels within 2 hours after insertion to replace the current Gem/Doce clinical protocol.

Method

An iterative device design process using the 3D computer-aided design (CAD) software SolidWorks was used to create a 197mm long, 0.75mm thick, 5mm wide tube-like conical-spiral device. The deformable device was 3D-printed using biocompatible Flexible 80A resin. A 2-hour time-delay burst-release of docetaxel was enabled by isomalt end-plugs coated in a dissolvable fluorinated polymer. In addition, intravesical placement of the device was assessed through lubrication and insertion through a 12-French foley catheter.

Findings

Coating the isomalt-coated end-plugs with 3 layers of Fluoropel 20% yielded dissolution times ranging from 100-120 mins. The device design was amenable to insertion through a foley catheter and depositing into the bladder.

Overall Significance

Optimal dissolution kinetics of the fluoropel coating on the plugs ensures delayed release of docetaxel after the 2-hour gemcitabine rinse. Drug quantification using UV-HPLC will be assessed using synthetic urine in a simulated bladder prior to large animal safety and pharmacokinetic studies in sheep. The results of the study will allow for the device to be translated into clinical practice.

Quantifying value loss due to presenteeism and absenteeism in worker's compensation spinal fusion patients

Francis Ogaban, Alex Coffman, Natalie Glass, Venous Roshdibenam, Jill Corlette, Cass Igram, Andrew Pugely, Catherine Olinger

Background:
The upfront costs of surgical spine interventions for lower back and leg pain are comparatively higher than nonsurgical treatments, but the overall improvements in patient reported outcomes may indicate that surgery is ultimately more cost effective. Some recent studies suggest that better outcomes in work productivity following spine surgery eventually offset the higher cost of treatment. To measure work productivity, researchers commonly investigate presenteeism – inhibited at-work performance – and absenteeism – time spent away from work. By analyzing preoperative and postoperative changes in work productivity, studies can determine if surgery is cost effective and give patients more valuable information to make decisions about treatment in the future. Prior studies reviewing outcomes in work performance after spine surgery, however, have largely excluded patients on worker's compensation from the overall cost analysis.

Purpose:
The aim of this study is to quantify the value of absenteeism and presenteeism among patients on worker's compensation receiving lumbar spinal surgery. This study additionally identifies gaps in patient reported outcomes at the Work Injury Recovery Center at the University of Iowa Hospitals and Clinics and assess the need for additional survey questions to quantify absenteeism and presenteeism more accurately.

Method:
We present a retrospective review of work performance from patients on worker's compensation receiving lumbar surgery from 2008 to 2023 at the Work Injury Recovery Center at the University of Iowa Hospitals and Clinics. The preliminary review identifies presenteeism and absenteeism from designated work restrictions recorded in a patient's medical chart.

Results:
A retrospective review of 278 patients was conducted, among whom 92 (33%) underwent spinal surgery of ≤ 3 levels and had an eligible worker's compensation case related to a spine injury. 101 spinal operations were performed for the 92 patients included in the study. 84 (83%) spinal surgery cases were able to return to work, 60 (59%) were able to return to work with no restrictions, 26 (26%) received permanent work restrictions, and 12 (12%) were still undergoing treatment. 86 (85%) experienced some form of presenteeism and 99 (98%) experienced some form of absenteeism. Of the cases that were able to return to work without permanent work restrictions, the mean presenteeism length postoperatively was 287.4 days (median 191 days) and the mean absenteeism length postoperatively was 232.5 days (median 142 days). 72 patients with recorded employment descriptions were identified as having sedentary or non-sedentary labor. After excluding outliers, the average return-to-work length, calculated as the date of a patient's injury to the date they were able to return to work with no restrictions, was 988.62 days for patients classified with sedentary employment types and 952.15 days for patients classified with non-sedentary employment types ($p=0.116$).

Conclusion:
After receiving spinal surgery, our worker's compensation patient population's 83% return-to-work rate taking an average of 232.5 days (median of 142 days) exhibited considerably worse outcomes than a prior study's measurement with a population excluding worker's compensation patients. Presenteeism length within our worker's compensation population contributed more to decreased work productivity postoperatively than absenteeism length. Additionally, our results found no significant difference in return-to-work length between patients with sedentary and non-sedentary employment types from the date of their injury to the date they were able to return to work.

Future studies utilizing a tailored, prospective survey method can bridge the gap in current patient reported outcome measures that prevent us from accurately quantifying presenteeism, absenteeism, and return-to-work rates. These survey questions can include asking patients directly about how many hours they worked, how many hours they are expected to work, and how they would rate their at-work performance between 0-10.

Exploring iron as a biomarker of neurodegeneration in Huntington's Disease: a longitudinal analysis

Lucy Olson, Mohit Neema, Peggy C. Nopoulos

Background:
The current research on Huntington's disease is concentrated on the pathogenesis of the disease and how it influences brain development. A growing body of evidence suggests that loss of the normal HTT protein has effects on brain development well before symptoms emerge in HD subjects. In order to better understand the early pathogenesis of HD, studies are attempting to identify potential new biomarkers of early disease activity. Research has established iron as a biomarker in many neurodegenerative diseases, including Huntington's disease, with studies confirming the presence of iron deposition as early as 20 years to onset (YTO) in individuals with HD. The exact timing and interplay between iron deposition and HD pathogenesis still remains unclear, and it is crucial to identify the earliest timepoint of iron accumulation in HD in order to fully understand the developmental pathogenesis of this disease.

Objective:
This study had three main objectives. Firstly, it aimed to determine if there is a difference in the age trajectories of iron deposition in deep gray matter (DGM) areas between gene expanded (GE) and gene non-expanded (GNE) groups. Secondly, the study aimed to determine if there is YTO-related changes in iron deposition in GE groups. Lastly, the study aimed to determine if there is a dose effect of CAG repeats on iron deposition.

Methods:
We analyzed T2 hypointensity MRIs from participants (n=124) and control subjects (n=162) of ages 6-18. MRI scans were from the KidsHD study that was conducted by the Nopoulos laboratory. 4 mm circular regions of interest (ROIs) were placed on four DGM structures: caudate, putamen, pallidum, and thalamus. Regions of interest were placed bilaterally in the CSF to address intersubject variations in system scaling/gain. The mean signal intensity was measured using the ITK-snap application. Linear and non-linear regression modeling controlling for age and gender was used to compare iron deposition between the GE and GNE groups, YTO trajectories. The effect of CAG repeats was also evaluated. RStudio was used for statistical analysis.

Results:
The GE vs GNE group analysis revealed no significant interactions for any of the DGM structures. There was a trend for each structure, such that at the youngest ages, the GE group had the lowest t2 intensity (highest iron deposition) compared to the GNE group. In contrast, at the oldest ages, the GE group had the highest T2 intensity (lowest iron deposition) compared to the GNE group. The GE vs GNE non-linear age analysis revealed similarities with the linear models. The effect of gender did not have significant findings, and there were no significant findings between YTO groups and T2 intensity in the GE group. Additionally, there were no significant findings between CAG repeat and T2 intensity in the GE group.

Conclusion:
Based on this initial analysis, we cannot conclude that there is an increase in iron in far from onset HD patients compared to controls. The initial increase in iron accumulation during early stages within the GE group, as opposed to the GNE group, could be associated with hypertrophy of the caudate and pallidum or changes in cell type (iron rich ologo). The following decrease could be a result of volume loss in these structures. Notably, research from our lab has indicated that in individuals with HD, there is an initial hypertrophy in DGM structures compared to GNE subjects, followed by a subsequent decrease in volume as disease onset approaches. In summary, these findings do not support the initial hypothesis suggesting a gradual rise in iron deposition among HD patients as the onset of disease approaches. Currently, we are engaged in investigating iron-related changes using advanced statistical modeling and these results will be presented during the summer conference.

Prevalence of the Post-Acute Sequelae of COVID-19 Among Frontline Workers in the Midwestern United States and Co-Prevalence of Associated Social and Structural Determinants of Health

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Introduction: Post-acute sequelae of SARS-CoV-2 infection (PASC), colloquially known as long COVID, causes persistent symptoms in up to 80% of individuals who have recovered from an initial COVID-19 episode. PASC includes many symptoms, such as shortness of breath, pain, headaches, cognitive difficulties, fatigue, and mental health effects, which may last for months or years. Despite widespread recognition of the disparate impacts of COVID-19 itself on frontline workers during the earliest phases of the pandemic, including severe SARS-CoV-2 infections in the pre-COVID-19-vaccine era, little is known about the experiences of frontline workers with PASC or about the social and structural factors that contribute to the development, persistence, or impact of long COVID in this group.
Purpose: This study aims to investigate the relationship between PASC and social and structural factors, including demographics (e.g., race/ethnicity, age range, urbanicity, and proximity to care), clinical factors (e.g., COVID-19 severity and vaccine status), and social factors (e.g., healthcare discrimination and trust).
Methods: Using data from a community-engaged, cross-sectional survey of frontline workers (total n=889), the association of social and structural factors with persistent symptoms after COVID-19 was assessed among 447 (50.2%) respondents with a self-reported history of COVID-19 at the time of the survey in May-July 2022. A directed acyclic graph was created to outline the hypothesized relationships of social and structural variables with PASC. To determine the association between PASC in frontline workers and these social and structural factors, multivariable and hierarchical logistic regression analysis was conducted using the SAS statistical software package. In this analysis, the dependent variable was a binary indicator (Yes/No) for whether the study participant experienced persistent symptoms after COVID-19 (PASC); and the independent variable was any of the social or structural variables measured by the survey, including race/ethnicity, age range, urbanicity, proximity to care, COVID-19 severity, vaccine status, healthcare discrimination, and provider trust.
Results: Most frontline workers (n=408, 91.3%) reported persistent symptoms after the initial COVID-19 episode. In unadjusted analyses, severe COVID-19, minoritized race/ethnicity, longer distance from healthcare, urban residential location, age < 50, prior experience with healthcare discrimination, and lack of access to a trusted healthcare provider were all associated with PASC. After adjustment for covariates, PASC remained independently associated with COVID-19 severity (adjusted odds ratio, OR: 7.06; 95% confidence interval, CI: 1.53, 32.61); prior experience with healthcare discrimination (OR: 9.76; 95% CI 2.20, 43.34); and lack of access to a trusted healthcare provider (7.06, 95% CI: 1.46, 34.16). In multivariable and hierarchical logistic regression models, prior experience with healthcare discrimination and lack of access to a trusted healthcare provider were consistently and independently associated with PASC at a magnitude at or above the magnitude of association between PASC and COVID-19 severity.
Conclusion and Significance: This study illustrates that the initial severity of COVID-19 symptoms, prior experience of healthcare discrimination, and lack of access to a trusted healthcare provider are strongly associated with the prevalence of PASC among frontline workers in the Midwestern United States. Furthermore, these factors statistically attenuated—and, thus, may partially explain—the disparately high prevalence of PASC among minoritized populations, persons with geographic barriers to care, and age in the study. These results reinforce the importance of addressing social and structural factors in response to the pandemics of both COVID-19 and PASC, by demonstrating that social and structural factors can have a sizable impact on clinical outcomes and that the magnitude of this impact may be at or above the magnitude associated with other clinical factors. These findings should immediately inform responses to PASC in healthcare settings and public health initiatives to effectively address the social and structural determinants of health in collaboration with patients and communities.

Implementation of a Mediterranean Diet Exacerbates Visual and Motor-Sensory Impairment in an Animal Model of Multiple Sclerosis

Julian B. Pablo, Jeffrey J. Anders, Benjamin W. Elwood, Randy H. Kardon, Oliver W. Gramlich

Introduction: Multiple Sclerosis (MS) is a chronic neurodegenerative autoimmune disease that leads to demyelination of the central nervous system (CNS). This can lead to increasing paralysis and visual dysfunction. Around 2.5 million people worldwide currently live with MS. Approximately 20-45% patients experience optic neuritis (ON) as the initial presenting symptom. Various studies report ameliorative effects when implementing a Mediterranean diet in regard to motor-sensory and visual symptoms of MS-ON patients. Therefore, the aim of this study was to determine the neuroprotective effects of the Mediterranean diet (MD) on an experimental autoimmune encephalomyelitis (EAE) mouse model of MS-ON.

Methods: EAE was induced in 80 female C57BL/6J by immunization with MOG_{33-55}. Complete Freund's Adjuvant, and pertussis toxin. Cohorts of EAE mice (n=20/group) were assigned to stay on standard rodent chow (EAE group), or to start the Mediterranean diet either 2 weeks prior EAE induction (pre[conditioning] MD group), at the time of EAE induction (pro[phylactic] MD group), or at the onset of initial presentation of symptoms (late MD group). A separate naïve group was made up of 20 unaffected mice. Mice were scored everyday based on motor-sensory symptoms from 0 (normal) to 5 (death) during the totality of the 6-week study. Visual acuity was tested via their optokinetic responses on a weekly basis. Retinal ganglion cell (RGC) complex layer thickness was measured at baseline, day 21, and day 42 using optical coherence tomography (OCT). Retinas, optic nerves, brain, and spinal cord were all harvested for analysis. Data was analyzed using one- and two- way ANOVA followed by post hoc tests.

Results: Preconditioned and Prophylactic animals showed significantly worse EAE scores when compared to untreated EAE animals (Area under curve EAE score: EAE: 53.31.5x, EAE + pre MD: 64.8±2.5, p=0.0013; EAE + pro MD: 71±2, p<0.0001; EAE + late MD: 57.6±2.5). Animals from the prophylactic group also had lower visual acuity when compared to untreated EAE animals (EAE: 0.267±0.1 cycles/degree vs. EAE + pro MD: 0.166±0.13 cycles/degree, p=0.01). The preconditioned group (0.213±0.12 cycles/degree) and late group (0.244±0.13 cycles/degree) both showed no significant difference in visual acuity scores compared to the EAE group. A significant decrease in RGC complex layer thickness was observed in all EAE groups compared to naïve controls (67.7±2.3 µm, p<0.001), but also between the prophylactic group and the EAE group (EAE: 64.7±3.2 µm vs. EAE pro MD: 62.6±3.8 µm, p=0.029).

Conclusion: This study found that the implementation of a Mediterranean diet worsened motor-sensory impairment and exacerbated the visual system's decline in structure and function in all EAE -ON animals. Moreover, EAE mice in the prophylactic MD group experienced significantly worse outcomes in visual acuity and RGC complex thickness as measured by OCT. Subsequent histopathologic examinations will provide a more in-depth insight in the pathobiology of ON which are likely to confirm the ophthalmic outcome measurements. However, the results indicate that the Mediterranean diet may have a negative effect on MS patients and further studies are needed to determine the optimal diet for neuroprotection and rehabilitation of the CNS after demyelination.

The Validation of an Endurance Static Hold in Assessing Functional Status

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Other Collaborators: Caleb McCabe, BS, Dr. Michael Marinier, MD, Victoria Tappa, MS

Introduction: Sarcopenia is a disease of muscle failure fixed in muscle mass or function decrement that builds up over time. Sarcopenia has been associated with an increased risk of complications following a total joint arthroplasty. Commonly, maximal hand grip strength (HGS) can be used to diagnose sarcopenia and assess muscle function. While HGS is a well-accepted measure of overall physical fitness, it only tests a limited set of muscle groups and does not test muscle endurance. An endurance static hold (ESH) combines the principle of a traditional HGS assessment while looking at more generalized muscle function and testing muscle endurance at the same time. Overall, this study seeks to validate ESH in assessing muscle function by comparing it against other accepted measures of muscle function, namely, maximal HGS, timed up and go (TUGT), and body composition including skeletal muscle mass (SMM) and appendicular skeletal muscle index (SMI).

Hypothesis: ESH is a measure of muscle function.

Methods: This prospective cohort study included two cohorts: study patients with history of knee or hip osteoarthritis and control without. All subjects underwent the same study protocol, and consent was obtained from each participant before the study procedure began. Study procedures included bioimpedance analysis (BIA; InBody 770 or 970) to evaluate body composition variables like body fat mass (BMI), SMM, and SMI, TUGT, bilateral maximal HGS, ESH, and filling out patient reported outcomes (PROs). Participants underwent two ESH trials: the mass held during trial 1 was equal to half of each participant's mean HGS, and trial 2 mass was 10^{th} percentile HGS by age and sex. The PROs included KOOS JR, HOOS JR, SF-36, PROMIS Physical Health, PROMIS Global Health, and the Baecke Questionnaire. Comparisons between and among the cohorts were done through t tests, Mann-Whitney U tests, and correlation analyses. Correlation analyses were also used to analyze all participants. Significance was set at alpha equal to 0.05 and normality was determined through Kolmogorov-Smirnov and Shapiro-Wilk tests. This study was approved by the institutional review board prior to study initiation.

Results: 50 patients and 50 controls were enrolled in this study. The average age of the study group was 64 ± 12 years and the average age of the control group was 33 ± 16 years. 42% of the study group was male and 54% of the control group was male. Within the study group, 44% of patients had a BMI over 40 kg/m^2, classified as severely obese. The study group had more medical comorbidities than the control group. For instance, 50% of the study group had hypertension, compared to 2% of the control group. In general, the study group had weaker HGS, longer TUGT, larger SMI, and lower PRO results than the control group. Interestingly, the two cohorts did not significantly differ in terms of SMM (95% CI [-2.9, 3.2]; $p = 0.93$). However, SMM significantly differed in the intra-cohort comparison of patients with a BMI over 40 kg/m^2 versus patients with a BMI under 40 kg/m^2, with severely obese patients having a larger SMM (95% CI [-9.9, -1.62]; $p = 0.0073$).

In all participants, SMM correlated significantly with HGS ($r = 0.68$, $p < 0.0001$) and ESH, specifically the 10^{th} percentile HGS by age and sex trial ($r = 0.28$, $p = 0.0051$). Similar results occurred in both the study group (SMM versus HGS: $r = 0.70$, $p < 0.0001$; SMM vs ESH: $r = 0.30$, $p = 0.0363$) and the severely obese subset of the study group (SMM versus HGS: $r = 0.60$, $p = 0.0034$; SMM vs ESH: $r = 0.47$, $p = 0.0282$).

Conclusion: Given that SMM correlates with ESH positively and significantly, ESH is a measure of muscle function. Moreover, given that SMM correlates with ESH positively and significantly in both the study group and the severely obese subset of the study group, ESH is a measure of muscle function in an osteoarthritic population and in osteoarthritic individuals with severe obesity. Furthermore, a sizeable amount of SMM was present in both the study group and the severely obese subset of the study group. Thus, ESH could be used as both a diagnostic tool and an exercise tool in helping patients know if they are gaining muscle mass, especially when analysis of SMM through BIA is unavailable. The limitations of this study include the control population not matching the osteoarthritic population in terms of age, the handle for the ESHs not being conducive to all hand sizes, and the ESH trials did not involve all participants lifting what could be their maximum weights. In light of these limitations, refining the ESH setup by having participants lift a heavier or standard weight or by creating deadlift handles specific to various hand sizes could help produce a stronger correlation between SMM and ESH.

Identifying patient perspectives on a low-threshold medications for addiction treatment (MAT) clinic

Linda Peng BA, Nicholas Bormann MD, Andrea Weber, MD

Introduction: Patients with substance use disorders (SUD) report many difficulties in accessing care, indicating a clear need for low-threshold treatment models. On December 8, 2021, the University of Iowa Hospitals and Clinics (UIHC) opened the Medications for Addiction Treatment (MAT) Walk-In Clinic, which operates on Wednesday afternoons at a community clinic site off Scott Boulevard in Iowa City. To our knowledge, this is the first low-barrier office-based clinic providing same day MAT in Iowa.

Purpose: This quality improvement study aimed to attain the critical patient perspective on successes and suggestions for the walk-in MAT clinic and characterize treatment outcomes. We focused on patients who presented with opioid use disorder (OUD) and received same-day buprenorphine prescriptions.

Hypothesis: By presenting to the UIHC MAT walk-in clinic, patients start evidence-based medications for OUD (MOUD) earlier compared to usual care, experience positive interpersonal interactions with clinic staff, and access a wide range of resources that lead to higher treatment retention.

Methods: Patients (N=12) with OUD who presented to the walk-in MAT clinic in its first year of operation participated in semi-structured interviews in which they described their clinic experiences. Among the interviewees, seven patients attended their one-week follow-up appointment, while five patients did not. Initial coding of interview transcripts was completed by two blinded reviewers using Dedoose. A shared codebook was developed using a mixed inductive-deductive approach. Codes were organized into four broad categories: barriers, facilitators, perspectives/experiences, and unmet wants/needs. These shared codes were then applied to all interviews by both reviewers a second time for reliability.

Findings and Results:

Facilitators: Participants reported referrals from harm reduction organizations, receiving other medical care at UIHC, and the walk-in nature of the clinic as facilitators of attending their first appointment.
Barriers: The most common barriers included distance to the clinic and lack of transportation, as the minority of participants lived in or near Iowa City. Patients remarked that the clinic's hours were limited.
Perspectives/Experiences: All patients interviewed endorsed having positive experiences at the MAT walk-in clinic. Participants reported feeling heard, comfortable, and accepted by staff. Ten out of twelve participants mentioned that their MAT clinic experience differed from past experiences of SUD treatment; these excerpts centered around positive interactions with the medical team, and the ease of obtaining a buprenorphine prescription and scheduling continued care. Patients noted that case managers were very responsive, and facilitated access to resources. Interviewees noted it was beneficial to have peer recovery specialists at the clinic, who had shared experiences and could be contacted in the initial steps of their recovery. Four patients remarked that they or a family member who had also visited the clinic utilized resources provided by the Bridge Program (a grant-funded UI ARC recovery support services project), and spoke positively about this program's impact.
Unmet wants/needs: Half of the participants stated that the clinic met all their needs at their first appointment. Unmet needs included outpatient therapy, access to methadone, and desiring increased contact with providers.

Conclusion and Overall Significance: Our data reaffirm the positive impact of low-barrier, walk-in models of SUD treatment, as well as the importance of MOUD accessibility. Although five of the participants did not follow up within one week of their walk-in appointment, eleven out of twelve participants reported eventually continuing care and currently following with UIHC ARC. The large majority of participants remarked on the unique structure of the MAT walk-in clinic and spoke to the difficulty of finding similar low-barrier MAT clinics in their hometown or the state of Iowa at large. This feedback indicates the need for more low-threshold clinic models to increase access but also address ongoing patient barriers, such as lack of transportation, limited clinic hours, and challenges with accessing prescriptions at local pharmacies. Overall, patients reported high satisfaction with receiving prescriptions and interactions with staff, and identified the need for expanded hours, social services, and proactive referrals to outpatient therapy.

Incidence and Risk Factors for Bilateral Patellofemoral Instability

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Background: Patellofemoral joint instability is common in young athletes and often requires surgical intervention. Incidence and risk factors for ipsilateral instability recurrence have been more discussed in the literature than contralateral instability events.

Purpose: To evaluate the incidence and risk factors for contralateral patellofemoral instability in patients who have undergone patellar stabilization surgery.

Methods: This retrospective study included 543 patients who had undergone medial patellofemoral ligament reconstruction and/or Fulkerson osteotomy as surgical management for lateral patellofemoral instability. The medical records of these patients were examined to evaluate the non-surgical knee. Available imaging of each affected knee was examined to evaluate for patella alta, skeletal maturity, trochlear dysplasia, tibial tubercle to trochlear groove (TT-TG) distance, and tibial tubercle to posterior collateral ligament (TT-PCL) distance. Demographic factors such as BMI, age, and sex were also examined. A second study was done excluding patients with previous history of bilateral instability, assessing risk factors using the same methods. This yielded information about incidence and risk factors of "new onset" contralateral instability post-surgery.

Results: Of the 543 patients examined, 205 (37.8%) had evidence of contralateral instability in the medical record. Patella alta (OR, 2.4), skeletal immaturity (OR, 2.67), and lower age ($p<0.0001$) were associated with increased risk of bilateral instability in this cohort. Sex, BMI, TT-TG distance, and TT-PCL distance, and trochlear dysplasia were not shown to be associated with increased risk of bilateral instability. In the second study, 63 out of 401 (15.71%) of patients had evidence of new onset contralateral instability post-surgery. Skeletal immaturity (OR, 6.64) was found to be associated with increased risk of instability.

Conclusion: Incidence of contralateral (bilateral) patellofemoral instability was found to be 37.8% in the present series. Lower age, skeletal immaturity, and patella alta were found to be associated with increased risk of bilateral instability. Incidence of new onset contralateral instability was found to be 15.71% and was associated with skeletal immaturity.

Knowledge, attitudes, and practices regarding malaria in women of the Orang Rimba

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Abstract

Despite the success of insecticide treated nets (ITNs) and indoor residual spraying (IRS), malaria remains a global concern due to insecticide resistance and changes in vector behavior, highlighting the need for novel tools. Efficacy trials of a novel spatial repellent (SR) are ongoing, but knowledge, attitudes, and practices (KAP) are critical to community uptake and acceptance of such interventions. This sub-study to the efficacy trial explored malaria KAP among women of the Orang Rimba, an ethnic minority group who live throughout the lowland forests of southeast Sumatra. Little health information on this population is available, though they may be especially vulnerable to malaria because of living in outdoor housing structures in the forest. We conducted a cross-sectional KAP survey with 39 people from February to April 2021. Perception of malaria risk and prevention practices were analyzed using logistical regression to test for differences based on age, education, malaria knowledge, parity status, medical care during recent pregnancy and having a child under 5-years-old. Most women saw malaria as a serious health risk for the general population (63.9%), pregnant women (61.1%), and children under 5-years old (75%), but prior night use of ITNs was moderate (47.2%). About one quarter of women sought medical care during their most recent pregnancy (27.8%); and reported use of an ITN during pregnancy was moderate (44.4%). A positive link was found between malaria knowledge level and perception of malaria as a serious health risk. The health belief model posits that perception of a disease as severe increases preventive behaviors; research has shown a positive relationship between perceived severity and use of malaria prevention tools. One approach to increasing current preventive health behaviors, such as the adoption of a novel SR by Orang Rimba women, should include enhanced education on the risks of malaria. Theoretically informed research should advise the implementation of future interventions for increasing malaria prevention behaviors among this vulnerable group.

Exploring Early Life Experiences as Predictors of Addiction in Mothers

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Mentor: Lane Strathearn, MBBS, PhD, FRACP

Background: Maternal addiction presents a critical concern, with far-reaching implications for both maternal health and the well-being of the child. In addition to the adverse impacts on the developing fetus, maternal addiction in early childhood carries lasting psychological, social, and emotional consequences. As such, understanding the forces behind addiction is crucial for addressing its effects. This involves looking beyond current life circumstances and considering early childhood experiences. By studying how these relate to addiction risk, we can uncover insights that may guide interventions and preventative strategies, enhancing our understanding of the factors driving addiction.

Purpose: To examine the relationship between early childhood experiences and maternal addiction. Specifically, we hypothesize that higher self-rated levels of parental care and autonomy/lower levels of indifference and overprotection will be associated with addiction. Additionally, we hypothesize that higher levels of childhood abuse and neglect (emotional, physical, and sexual) will be associated with addiction.

Methods: This study conducted an analysis on a pre-existing dataset comprising 59 mothers with infants under one year of age, as a subset of a broader investigation into the impact of intranasal oxytocin on brain responses in addicted mothers compared to controls. Approximately half of the participants were categorized into an addiction group, while the remaining participants formed the control group. This classification was determined through assessments utilizing the Addiction Severity Index (ASI) and the Mini-International Neuropsychiatric Interview (MINI), encompassing a range of substances including alcohol, tobacco/nicotine, cannabis, cocaine, opioids, amphetamines, sedatives, hallucinogens, inhalants, and others. Participants completed several assessments, including the Parental Bonding Instrument (PBI) and the Childhood Trauma Questionnaire (CTQ) to assess early life experiences, as well as the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI) to gauge psychological well-being. Additionally, participants provided responses to various demographic inquiries. Statistical analysis through SPSS involved the utilization of binary logistic regressions to explore the associations between maternal addiction and a range of childhood factors, considering maternal anxiety and depression as potential mediators. Odds ratios, confidence intervals, and significance levels were calculated to quantify the relationships between the variables.

Results: Of the childhood factors analyzed, those significantly associated with addiction included maternal level of care (OR: [0.874]; 95% CI: [0.809-0.943]), paternal level of care, (OR: [0.93]; 95% CI: [0.873-0.991]), paternal level of overprotection (OR: [1.178]; 95% CI: [1.056-1.313]), maternal level of indifference (OR: [1.293]; 95% CI: [1.12-1.492]), paternal level of autonomy (OR: [0.794]; 95% CI: [0.672-0.939]), emotional abuse (OR: [1.245]; 95% CI: [1.079-1.436]), emotional neglect (OR: [1.403]; 95% CI: [1.133-1.736]), and physical neglect (OR: [1.28]; 95% CI: [1.047-1.564]). While both maternal anxiety and depression were independently associated with addiction (anxiety: [1.13]; 95% CI: [1.017-1.256]; depression: [1.134]; 95% CI: [1.028-1.252]), the inclusion of early childhood factors in regression analyses revealed a mediating effect. Maternal anxiety was no longer significantly associated with addiction when adjusting for maternal level of care (OR: [1.073]; 95% CI: [0.96-1.199]), maternal level of indifference (OR: [1.075]; 95% CI: [0.963-1.20]), and emotional neglect (OR: [1.053]; 95% CI: [0.936-1.186]). Maternal depression was no longer significantly associated with addiction when adjusting for maternal level of care (OR: [1.049]; 95% CI: [0.939-1.171]), maternal level of indifference (OR: [1.056]; 95% CI: [0.946-1.18]), emotional neglect (OR: [1.008]; 95% CI: [0.887-1.146]), and emotional abuse (OR: [1.005]; 95% CI: [0.888-1.137]).

Conclusion: Our findings support our hypothesis that higher levels of self-rated parental care and autonomy were significantly associated with reduced odds of addiction. Similarly, lower levels of parental indifference and overprotection were found to be significantly correlated with decreased addiction risk. Through our analysis however, we discovered that while this was true both maternally and paternally for levels of care, this was only true maternally for levels of indifference and paternally for levels of autonomy/overprotection. Examining the role of childhood abuse and neglect, our analysis demonstrated a noteworthy association between psychological maltreatment (emotional abuse and neglect) and addiction risk. Specifically, emotional abuse and emotional neglect exhibited significant correlations with maternal addiction. In contrast, physical abuse and sexual abuse did not show significant associations with addiction. With these key findings, we reveal the distinct impact of psychological maltreatment on addiction risk. Our analysis between early childhood factors, anxiety/depression, and addiction revealed that there appears to be a partial mediation. One additional key finding was that only the association of maternal factors (level of care/indifference) with addiction was significantly mediated through anxiety and depression. Our study underscores how traditional maternal and paternal roles uniquely impact addiction risk in mothers. These insights highlight the importance of understanding familial dynamics in promoting infant-well-being.

Association of preoperative ACL integrity and patient-reported outcome measures after total knee arthroplasty: Initial impressions after 3 months

In association with Carver College of Medicine Summer Research Fellowship.

Student: Wade Pingel
Mentor: Andrew Schwartz

Background: With the perpetual rise in demand for TKA across the globe, the literature suggests that 19% of patients are dissatisfied with their surgical outcome based on patient reported outcome measures (PROMs). Identifying commonalities in the satisfied and dissatisfied cohorts may help providers prognosticate success after treatment, as well as help appropriately manage expectations for these patients' recovery. To date, there are no studies investigating the association of ACL integrity and post operative patient reported outcome measures after TKA.

Purpose: A case series presentation to highlight initial impressions of ongoing research studying the association of preoperative ACL integrity with patient-reported outcome measure after total knee arthroplasty.

Study Design: Prospective Cohort Study; Level of evidence, 3

Methods: Pre-operative, and 4 week post-operative PROMs were collected for three patients (n=3) undergoing TKA for primary osteoarthritis. PROM scores include were as follows: Knee Injury and Osteoarthritis Score (KOOS Jr), Patient-Reported Outcomes Measurement Information System (PROMIS), The Single Assessment Numeric Evaluation (SANE) score, and Minimal Clinically Important Difference/Substantial Clinical Benefit (MCID/SCB). Patient ACL integrity status was identified in-situ during elective TKA operations. Statistical analysis was performed to test for associations between ACL degenerations status and patient-reported outcome measures using logistic regression to determine significance as well as a chi- squared test for a possible relationship between the categorical variables. Statistical Package for the Social Sciences (SPSS) as well as RStudio 3.3.0+ will be used for statistical analysis.

Results: A total of three patients ACL's were observed (n=3), one presenting as healthy, and two presenting as diminutive. At 4 weeks follow up, diminutive ACL patients average PROMs were as follows: PROMIS Mental Health T-score 49.55 (20-70), Physical Health T-score 50.8 (15-70), PROMIS General Health Score 3.5 (1-5), PROMIS Social Activity and Roles Score 3.5 (1-5), KOOS Jr. 68.28 (0-100), SANE 59 (0-100), MCID 4 (1-5). At 4 week follow up, the one patient with observed healthy ACL status reported PROMs were as follows: PROMIS Mental Health T-score 62.5 (20-70), Physical Health T-score 61.9 (15-70), PROMIS General Health Score 4 (1-5), PROMIS Social Activity and Roles Score 5 (1-5), KOOS Jr. 79.91 (0-100), SANE 71 (0-100), MCID 4 (1-5).

Conclusion and Discussion: To our knowledge, the current study is the first to analyze the possible relationship between pre-operative ACL status and PROMS in primary total knee arthroplasty. After the first 3 months, no conclusions can be made from the initial data. This project is currently ongoing and an update will be provided when a sufficient patient population is achieved.

Title:
Maternal Hypertension Reveals Potential Neuroinflammatory Mechanisms of Epilepsy

Authors:
Faith Prochaska
Baojian Xue, PhD
Alexander Bassuk, MD, PhD

Abstract:
Pre-eclampsia and gestational hypertension are common conditions wherein blood pressure is elevated during pregnancy and can result in lifelong implications for maternal and infant health. The mechanisms driving these increased risks are largely unknown. Epilepsy is a chronic neurological disorder characterized by recurrent seizures, and the mechanisms underlying its development are not understood. Human cohort studies have shown that pre-eclampsia leads to an increased risk for epilepsy in children, and as the severity of pre-eclampsia increases so does the risk of epilepsy. This suggests that an adverse prenatal environment is a pivotal factor resulting in neurodevelopmental disorder and increased risk for epilepsy. Previous studies in mice have uncovered differential gene expression and neurodevelopment utilizing an arginine vasopressin model of pre-eclampsia. However, there have been no animal studies on effects of pre-eclampsia/maternal hypertension on induction of epilepsy in offspring or the related CNS mechanisms. To address this gap in knowledge, mice dams were implanted with osmotic minipumps for infusions of saline or ANG II (1500 ng/kg/min) 3 days before mating and continuing through the duration of pregnancy. Individual subjects were randomly selected from different litters to comprise each experimental group. Quantitative PCR was performed on hippocampal tissue, looking at markers of inflammation, blood-brain barrier damage, and components of the renin-angiotensin-aldosterone system. Our results help identify central mechanisms underlying increased risks for seizures, and will inform further behavioral characterization, testing sensitivity and severity of chemically and electrically induced seizures, and exploration of treatment effects of anti-hypertensive and anti-epileptic drugs.

The Value of Inpatient Dermatology Consultations: Improving Patient Outcomes Through Expert Management

Sydney Rand, BSBA and Vincent Liu, MD, FAAD

Introduction: The dermatology consultation service is a valuable tool for optimizing inpatient diagnosis and management of a broad scope of dermatologic conditions including a spectrum of potentially acute and often critical diagnoses. Such consultations ideally provide accurate and prompt diagnoses of cutaneous diseases which then can be most effectively treated. While there is support for the effectiveness of the service at diagnostics, there is little data to reflect the efficacy of post-consultation management and outcomes leading to service underutilization and limitations of comprehensive treatment necessary for patient improvement.

Purpose: Our study aimed to identify confirmations or changes of initial diagnosis made by the primary team, confirmations or changes to management initiated by the primary team, and improvement in dermatologic conditions following dermatologic consultation. Additionally, we aimed to assess how identity of the requesting service, nature of the dermatologic condition, medication complexity of the patient, length of time between admission to consultation, age at admission, and sex of the patient influenced our primary study outcomes. Going forward, evidence-based knowledge on this topic can minimize delayed treatment, improve patient's dermatologic condition earlier in hospital stay, and improve inpatient care teams' efficacy of diagnosing and managing common dermatologic conditions.

Methods: Patient data was manually collected from the electronic medical records of patients seen in 2019 and 2021 by the Department of Dermatology at University of Iowa Hospitals and Clinics. Chi-square or Fisher's exact tests, where applicable, were used to estimate differences in categorical patient characteristics and ANOVA was used to estimate differences in continuous patient characteristics between patients with and without a pre-consult diagnosis. Logistic regression was used to estimate the effect of demographic and clinical characteristics on the odds of a change in diagnosis, change in management, and improvement of dermatological condition post-consult. All statistical testing was two-sided and assessed for significance at the 5% level using SAS v9.4 (SAS Institute, Cary, NC). The reference group for requesting medical services is the internal medicine service as it is the mainstay of inpatient care and has broad diversity between patient demographics and medical care received.

Results: Requesting service ($p=0.02$) and reason for hospitalization ($p<0.01$) were found to be significantly associated with the odds of a change in a pre-consult diagnosis when controlling for sex, age at admission, number of comorbidities, and time from admittance to consult. Psych consults were associated with 69% decreased odds of a diagnosis change when compared to Internal Medicine consults. Dermatology-related hospitalizations were associated with 72% decreased odds of a diagnosis change when compared to non-dermatology-related hospitalizations. Requesting service ($p<0.01$), reason for hospitalization ($p<0.01$), and age at admission ($p=0.04$) were found to be significantly associated with the odds of a change in pre-consult treatment when controlling for change in diagnosis, sex, number of comorbidities, and time from admittance to consult. Dermatology-related hospitalizations were associated with 88% increased odds of a treatment change when compared to non-dermatology-related hospitalizations. A 10-year increase in age at admission was associated with 11% decreased odds of a treatment change when average age at admission was 44.8 years old. Change in pre-consult treatment ($p<0.01$) and requesting service ($p<0.01$) were found to be significantly associated with the odds of improvement when controlling for change in diagnosis, sex, reason for hospitalization, age at admission, number of comorbidities, and time from admittance to consult. A change in management was associated with 72% increased odds of improvement. ED consults were associated with 92% decreased odds of improvement when compared to Internal Medicine consults.

Discussion and Conclusions: Our data supports that a change in management is a stronger predictor of patient improvement than a change in diagnosis. Minute differences in underlying pathophysiology contributed to high rates of change in management progressing towards comprehensive treatment. Findings also highlight unique subsets of patients that stand to gain significantly improved outcomes including those admitted for dermatologic-related conditions and those of specific services including, but not limited to, psychiatry and emergency medicine. Thus, the change in management and improvement of dermatologic condition that subsequently followed is a testament of the knowledge, experience, and value held by the dermatology consultation service.

The Accuracy of Self-Reported Height in Orthopaedic Clinics

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INTRODUCTION: Body mass index (BMI) plays a vital role in a myriad of healthcare processes including surgical planning, health risk assessment, and pharmacologic dosing. BMI is calculated by weight (in kilograms) divided by the square of height (in meters). In orthopedics and namely arthroplasty, BMI has traditionally been implemented as a surgical guide, where patients with class III obesity (BMI >40kg/m^2) are refused surgery. Studies have questioned the validity and accuracy of patients' heights – specifically when self-reported height measurements are utilized. This study aimed to identify the accuracy of self-reported height measurements in multiple orthopaedic clinics.

METHODS: This study was approved by the institutional review board. This study recruited patients to self-report their height prior to height measurement at their regularly scheduled arthroplasty, spine, hand, and sports medicine clinic visits. Height measurements were completed using a calibrated, wall-mounted stadiometer. Differences among height measurements, BMI calculations, descriptive statistics, ANOVA were calculated.

RESULTS SECTION: Data included 600 total patients: 200 arthroplasty patients (mean age: 63.39 ± 11.63 yrs), 100 hand patients (mean age: 46.98 ± 14.68 yrs), 200 spine patients (mean age: 58.55 ± 16.98), and 100 sports patients (31.92 ± 13.06 yrs). Arthroplasty clinic patients (2.56 ± 2.64 cm) overestimated their heights more than spine (2.12 ± 2.67 cm), hand (2.18 ± 2.31 cm) and sports medicine (0.74 ± 1.96 cm) patients. Arthoplasty height overestimation was not significant versus spine ($p = 0.0965$) or hand ($p = 0.2038$) but was significant versus sports medicine ($p < 0.0001$). There was no significant difference between spine and hand clinics ($p = 0.8302$). Spine height overestimation was significant versus sports medicine ($p < 0.0001$) and so was the hand clinic ($p < 0.0001$). Across all clinics, patients overestimated their heights by 2.04 ± 2.57 cm, on average. Age correlated significantly with increasing height overestimation significantly ($r = 0.2812$, $p < 0.0001$). Across all clinics, males (2.54 ± 2.50 cm) significantly overestimated their heights more egregiously compared to females (1.56 ± 2.55 cm) ($p < 0.0001$). Arthroplasty had the largest average change in BMI (-1.08 ± 1.30 kg/m^2) due to height overestimation and was significantly greater than spine ($p = 0.006$), hand ($p = 0.0112$) and sports medicine ($p < 0.0001$) There was no difference between spine and hand patients ($p = 0.9279$). Spine patients had greater BMI change than sports medicine patients ($p < 0.0001$). Likewise, hand clinic patients had greater BMI change than sports medicine patients ($p < 0.0001$). In all clinics, using corrected BMI, 13 (2.17 %) patients crossed 40 kg/m^2, 10 (1.67 %) crossed 45 kg/m^2, and 8 (1.33 %) crossed 50 kg/m^2.

DISCUSSION: This study demonstrates that patients, on average, overestimated their height by 2.04 cm (0.803 in). Additionally, patients reporting to arthroplasty, spine, and hand clinic had the most egregious overestimations of their height This may be due to each clinics' patient demographics, namely age; with senior patients more commonly suffering from arthritic changes they likely experience gradual height loss. Therefore, this study confirms prior reports regarding height loss in the orthopaedic spine population and highlights that similar precautions regarding self-reported heights need to be taken in all orthopaedic clinics as well. In this study there were patients who crossed BMI thresholds when accurate heights were obtained. To make sure obesity is correctly captured as a comorbidity and post-operative complications are accurately assessed, uniform measured heights are important. Additionally, surgeons who operate on a patient with a BMI ≥ 40kg/m^2 are generally entitled to more compensation via modifier-22 for a complex procedure requiring significantly more effort. With an incorrect BMI calculation surgeons may be missing out on compensation for a procedure that takes more time and effort due to a patient's morbid obesity, but it is not being accounted for due to inaccurate patient reported heights. With height contributing to BMI calculations, and prior literature describing reliance on the likely widespread self-reporting of heights at large institutions, this current study highlights the need for uniform, accurate height measurements to avoid clinical, surgical, pharmacologic, and billing errors.

SIGNIFICANCE/CLINICAL RELEVANCE: Overall, this study demonstrated that patients frequently over-report their height in multiple orthopaedic practices, which, in turn, affects their BMI calculation and contributes to downstream medical and financial consequences.

Investigating Embedded Microspheres for Sustained Release of Neurotrophic Factors in Cochlear Implants

Madeline Rhomberg: Mentored by Marlan Hansen, Collaborating with Allan Guymon and Aliasger Salem

Background: The physiologic ability to hear relies upon differentiation of varying sound frequencies. This process is encoded within the cochlea and depends upon the intricate tonotopic organization of spiral ganglion neurons (SGNs) and their respective hair cells. When there is a breakdown in this system, such as with sensorineural hearing loss, cochlear implants can restore hearing by directly stimulating SGNs. Furthermore, the act of cochlear implantation leads to an inflammatory foreign body response that is toxic to SGNs. An objective of our research is to promote the survival of SGNs following cochlear implantation by providing long-term neurotrophic support. There are multiple strategies for intracochlear drug delivery, but most are predicated on delivering a single dose of the drug to the inner ear at the time of cochlear implantation. Our approach is to provide a controlled, sustained drug release that can maintain therapeutic levels of drug to the cochlea for an extended period of time. We chose to utilize a novel method for encapsulating small molecules in biodegradable poly lactic-co-glycolic acid (PLGA) microspheres and embed them within an ultra-low fouling, antifibrotic zwitterionic thin film coating to provide a reservoir for controlled-release drug delivery. This would allow localized delivery of neurotrophins at high local concentrations that can be released over the course of several weeks-months. Before this could be implemented clinically, we must determine the release kinetics of microspheres in artificial perilymph as well as demonstrating that SGNs will respond favorably to the drug-loaded microspheres.

Aims: Embed drug-loaded microspheres in zwitterionic thin film coatings. Measure the release of neurotrophic factor from microspheres aged in artificial perilymph using high-performance liquid chromatography (HPLC) and investigate the effects of neurotrophic-releasing microspheres on SGN survival.

Methods: PLGA microspheres were aged in artificial perilymph at 37ºC. Samples were collected at several timepoints and analyzed for release concentrations using HPLC. To investigate the effect of microspheres on SGNs, cochleae of rats post-natal day 5 (p5) were isolated from their temporal bones. Following enzymatic dissociation, isolated ganglia were plated on a 8-well plate with media supplemented with 50ng/mL BNDF, and 50ng/mL NT-3 for 24 hours. The media was then withdrawn and replaced with media containing microspheres for 48 hours. The cultures were fixed and immunolabeled with mouse monoclonal anti-NF200 antibody followed by Goat anti-mouse Alexa Fluor®546. These samples were then mounted and imaged with epifluorescent microscopy. ImageJ software was used to quantify the growth and survival of SGNs, as previously described.

Results: HPLC data indicated that the microspheres had continued release over the eight-week period. Additionally, SGNs showed no decreased survival in the presence of both blank and drug-loaded microspheres. Drug-loaded microspheres were successfully incorporated into zwitterionic thin film hydrogels.

Conclusion: By providing **a** controlled release of neurotrophic factors was sustained on a time course on the order of months, we believe we can significantly increase the survival of SGNs and, thus, greatly improve the efficacy of cochlear implants at transmitting complex auditory stimuli to patients with sensorineural hearing loss. Additionally, such findings may extend across systems of implanted devices as well as provide insight into the potential widespread utility of biodegradable polymer microspheres for controlled-release drug delivery.

Title: Nanoparticles as Immune Enhancing Agents for Melanoma Vaccines

Authors: Zachary Rinke; Pornpoj Phruttiwanichakun, PharmD

Mentor: Aliasger Salem, PhD

Background: Advanced stage cutaneous melanoma is widely known for being resistant to conventional chemotherapy and radiation therapy. Patients with advanced stage melanoma cancer therefore have a less than 33% 5-year survival rate. Immune-based therapies for cutaneous melanomas, such as immune checkpoint modulation (ICM) and cancer vaccine therapy (plus ICM) have demonstrated promising clinical outcomes, creating combined objective response rate of up to 17% in patients. There are limitations to effective vaccine therapy, including insufficient T-cell activation leading to low levels of tumor-specific T-cells and inefficient tumor targeting, the inability of tumor-specific T-cells to target the tumor due to the non-inflammatory tumor microenvironment, and the immunosuppressive nature of the tumor microenvironment. Recently, a 150-200 PLGA-PAMAMG5 (PMG5) nanoparticle formulation, when used in combination with a melanoma vaccine, has been shown stimulate an inflammatory environment at the site of the tumor. The PMG5-vaccine combination significantly increased MHC class 2 markers in dendritic cells and cytotoxic T-cells at the site of the tumor, increasing median survival of melanoma challenged mice. With the strong therapeutic benefit PMG5 delivers, new nanoparticle sizes and formulations are being investigated to further increase the survival rate and understand the mechanism by which the nanoparticles stimulate dendritic cells and T-cells.

Methods: Small, mid-size, and large PLGA nanoparticles were solubilized in acetonitrile and formulated in a polyvinyl alcohol solution using microfluidics, nanoprecipitation, or single emulsion methods respectively. Murine BMDC were harvested from C57BL/6 mice femurs and Tibias for in vitro studies. BDMCs were treated with respective nanoparticles size at day 8 of culturing. Flow cytometry was performed on day 10 to measure changes in expression of key immune markers; cd11c, MHC I, MHC II, cd40, and cd80. SEM was subsequently performed to monitor cellular changes and identify the behavior of nanoparticles after assembly.

Results: The optimized microfluidic formula produced particles of 79.34 ± 0.271 nm (PDI 0.147 ± 0.012). Nanoprecipitation method produce particles of 185.2 ± 2.55 nm (PDI 0.143 ± 0.021). Single emulsion method formed 453.3 ± 9.78 nm (PDI 0.307 ± 0.031) sized particles. In vitro data of BMDC showed a 4-fold increase in MHC class 1 expression after treatment with mid-size particles. Small particles induced insignificant changes to BMDC markers. Large particles showed strong aggregation in solution with no effect on BMDC markers.

Discussion: Cancer vaccines have great potential for treatment of late stage, high mutation burden cancers such as melanoma. Vaccines in these settings however have not shown as promising results when compared to other therapies. PMG5 has been shown to be a substantial adjuvant in stimulating the suppressive tumor microenvironment when combined with a melanoma vaccine. Particles of different sizes are taken up via different mechanisms; endocytosis, phagocytosis, eliciting responses in dendritic cells of differing degrees and pathways .Particles additionally attract a corona of proteins of different properties when in vivo such as Immunoglobulins and compliment factors. Further investigation into the protein corona created at the tumor microenvironment, mechanism of PLGA stimulation of dendritic cells, and in vivo impact of PLGA nanoparticles with a melanoma vaccine is necessary to develop an optimized method to treat late stage melanoma.

Determining the Immuno-Modulatory Effects of Electromagnetic Fields

Authors
Student: Nathan Robillard
Collaborators: Sunny Huang, MD PhD, Jen Petsche
Mentors: Calvin S. Carter, PhD and Val C. Sheffield, MD PhD

Background
Metastatic cancer requires that tumor cells have mechanisms to evade the immune response. One such mechanism is the reduction of T-cell responses through their exposure to the tumor microenvironment. While current cancer immunotherapies have increased survival among patients with metastatic disease, there remains a need for effective alternatives in those that do not respond to initial treatment. Electromagnetic fields (EMFs) are an attractive modality because they are non-invasive and penetrate all tissue evenly, eliminating concerns regarding bioavailability.

Purpose
The purpose of this project is to explore a novel method of activating an anti-tumoral T-cell using a non-toxic and noninvasive approach.

Methods
Peripheral blood mononuclear cells (PBMC) were isolated from spleens of C57BL/6 mice. CD8 T-cells were isolated from PBMCs, verified by flow cytometry and stimulated with anti-CD3 and anti-CD28, IL-2, and IL-7 transiently or long-term with and without EMF stimulation. The extent of immune activation was assessed via flow cytometry.

Results
EMF exposure resulted in significantly reduced expression of CD11a, CD25, CD69, and PD-1 in transiently activated $CD4^+$ and $CD8^+$ T-cells isolated from spleen, whereas long-term immune activation led to significant increases in PD-1 expression in both $CD4^+$ and $CD8^+$ T-cells. Changes in T-cell populations were only observed in transiently activated $CD4^+$ cells following EMF exposure, not in long-term immune activated cells. Moreover, EMF exposure did not elicit significant differences in the absence of immune activation.

Conclusions
Immune cells are sensitive to EMF stimulation. Analysis of data obtained via flow cytometry suggests differential responses among $CD4^+$ and $CD8^+$ T-cell activation markers following EMF exposure. Further work should be directed at understanding the underlying mechanisms.

Admission Lymphopenia is Associated with Discharge Disposition in Patients Hospitalized for Concomitant Chest Wall Trauma and Burn Injuries

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Background. Lymphopenia is recognized as a predictor of illness severity and risk of mortality among critically ill hospitalized patients. Koch et al. demonstrated that patients who were lymphopenic on admission were more likely to need a higher level of care and increased resources upon discharge. Further work is needed to assess whether this relationship exists in other hospitalized populations. Herein, we extended our study to a subgroup of patients with burn injuries that were excluded in the original analysis.

Hypothesis. We hypothesized that admission lymphopenia is associated with a higher level of resources needed at discharge, a longer hospital stay, and poor burn injury-specific outcomes.

Methods. The University of Iowa Hospitals and Clinics trauma registry was queried to identify patients with concomitant chest wall trauma and burn injuries between May 2009 and December 2018. Patients with absolute lymphocyte counts (ALC) collected within 24 h of admission were included. Patients who died within 24 hours of admission, had bowel perforation on admission, penetrating trauma, and head injuries were excluded. Lymphopenia was defined as an ALC of ≤1000/μL. Demographics, comorbidities, absolute lymphocyte count (ALC) on admission, burn injury information, hospital length of stay (LOS), ventilator days, discharge disposition, burn-related complications (skin graft loss), and mortality were collected. Univariate and multivariate analyses were performed to assess the relationship between lymphopenia and outcomes. Spearman's Rho correlation coefficient was used to assess the relationship between ALC and hospital LOS.

Results. Seventy patients with a Chest Abbreviated Injury Score (CAIS) ≥2 and concomitant burn injuries as well as a documented absolute lymphocyte count (ALC) within 24 hours of admission were included; 18 patients were lymphopenic and 52 were not. Demographics (besides BMI), comorbidities, burn injury-related variables (TBSA, %TBSA of 2nd and 3rd degree burn, presence of inhalation injury), hospital length of stay, and burn injury-related and non-related complications were not significantly different between the lymphopenic and non lymphopenic group. Lymphopenic patients presented with a lower BMI (24 [22.3-31.7] vs. 30 [24.5-37.6], p = 0.021) and were more likely to require a higher level of care upon discharge than their counterparts (68.8% vs. 37%, p = 0.044). Adjusting for only a trending association between lymphopenia and discharge requiring higher level of care was observed (14.450 [- 301.5; p = 0.085]. While no significant difference was observed between the lymphopenic and non-lymphopenic group regarding hospital, ALC count was negatively correlated with hospital LOS (Spearman's Rho = -0.281, p = 0.019).

Conclusions. In this small cohort, admission lymphopenia tended to be associated with discharge disposition requiring higher level of care in patients presenting with concomitant burn and chest wall-trauma injuries. Additionally, lower ALC correlated with longer hospital LOS. These preliminary data support the need for future studies exploring the use of admission lymphopenia or ALC as potential prognostic marker for longer recovery in this patient population.

Post-Procedure Protocols After Intraarticular Orthobiologic Injections - A Review

Student: Kristina Rossmiller
Mentor: Ryan Kruse, MD
Collaborators: Timothy Fleagle, DPT

Background: Osteoarthritis is a chronic degenerative disease affecting more than 300 million people throughout the world. While orthobiologics have been proposed as a disease modifying treatment for osteoarthritis there is significant heterogeneity in the results of the orthobiologic procedures in the literature. One possible explanation for the heterogeneity is the inconsistent reporting and description of the post-orthobiologic protocols.

Hypothesis/Purpose: The goal of this literature review was to identify the current literature on the use of orthobiologics for osteoarthritis, and critically evaluate the post-orthobiologic protocol within these studies. We hypothesized that only a small number of studies would adequately discuss their post-orthobiologic protocol and that there would be a large degree of variability in those protocols.

Methods: A scoping review of the literature on post-orthobiologic protocols for osteoarthritis was performed using PubMed, EMBASE, and Web of Science. English language studies that investigated platelet-rich plasma, bone marrow aspirate concentrate, and microfragmented adipose tissue for osteoarthritis since 2013 were included. Non-clinical studies, clinical studies with less than 10 participants, and studies investigating any other orthobiologic product were excluded. Studies were first reviewed to identify those that made mention of a post-orthobiologic protocol. Subsequently, the specific components of the post-orthobiologic protocols within those studies were examined, including: (1) post-procedure rehabilitation, (2) weightbearing status, (3) use of orthotics or other durable medical equipment, (4) nonsteroidal anti-inflammatory medication (NSAID) restriction, and (5) corticosteroid or immunosuppressant therapy restriction.

Results: 200 out of 234 identified studies met inclusion criteria. In 37.5% of studies, there was no mention of any component of a post-orthobiologic protocol. Of the 125 studies that did mention a post-orthobiologic protocol, only 38.4% included a rehabilitation protocol. 21.6% included post-procedure weightbearing restrictions, while only 2 (1.6%) mentioned the use of durable medical equipment. NSAID restriction was described in 91.2% of study protocols, while corticosteroids and immunosuppressants were restricted in 84.8% and 19.2% of protocols, respectively.

Conclusion: Our scoping review found that close to 40% of studies on the use of orthobiologics for osteoarthritis did not report any post-procedure protocols. In the studies that did report a post-procedure protocol, there was a large amount of heterogeneity in the protocol specifics, with the most common feature being the restriction of NSAIDs before and after the procedures. These findings highlight the need for future research and improved reporting of post-orthobiologic protocols.

Characterization of paravalvular leak in surgically placed aortic valves

Background

Paravalvular leak (PVL) is a rare, but serious complication of surgical valve replacements in which an inadequate seal is made between the sewing ring of a prosthetic valve and the surrounding native tissue[1]. This leak leads to hemodynamic repercussions such as congestive heart failure, hemolytic anemia, endocarditis, and death[2,3]. Current surgical practice does not allow for discovery of PVL until after reperfusion, which forces surgical re-operation and risk of further complications[4]. Additionally, PVL in surgical valve replacements, especially those of trace to mild grade, have not been well described. Here, we characterize PVL in surgically placed aortic valves with echocardiography flow parameters.

Methods

We performed retrospective analysis of 76 patients who suffered PVL after surgical aortic valve replacement from May 2010 to May 2023 at the University of Iowa. PVLs were characterized by size, number, density, and pressure half-time, and these were compared to each other based on point of discovery and intra-operative decisions.

Results

Conclusions

Loss of Muscarinic Receptors Innervation Increases Cell Proliferation in Acute Airway Injury.

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Introduction: Lung transplantation can be an effective treatment strategy for select patients with end-stage lung disease. In the lungs, cholinergic stimulation is known to interact with the various populations of resident stem cells that contribute to repair and regeneration of injured lung tissue. However, cholinergic outflow in lung transplant surgery is interrupted by unavoidable denervation during the explant of the allograft.

Hypothesis: We hypothesized that loss of activation of muscarinic receptors due to vagal denervation may contribute to unregulated cell proliferation in response to acute injury.

Methods: Tracheas were harvested from ferrets (n=7), brushed with a stiff nylon brush to induce a partial scratch injury, and cut into 1cm pieces. Explants were cultured for five days in F-medium and pulsed every 48 hours with treatment conditions and EdU, a nucleotide analog to quantify proliferation. Conditions included control, bethanechol (muscarinic receptor agonist, 10μM), acetylcholine (muscarinic and nicotinic receptor agonist, 10μM) and atropine (muscarinic receptor antagonist, 10μM). On day 5, tissues were fixed, cleared and stained for imaging by confocal microscopy. Submucosal glands were identified by glandular morphology, and the Z-stack range containing single glands was determined. EdU positive pixel area was quantified as a percentage of total gland area. The surface plane was identified as the Z slice superficial to the gland slices, and EdU positive area was quantified as a percentage of total nuclei stain area.

Results: In the glandular epithelium, treatment with acetylcholine induced a significant decrease in EdU+ area, suggesting inhibition of proliferation, compared to the untreated control explant (Ach 2.45% *vs.* Control 9.34%, P=0.02). A non-significant decrease was seen with bethanechol treatment (Bet 6.02% *vs.* Control 9.34%, P=0.15). On the surface airway epithelium, bethanechol treatment (Bet 12.5% *vs.* Control 34.4%, P=0.02) and acetylcholine treatment (Ach 10.5% *vs.* Control 34.4%, P=0.03) significantly inhibited cell proliferation compared to untreated control. When explants were treated with atropine alongside bethanechol or acetylcholine, rescue of cell proliferation was observed (Bet/Atrop 32.9% and Ach/Atrop 25.4%, P=0.03 and P=0.02, respectively) compared to bethanechol only and acetylcholine only treatments. Meanwhile, compared to control, no changes were observed in the bethanechol/atropine treatment group (P=0.87), the acetylcholine/atropine treatment group (P=0.40) and the atropine only treatment group (P=0.55).

Conclusion: Our study suggests that the muscarinic branch of the cholinergic pathway plays an important role in vagal parasympathetic control of airway epithelial cell proliferation in response to injury. Further investigation is needed to understand how innervation-specific mechanisms regulate proliferation, elucidate the interplay between glandular and surface epithelial response, and reveal useful targets in the management of patients who underwent lung transplantation.

Radiomic Characterization of Brain Aneurysms

Student: Arshaq Saleem, M2

Mentor: Edgar Samaniego, MD, MS

Collaborators: Sricharan Veeturi, Diego Ojeda, MD, Andres Gudiño, MD, Elena Sagües, MD, Bincheng Wang, MS, Sebastian Sanchez, MD, Jacob Miller, Ashrita Raghuram, Vincent Tutino, Ph.D

Introduction: Intracranial aneurysms (IAs) are dilatations of cerebral blood vessel walls that affect around 3% of the population. While 85-90% of IAs do not rupture or cause symptoms, ruptured IAs lead to subarachnoid hemorrhage which carries a 25-50% mortality rate. Thus, accurate estimation of IA rupture risk can help guide management decisions. Aneurysm wall enhancement (AWE) extracted from high-resolution vessel wall imaging (HR-VWI) is a promising tool for assessing IA stability, as it has been observed that symptomatic IAs show increased wall enhancement. Radiomics is another emerging technology which allows for detailed analysis of the signal intensity, shape, and texture of medical images. Radiomics initially emerged as a method for predicting cancer chemotherapy susceptibility, and recently it is starting to be used for IA analysis.

Hypothesis: Given the morphological differences between symptomatic and asymptomatic IAs, machine learning models can be built using clinical information and AWE/radiomic data to classify symptomatic status.

Methods: Complete clinical (symptomatic status, age, sex, smoking status, HTN/HLD/DM status) and morphological (Irregular morphology, blebs, IA size, neck size, size ratio, aspect ratio) data were obtained for 104 IAs that underwent HR-VWI MRI. Symptomatic IAs were defined as IAs that ruptured/grew, caused sentinel headache, or presented with cranial nerve neuropathy due to compression. IAs were segmented by hand in 3D slicer and run through a MATLAB pipeline that extracts the signal intensity of the IA wall and generates 3 key AWE metrics. Additionally, the conventional enhancement metrics of corpus callosum ratio (CC_{ratio}) and pituitary stalk (CR_{stalk}) were also calculated. Radiomic features (RFs) were automatically extracted using the Python Interactor Module in 3D Slicer, with the segmentation of the IA wall serving as the region of interest. Four different machine learning models were built to classify symptomatic status: 1) Clinical/morphological data + RF data, 2) Clinical/morphological data+ AWE metrics, 3) Clinical/morphological data + CC_{ratio} data and 4) Clinical/morphological data + CR_{stalk} data. These models were converted to nomograms whereby the values for different features were assigned different point values, with higher point totals corresponding to higher likelihood of symptomatic status.

Results: The nomogram built using RFs had the highest diagnostic accuracy (AUC = 0.741), followed by the AWE (AUC = 0.712), CC_{ratio} (AUC = 0.705) and CR_{stalk} (AUC = 0.701) models. The sensitivity of all the models was identical but the RF model also had the highest specificity.

Conclusions: Machine learning models built using RFs and clinical and morphological data have the potential to serve as valuable tools for predicting symptomatic status in intracranial aneurysms. However, a limitation of the approach used in this project is the use of manual segmentation of aneurysms to generate data for radiomics and AWE, which consumes a significant amount of time. Going forward, the prospect of automating IA segmentation through machine learning, coupled with classification techniques, holds promise as an efficient tool for clinical decision-making.

Resident Exposure to Oculofacial Diagnoses on Call at an Academic Level I Trauma Center

Peter Sanchez BA (presenting), Ryan Diel MD, Margaret Strampe MD, Chau Pham MD, Keith Carter MD, Pavlina Kemp MD, and Erin Shriver MD (mentor).

Introduction

Significant institutional variability exists regarding which specialties care for periocular and orbital trauma. As ophthalmology departments become more removed from the trauma hospital setting and stand-alone eye centers become more common, resident exposure to these injuries is decreasing. Adequate experience evaluating and managing orbital fractures and other oculofacial injuries is critical to developing a strong foundation of knowledge, especially if ophthalmology-trained orbital surgeons are to remain the experts of the orbit.

Methods

A retrospective review of all patients in 2019 who received ophthalmology consultations from the Emergency Department (ED) at an academic, Level I trauma center was performed. All patients were evaluated by ophthalmology residents. The principal diagnoses from each consult note were recorded along with the date, day of the week, and month the consult was placed. For the purposes of this oculofacial plastics focused study, orbital fractures and eyelid lacerations were evaluated.

Results

The study identified 910 patients for whom a resident performed an ophthalmology consult in the ED in 2019. The most ED consult patients were seen on Saturday, Friday, and Sunday (173, 157, and 150 patients respectively). Of the 128 different diagnoses seen by residents on call, orbital fractures (150 patients) were the most common and they were twice as common as the second leading consult descriptor of “papilledema rule-out” (75 patients). Eyelid lacerations (72 patients) were the third most common diagnosis. Monthly consultations for patients with orbital fractures were highest in August, July, and April (19, 18, and 17 patients respectively). Orbital fracture was the most common diagnosis every day of the week except Thursday, where it was the second most common diagnosis. Throughout the year, most orbital fractures were diagnosed on Fridays, Sundays, and Saturdays (29, 27, and 24 patients respectively).

Discussion

At the study institution ED, orbital fractures are the most common diagnosis evaluated by ophthalmology residents. Orbital fractures are more commonly seen during the summer months and on Fridays through Sundays. A previous study determined that orbital fractures and eyelid lacerations were only in the top 20 most common diagnoses seen by residents at 1 of 4 high-acuity Eye EDs. In sharp contrast, the present study demonstrates that orbital fractures are the most common diagnosis evaluated by residents at the study institution and eyelid lacerations are common as well. It is important to note that Eye EDs and tertiary trauma centers are two very different settings and residents training in these varied settings will have drastically different experiences.

According to a recent survey of 2018 primary-surgeon case logs, graduating ophthalmology residents performed an average of 0.49±1.4 orbital fracture repairs and 8.66±6.94 eyelid laceration repairs. This highlights just how few oculofacial trauma cases graduating residents are performing. It is imperative that ophthalmology residents, regardless of institution, be well prepared to identify and manage patients with orbital and periorbital trauma. Future studies should attempt to gain a better understanding of the ever-changing practice patterns in ophthalmology to ensure all residents build a strong foundation caring for patients with orbital and periocular trauma.

Vaughan Schwob
Mentor: Jacob Michaelson
Other Collaborators: Lucas Casten, Taylor Thomas, and Ethan Bahl

Predictors of later diagnosis in autistic females

Background: Autism spectrum disorder (ASD) is a broad diagnosis applied to individuals with impairments involving social communication, and restricted/repetitive behaviors and interests (Lord et al., 2020). Due to its developmental origins, ASD symptoms usually receive clinical attention early in life. Diagnosis of ASD is based on developmental history and direct observation of behavioral features, and observations are performed in various settings to capture the most complete picture of behavior. Many of the diagnostic features, such as outbursts and meltdowns, are more typical in boys than girls. Since most diagnostic processes are more sensitive to ASD in boys than in girls, many autistic girls are misdiagnosed or endure delayed diagnosis (Young, Oreve, & Speranza, 2018). This study investigates if there is a significant correlation between internalizing behavior and later diagnosis in females, but there would be no correlation in males. The aim was to identify factors contributing to sex-based discrepancies in age of diagnosis; we correlated age of diagnosis with several mental health rating scales in a sex-stratified manner. **Methods:** To examine the hypothesis, the Adult Self Report (ASR) questionnaire from SPARK data version nine was used. The ASR separates its internalizing items into three factors: anxious/depressed, withdrawn, and somatic complaints. Four variables were created, one for each subscale and a general internalizing variable; by adding together scores from the items on each factor, no items were reverse coded. Preliminary correlations were run using the subscale and internalizing variables to get an initial picture of the data. General linear models (GLMs) were performed to better determine significance and interactions between the internalizing score and sex in predicting age of diagnosis. After examining the results of the GLMs, a random forest on independent adult women with a diagnosis of autism was performed to determine what items of the ASR best predict age of diagnosis. **Results:** The GLM analysis revealed no significant main effects of internalizing symptoms on age of diagnosis. There was an almost significant interaction effect between internalizing symptoms and sex on age of diagnosis, suggesting that the relationship between internalizing symptoms and age of diagnosis might vary by sex. There were no significant main effects or interaction effects for the anxiety/depression subscale. There was a significant main effect of somatic complaint score and a significant interaction effect of somatic complaint and sex. There was a significant main effect of sex in the withdrawn subscale. The random forest revealed that a positive endorsement of ASR items about honesty, being alone, not being liked, being withdrawn, and trying to be fair are correlated to a lower age of diagnosis. A positive endorsement of ASR items about having mood swings, enjoying people, making use of opportunities, sleeping more, and thinking that they are too dependent are correlated to a later age of diagnosis. **Discussion:** The results of the GLMs and random forest indicate that general internalizing symptoms are not associated with a later age of diagnosis. Instead, social internalizing variables appear to be related to age of diagnosis. Autistic people who socialize differently with their peers are more likely to be noticed and therefore are more likely to receive an earlier diagnosis. A study conducted by Oredipe et al. (2022) found that early diagnosis empowers children, as it grants them access to support and a fundamental understanding of themselves, leading to improved well-being and success in adulthood. Social differences and age of diagnosis should continue to be studied, so young girls with autism can be properly diagnosed and access the support they need.

Title: The Effect of Full-Body Weight-bearing on Palmar Pressure Distribution
Student: Noah Scigliano
Mentor: Jessica E. Goetz, PhD
Co-mentor: Joseph A. Buckwalter V.

Introduction: Axial loading of the wrist stresses the distal radioulnar joint, increasing susceptibility to triangular fibrocartilage complex injury and ulnar abutment. Athletes such as gymnasts regularly bear high loads through the wrist, while the geriatric demographic often exerts additional pressure on the upper extremity thorough use of assistive devices such as canes. Despite the high prevalence of wrist load-related injuries, there is limited research on load transmission across the wrist and into the hand.

Objectives: Our study examined the distribution of palmar pressure during a weight-bearing activity (handstands) to discern high-pressure regions and their correlation with wrist joint anatomy. Additionally, we investigated the role of hand dominance in maintaining balance and center of pressure (COP).

Methods: Fifteen participants conducted a 45-second handstand on an emed pressure platform system after approval by the institutional review board (IRB) and informed consent was obtained. Within a 35-second window during which the participant was stable in the handstand position, COP and force distribution on the palmar surface were analyzed. The palm was subdivided into four anatomical regions (hypothenar, thenar, metacarpals, and fingers) and within each, the maximum force (MF), mean pressure (MP), and contact area were calculated. Ulnar variance (UV) values were measured on images obtained in a weightbearing CT machine (WBCT), in which participants completed an additional handstand hold. The relationship between MP and palmar region was assessed using ANOVA with pairwise Tukey's HSD tests. Regression analysis was used to relate mean thenar/hypothenar pressure to UV. The influence of hand dominance on COP location and MF was analyzed using binomial and paired t-tests.

Results: Mean pressure was significantly higher in the thenar and hypothenar regions than in the fingers and metacarpal regions ($p<0.05$ for all). There was not a significant difference in MPs between the hypothenar and thenar regions (9.7 kPa difference, $p=0.183$). Every 1.00 mm increase in UV corresponded to a 2.8% increase in MF in the hypothenar region ($p=0.0371$). In 93% of participants, the COP was closer to their dominant hand during the stabilized phase of a handstand ($p<0.05$), and among all participants the dominant hand had an average 26.9 N (95% CI [12.7, 41.2]) greater MF than the nondominant hand ($p<0.05$).

Conclusions: This investigation underscores the equivalence of the thenar and hypothenar zones in distributing palmar pressure during handstands. The notable association of UV with hypothenar MF distribution indicates that force transmission to the palm through the wrist joint is contingent on radioulnar positioning. Furthermore, this research emphasizes the role of hand dominance in weight distribution among athletes. Collectively, our findings shed light on the biomechanics underpinning upper extremity loadbearing. Our findings are of interest as altered values in UV are associated with chronic wrist conditions, such as Kienbock's disease in the setting of negative variance and ulnar abutment in positive variance. Palmar pressure distributions during weight-bearing activities may assist in the development of these disease processes, and by utilizing pressure mapping devices and WBCT, activity modification strategies can be created for early treatment prior to severe pathologic consequence. Future research into palmar pressures after soft-tissue injury may give rise to advanced diagnostics and therapeutics for common sports ailments, such as triangular fibrocartilage complex tears, and related conditions affecting the general population.

Total Spinal Anesthesia in Pediatric Cardiac Surgery: Effects on Postoperative Pain and Opioid Utilization - A Propensity Matched Investigation

Student: Aravin Sivamurugan, M3
Mentor: Satoshi Hanada, MD
Collaborators: Rakesh Sondekoppam Vijayashankar, MBBS

The use of total spinal anesthesia (TSA) in combination with general anesthesia (GA) has been used pediatric congenital heart surgery due to the potential for expediting postoperative recovery. TSA is a technique where a local anesthetic such as bupivacaine is administered intrathecally to achieve total or near total sensory blockade. This, combined with intrathecal morphine allows for pain control during and immediately after surgery while minimizing use of intravenous opioids. We aimed to investigate the impact of TSA with concurrent intrathecal morphine on postoperative pain and opioid requirement in this patient population. We hypothesized that utilization of TSA be associated with lower postoperative opioid requirements with similar analgesic profiles. The results of this study are part of a larger project investigating perioperative outcomes related to TSA.

After obtaining approval of institutional review board (IRB number 201911151) we conducted a retrospective review on pediatric patients undergoing elective cardiac surgery between November 2011 and November 2021 at the UIHC). We included cases classified as Risk Adjustment for Congenital Heart Surgery-1 (RACHS-1) category 3 or less. Propensity score matching was employed to control for confounding variables. Opioid requirements were measured at 24 and 48 hours postoperatively and converted to milligram morphine equivalents (MME). Face, Legs, Activity, Cry, Consolability (FLACC) pain scores were measured at 24 and 48 hours postoperatively. A FLACC score of 1 indicates least pain, and 10 indicates worst pain.

Out of the 1188 pediatric cardiac surgery cases that were performed during the study period, 629 cases were eligible for this study. After propensity score matching, 197 patients were included in each group. In the TSA group, postoperative opioid requirements in the first 24 hours were notably lower compared to the GA group (TSA 6.2 ± 4.3 mg vs. GA 9.8 ± 5.7 mg $P < 0.001$). However, there was no significant difference in opioid use between the groups during the second 24-hour postoperative period (TSA 3.7 ± 3.1 mg vs. GA 3.9 ± 3.2 mg, $P = 0.617$). Regarding pain scores, the TSA group exhibited higher maximal and average FLACC pain scores in the first 24 hours postoperatively compared to the GA group (maximal pain score: TSA 4.9 ± 1.6 vs. GA 4.3 ± 1.4, $P = 0.002$; average pain score: TSA 3.2 ± 1.2 vs. GA 2.8 ± 1.1, $P < 0.001$). However, no significant differences were observed in maximal or average pain scores between the groups during the second 24-hour period (maximal pain score: TSA 3.7 ± 1.4 vs. GA 3.5 ± 1.3, $P = 0.067$; average pain score: TSA 2.5 ± 0.9 vs. GA 2.4 ± 0.8, $P = 0.226$). Complications related to TSA, such as intractable hypotension and epidural hematoma, were not observed in the TSA group.

Our propensity matched retrospective study demonstrated that the utilization of TSA in combination with GA is associated with significantly reduced opioid requirements in the first 24 hours after pediatric congenital heart surgery with comparable postoperative pain control. Though pain scores were roughly 0.6 points higher in the TSA group, it should be noted that a greater percentage of patients were sedated or intubated in the GA group. Our findings suggest the potential of TSA as an effective strategy for optimizing pain management and enhancing recovery in this population, warranting further investigation through prospective randomized studies. Overall, our results suggest that the combination of TSA with GA in pediatric congenital heart surgery is associated with significantly reduced postoperative opioid requirements in the initial 24 hours with similar pain scores during the same period, potentially reflecting optimized pain control in the TSA group.

Secondary Undertriage in a Rural Trauma System: Revisiting Twice-Transferred Patients to a Level 1 Trauma Center

Isaac Slagel, BA; Colette Galet, PhD, James Torner, PhD; Kristen Sihler, MD

Introduction:

Efficient trauma systems aim to provide timely care to patients with varying injury severity. Effective treatment relies on appropriate field triage, ensuring the rapid transport of patients to facilities equipped to treat their injuries. Ideally, field triage will minimize the time to treatment for critically injured patients and prevent extra transfers. Undertriage—where seriously injured patients are missed by field triage and transported to non-trauma hospitals—is a key metric of triage effectiveness. However, in rural trauma systems, undertriage is necessary due to extended distances to trauma centers.

Between 1996-1999, Sihler et al. (2002) identified twice-transferred trauma patients as an alternative study population that could provide better insight into undertriage in rural trauma systems. This study investigates twice-transferred trauma patients from 2017-2020 to deepen the understanding of trauma triaging within a mature rural trauma system.

Hypothesis/Purpose:

As a result of the implementation of the Iowa Trauma System in 2000, increased use of teleconsults and image sharing, and the loss of intermediate-level trauma centers, we expected the rate of twice-transferred trauma patients to decline over the last 20 years. We aimed to update knowledge on injuries and care decisions leading to consecutive transfers before definitive treatment.

Methods:

Multiple-transferred trauma patients were identified using the University of Iowa Hospital & Clinics (UIHC) Trauma Registry. We identified 100 patients transferred multiple times before arrival at UIHC for definitive care of trauma-related injuries between 2017 and 2020. Information extracted from the registry included patient demographics, injury date, injury time, injury zip code, transfer information (hospital, time, mode), injury severity score, trauma score and injury severity score, comorbidities, complications, abbreviated injury scale, mortality, and readmission to UIHC within 30 days.

Findings/Results:

Our final study sample included 86 patients—69 (80.2%) adults and 17 (19.8%) pediatric patients. Compared to 1996-1999, there was a significant decrease in the number of twice-transferred trauma patients as a percentage of total trauma volume (3.0% vs. 0.66%, $p < 0.05$). Twice transferred patients tended to be older, and a lesser proportion were male compared to the original study (37.5 vs. 47.3 years, $p < 0.05$ and 78% vs. 61.6%, $p < 0.05$, respectively). Out of 69 adults, 61 (88.4%) initially presented to a state-verified level 4 trauma center. Of those, 56 (91.8%) were transferred to a higher-level facility (Level 1: 14, Level 2: 14, Level 3: 28). Injury severity scores (ISS) of patients ranged from 1-45, with 87% of patients having an ISS under 25. We found that 99% of patients were injured more than 50 miles from UIHC, with 24.4% of patients injured within our hospital's 150-mile helicopter range. On average, it took patients 61.03 (±91.0) hours to be transferred to our facility for definitive care. 72.1% (62) of patients were transferred to our facility within 48 hours of injury.

Conclusion:

Undertriage is a necessity to provide care to patients in rural trauma systems. By studying twice-transferred patients, we can better identify shortcomings in rural settings. Our study demonstrates a significant decline in twice-transferred patients over two decades, reflecting improvements in trauma coordination in our state. As in previous work, patients tend to be transferred for specialized care for complex injuries instead of critical care. Further investigation is warranted to comprehend the potential impact of multiple transfers on healthcare outcomes.

Characterization of Melanoma Referrals to UIHC and Impact on Patient Outcomes

Smart, Jacqueline N., BSA; Rand, Sydney E., BSBA; Chen, Ailynna, MD; Milhelm, Mohammed, MBBS; Powers, Jennifer G., MD

Introduction with background/rationale:
The 1.2 million Iowa residents who live in rural areas present unique challenges in the diagnosis and treatment of melanoma across the state. Studying the demographic and geographical challenges in melanoma diagnosis, referral, and treatment in the state of Iowa will provide insight into the management of melanoma in many rural areas across the United States.

Purpose:
This project aims to analyze trends in provider practices by characterizing melanoma referrals from rural and urban communities to UIHC. We will explore the association with clinical outcomes to identify areas of concern while optimizing melanoma referral guidelines.

Methods:
Melanoma diagnoses and referrals to UIHC dermatology, surgical oncology, and hematology/oncology from 2016-2021 years were identified through TriNetx. A total of 234 patients were included in our data set thus far. Information on patient demographics, the referring provider, characteristics of the melanoma at diagnosis, treatments received (at UIHC and outside facilities), and outcomes were analyzed through electronic medical record review. Interim statistical data was retrieved from RedCap, with only categorical data examined in this abstract.

Findings/Results:
Most patients in this data set received their melanoma diagnosis outside of UIHC (65.2%), however, 85% of all patients received treatment for their melanoma at UIHC. Among all facilities of diagnosis, dermatologists made up 74.2% of all diagnosing providers. The data also demonstrated an upstaging from initial clinical to final pathological staging after excision was performed. This may indicate inaccurate initial Breslow depth due to the type of skin biopsy (shave vs. punch) performed at the time of diagnosis. There were additional discrepancies found in the rate of sentinel lymph node biopsies (SLNB) performed by outside providers vs. UIHC providers. Excisions performed at non-UIHC facilities had greater rates of SLNBs (51% vs. 31%) and performed more SLNB when the Breslow depth was below 1 mm (23% vs. 4%).

Conclusion/Overall significance:
In conclusion, while providers outside of UIHC are diagnosing most melanoma cases throughout the state, a majority of them are still referred to UIHC for treatment. The increase in clinical to pathological staging after excision may indicate an inaccurate initial Breslow depth due to the type of skin biopsy (shave vs. punch) performed at the time of diagnosis. This finding further argues for the use of punch biopsy for lesions suspicious for melanoma. Patients with excisions at non-UIHC facilities receive more SLNB and at shallower Breslow depths. This may lead to greater morbidity without offering additional survival benefit in these patients. This variation in practice offers an opportunity for standardization of SLNB indications throughout the state.

Retrospective Review of Clinicopathological Findings of Hereditary Leiomyomatosis and Renal Cell Cancer and Evaluation of FH/2SC Staining for Genetic Referral

Smrithi Mani BA, Dean Elhag MD, Rob Humble MD, Andrew Bellizzi MD, Vincent Liu MD, Yousef Zakharia MD

Background:

Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) has phenotypic manifestations that include uterine leiomyomas, piloleiomyomas, and aggressive renal cell carcinoma (RCC). At a single tertiary academic center, we aimed to identify clinical, histopathologic, and imaging findings in HLRCC families, and assess the utility of fumarate hydratase (FH) and 2-succinocysteine (2SC) immunohistochemistry (IHC) on piloleiomyomas as a prelude to genetic referral.

Methods:

We retrospectively reviewed 29 probands who met major clinical criteria for HLRCC (i.e. multiple cutaneous leiomyomas) or whom had a documented FH germline mutation. HLRCC positive family members of the 29 probands were also included in the analysis if the records were available. Thirty-nine individual records were reviewed (ages 4-75 years). FH germline mutations were documented in 28 individuals. A separate search of institutional pathology archives identified 64 piloleiomyomas from 41 patients between 1995 to 2023 on which FH/2SC IHC was performed.

Results:

28 of 39 individuals who had renal imaging were reviewed; 54% (15/28) exhibited renal cysts, 7% (2/28) angiomyolipomas, and 11% (3/28) adrenal adenomas. First or second-degree relatives with RCC were reported in 18% (5/29) of evaluable families with HLRCC. Piloleiomyomas were present in 63% (12/19) of women and 94% (16/17) of men over age 10. Uterine leiomyomas were present in 88% (15/17) of evaluable women over age 10 and 76% (13/17) underwent hysterectomy or myomectomy.

From our separate search of our institutional pathology archive, FH-deficiency/2SC-positivity was found in 41/64 piloleiomyomas and 18/41 patients. FH-loss and positive 2SC staining was demonstrated in 100% (12/12) of piloleiomyomas from individuals with more than one piloleiomyoma. Six solitary, piloleiomyomas from 6 different individuals, with unknown HLRCC status, were FH-deficient by IHC.

Conclusion:

Our study underscores the role of FH/2SC in identifying FH-deficient piloleiomyomas to aid in appropriate genetic referral. Notably, we report two HLRCC patients with angiomyolipomas, including a case of bilateral angiomyolipomas.

Acceptable susceptibility thresholds reported in hospital antibiograms for Gram-negative rod infections: a survey and contingent valuation study of infectious diseases specialists

Sadie Solomon BS, Shinya Hasegawa MD, Eli Perencevich MD MS, Kimberly Dukes PhD, Michihiko Goto MD MSCI

Background: Clinical guidelines recommend an antibiogram as a key component when making empiric therapy decisions. However, little is known about how clinicians utilize antibiograms. We aimed to assess the interpretation thresholds of hospital antibiograms among infectious diseases (ID) specialists when making empiric therapy decisions for Gram-negative rods (GNRs) infections.

Methods: We conducted an email-based survey of ID specialists practicing at Veterans Health Administration (VHA) facilities. We included four scenarios: i) a patient with urinary tract infection (UTI) in an outpatient setting, ii) a patient with UTI in an inpatient setting, iii) a patient with GNR bloodstream infection (GNR-BSI) in a non-intensive care unit (ICU) setting, and iv) a patient with GNR-BSI in an ICU setting. Each scenario randomly assigned antibiogram percentages and asked specialists if they would feel comfortable selecting a hypothetical empiric therapy agent with the given value. Contingent valuation analyses were done by logistic regression models to evaluate the relationship between the percentages offered to providers and their willingness to use offered agents.

Results: In the preliminary analysis, 112 of 599 providers (18.7%) responded and 104 provided effective responses. Hospital antibiograms are generally used infrequently, and only 30.8% of providers indicated that they use antibiograms more than once a month. The estimated median interpretation thresholds, meaning half of the ID providers would prescribe the hypothetical antibiotic in each case with the values given on antibiograms, were significantly higher for patients with more severe illnesses (85.6% [95% confidence interval [CI] 83.1-88.1] for an inpatient with UTI vs 74.1% [95%CI 69.7-77.6] for an outpatient with UTI; 86.0% [95%CI 83.1-89.4] for a patient with GNR-BSI in ICU vs 77.9% [95%CI 74.2-81.2] for a patient with GNR-BSI in non-ICU).

Conclusion: This study demonstrated that ID providers rarely utilized antibiograms and the median thresholds for hospital antibiograms influencing empiric antibiotic selection ranged from 74-86%, depending on the severity but not by the type of infection (UTI vs. BSI). Further analyses after we receive more responses will be completed.

BMI at delivery and associated maternal and neonatal outcomes

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Abstract

Objective: Current literature on the risks and outcomes of obesity in pregnancy almost exclusively utilizes pre-pregnancy body mass index (BMI). Given the rising obesity rate across the United States along with a paucity of available information on the relationship between delivery BMI and maternal and neonatal outcomes, our study aimed to determine the association of maternal BMI at delivery with antepartum, intrapartum, and neonatal complications at an academic referral hospital in women who delivered term singleton infants.

Study Design: This study is a secondary analysis of data collected for a prospective cohort study of COVID-19 in pregnancy. This analysis included all patients who delivered term singleton infants between May 1, 2020, and April 30, 2021, at the University of Iowa Hospitals and Clinics. Demographic and clinical data were obtained from the electronic medical record. The relationship between maternal BMI and maternal and neonatal characteristics of interest was assessed using logistic regression models. A statistical significance threshold of 0.05 was used for all comparisons.

Results: There were 1,996 women who delivered term singleton infants during the study period. The median BMI at delivery was 31.7 (interquartile range 27.9, 37.2), with 61.1% of women having a BMI ≥30.0. Increasing BMI was significantly associated with non-reassuring fetal status, unscheduled cesarean birth, overall cesarean birth rate, postpartum hemorrhage, prolonged postpartum stay, hypertensive diseases of pregnancy, neonatal hypoglycemia, neonatal intensive care unit admission, decreased APGAR score at one minute, and increasing neonatal birth weight. Even when controlling for pre-existing hypertension in a multivariate model, increasing BMI was associated with gestational hypertension and pre-eclampsia.

Conclusion: Increased maternal BMI at delivery was associated with adverse perinatal outcomes. These findings have implications for clinical counseling regarding risks of pregnancy and delivery for overweight and obese patients and may help inform future studies to improve safety, especially by examining reasons for high cesarean rates.

Keywords: Pregnancy outcomes; obstetric delivery; body mass index; cesarean delivery; fetal status, non-reassuring; neonatal intensive care

Key Points:

- 61.0% had a BMI >30 at delivery
- Increased adverse outcomes with elevated delivery BMI
- Higher cesarean rate with increasing delivery BMI
- Elevated BMI associated with prolonged hospital stay
- Per 5-unit increase maternal BMI, neonatal weight +57g

The Effect of Early Melatonin Agonist Administration on Delirium Outcomes Among Hospitalized Elderly Adults

Leon Sun, Brianna Mueller, Sydney Krispin, Eliezer Santos-Leon, Priyanka Vakkalanka, Sangil Lee

Background: Delirium is an acute, transient state of altered consciousness with defects in attention, focus, and organized thinking. Development of delirium is common in elderly and hospitalized patients and is associated with increased mortality, a longer length of stay, increased falls, lower quality of life, and increased institutionalization. Existing literature shows that distribution of melatonin agonists can improve delirium outcomes within the inpatient setting. However, these outcomes may not be generalizable to outpatient settings such as the emergency department (ED). To date, very little research has been conducted on interventions initiated within the (ED) and early in the process of hospitalization. This gap in the literature is important, as the majority of elderly patients are admitted to the hospital through the ED, and delays in delirium management lead to poorer outcomes. Our paper will fill this gap and create a greater understanding of delirium management in the crucial early stages of hospitalization.

Methods: Our study is a retrospective cohort study using a cohort of patients aged 65 and above admitted to the hospital from the ED from 2014 - 2020 who received a CAM-ICU or DOSS delirium screening. Data was acquired via ICTS. Our exposure is the administration of melatonin or melatonin agonist in the first 48 hours following entry into the ED. Our primary outcome is the incidence of delirium as defined by a positive DOSS or CAM-ICU delirium during an encounter. Individuals who had multiple documented visits to the ED will have their first encounter selected for inclusion. Patients who received melatonin agonist within 48 hours but screened positively before receipt are excluded from the analysis. Covariates are defined in the populations and will be balanced in analysis.

Results: Our early preliminary results contained 10,037 patients that fit into the study criteria, with 25,014 excluded due to a missing delirium screen. Among the patients that fit, 6476 (65.5%) screened positive for delirium and 3561 (35.5%) screened negative. The mean age of positive and negative patients was 79 and 74.8 years old, respectively. Both positive and negative patients were predominantly white (94.9% and 94.2%) and non-hispanic (96.8% and 97%). More females screened positively compared to males (52.5% vs 44.6%). We identified a total of 43 melatonin agonist exposures in our analysis. Positively screened individuals accounted for 12 exposures, negatively screened individuals accounted for 0 exposures, and the group missing screens accounted for 31 exposures. Covariates appear balanced between groups, but further statistical analysis was not conducted.

Discussion: Our preliminary results indicate that additional work is needed within the analysis model. Earlier work using our data set identified a far fewer number of missing screens (1104) and a positive screen percentage of 28.4%. Early subsequent analyses suggest that negative screens may have been erroneously coded as missing. Furthermore, despite the low number of melatonin agonist exposures in our analysis, 972 exposures were present in our data set. Additional work is needed to identify the cause of these missing exposures.

Pharmacological ascorbate modulates the expression of immunotherapy biomarkers in NSCLC

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Lung cancer is the leading cause of cancer-related death in the United States, accounting for more deaths annually than breast, prostate, and colorectal cancers combined. Non-small cell lung cancer (NSCLC) comprises 85% of new lung cancer cases and the 5-year overall survival is approximately 28%, primarily due to most patients presenting with advanced disease. Pharmacological ascorbate (P-AscH-), when given via intravenous infusions, can reach millimolar concentrations in plasma and has been shown to be selectively toxic to NSCLC and demonstrates low levels of toxicity to non-malignant cells. This selectivity is due to fundamental differences in oxidative metabolism between malignant and non-malignant cells. Malignant cells have both increased levels of steady-state reactive oxygen species (ROS) and an increased labile iron pool (Fe^{2+}). Oxidation of ascorbate in the presence of labile iron produces hydrogen peroxide (H_2O_2) that can further react with Fe^{+2} to produce hydroxyl radicals that cause extensive oxidative damage to DNA, proteins, and lipids. In a recently conducted clinical trial, it was shown that the addition of P-AscH- to platinum-based chemotherapy improved response in advanced stage NSCLC. Interestingly, this trial also found that treatment with P-AscH- improved progression-free survival in patients with minimal PD-L1 expression (tumor proportion score <1%), which is a known negative prognostic factor of immune-checkpoint blockade (ICB) response. This finding, in addition to ascorbate's essential role in regulating adaptive immune cell function, suggests that P-AscH- may have utility as an adjuvant to ICB. To begin investigating if P-AscH- may alter response to ICB and if it does so through an iron-dependent mechanism, we transduced Lewis lung carcinoma (LLC) cells (a mouse NSCLC line) with a doxycycline inducible system to overexpress ferritin heavy chain (FtH). Ferritin is the main protein involved in intracellular Fe storage and consists of two subunits, the light and heavy chains. FtH, unlike the light chain, has ferroxidase activity that allows for the conversion of Fe^{+2} to Fe^{+3} for incorporation into Ferritin. Since P-AscH- depends on both Fe^{+2} and Fe^{+3} to generate toxicity, sequestration of Fe in Ferritin is hypothesized to decrease the ascorbate-mediated generation of H_2O_2 and hydroxyl radicals. When FtH was overexpressed the radiation sensitivity, cell growth, and clonogenicity of LLC cells were unchanged. When LLC cells were treated with ascorbate (30 pmol/cell), the expression of pro-inflammatory cytokines CXCL9 and CXCL10 were significantly increased and the expression of the anti-inflammatory cytokine TGF-β was significantly decreased, as determined by RT-qPCR. Additionally, ascorbate treatment significantly increased the expression of cell surface markers involved in regulating the anti-tumor immune response including PD-L1, PD-1, CTLA4, and CD40; all of which have been shown to positively correlate with ICB response. Lastly, overexpression of FtH at the time of ascorbate treatment reduced the changes in gene expression observed with ascorbate treatment alone, supporting the hypothesis that these changes were partially driven by an Fe-dependent mechanism. Overall, our findings suggest that P-AscH- may be an effective adjuvant to ICB that warrants further investigation.

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Role of mediodorsal thalamic projections in temporal processing

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Parkinson's disease (PD) can present challenging cognitive symptoms that dramatically impact quality of life. Cognitive deficits are observed in the majority of PD patients but remain understudied with few treatment options. Interval timing, or the estimation of time over seconds-to-minutes, recruits multiple modalities of cognitive control such as attention and working memory. This cognitive function is vital for guiding everyday human behavior and is dysfunctional in many PD patients. Our lab has extensively studied the rodent medial prefrontal cortex (mPFC) which is crucial for normal cognitive processes in the context of interval timing. However, we have not yet studied how circuits projecting to the mPFC are involved. Mediodorsal (MD) thalamic projections to the mPFC may contribute to interval timing due to its involvement in both the basal ganglia pathway and mesocorticolimbic system, linking circuits with primary roles in movement and motivation, respectively. We will record MD thalamic neuronal ensembles to investigate how MD thalamus neurons and field potential encode time. Next, we will inactivate MD thalamic projections to the prefrontal cortex and investigate how inactivating these projections impact interval-timing behavior as well as temporal processing within the mPFC. Overall, these experiments will inform our understanding of temporal processing in MD thalamic projections to the mPFC. We will interpret these data in the context of normal cognitive control and how this circuit may contribute to cognitive symptoms in neurodegenerative disease.

Title: Bispectral EEG (BSEEG) effectively predicts delirium in older adults with low-energy femur fracture
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Mentor: Michael C. Willey, MD
Other Collaborators: Aspen Miller, BS; Elisabeth Martin, M2; Steele McCulley, M1; & Natalie Glass, PhD, MHCDS

Background: Delirium is common in elderly, hospitalized patients, especially among those who have undergone an operation, such as a hip fracture repair. Delirium has a strong association with adverse patient outcomes, including persistent cognitive decline; prolonged and subsequent hospital admissions; and higher rates of institutionalization, malnutrition, and mortality. Many screening and diagnostic tools are currently available for the early identification of delirium, but there are several challenges associated with their implementation, resulting in many cases of delirium going unnoticed. Bispectral electroencephalography (BSEEG) has the potential to be an effective, point-of-care device that can identify older adults at risk of delirium, which would allow clinicians the opportunity to prevent delirium more effectively.

Purpose: The aims of this study were to 1) validate the ability of the BSEEG to predict delirium in a high-risk patient population: patients aged ≥50 with low-energy fragility fracture(s) of the femur and 2) identify specific risk factors associated with the development of delirium after femoral fragility fracture, including physical function, body fat percentage, and malnutrition.

Methods: We prospectively enrolled adults ≥50 years old indicated for operative fixation of a low-energy femoral fragility fracture. Baseline demographics were collected including age, sex, and Charlson Comorbidity Index (CCI). Baseline cognitive function was evaluated using the Mini-Mental State Examination (MMSE). Baseline physical function and nutritional status were assessed with Patient-Reported Outcomes Measurement Information System (PROMIS) and the Mini Nutritional Assessment (MNA), respectively. Body composition was analyzed using bioelectrical impedance analysis (BIA). BSEEG was collected twice daily during hospital admission, for up to 6 days after surgical intervention. After each BSEEG recording, delirium was assessed clinically using the 3-Minute Diagnostic Interview for Confusion Assessment Method (3D-CAM). Power spectral density ratio (PSDR) was used to obtain a BSEEG score and classify subjects with or without delirium. A prediction threshold chosen in previous clinical trials was used. Descriptive characteristics were compared between delirious and non-delirious participants using t-tests and chi square tests.

Results: 63 participants (67% female) with a mean age of 76.6±9.6 years were enrolled. The incidence of delirium during hospital admission was 32%. Age, sex, and CCI scores did not differ between those with and without delirium. The performance metrics of BSEEG to detect delirium were: sensitivity, 90%; specificity, 60%; accuracy, 70%; positive predictive value, 51%; negative predictive value, 93%. Participants with delirium were more cognitively impaired at baseline (19.5±3.7 vs 24.9±3.0 MMSE points, $p<0.001$). Analysis of the MNA revealed that patients with delirium also had a higher prevalence of malnutrition at baseline (68.8% vs 48.3%, $p=0.0126$). Lastly, participants with delirium were found to have a lower body fat percentage (median value of 25.5% (IQR 29.0-21.6) vs 40.5% (IQR 49.30-33.3), $p=0.0265$). Baseline physical function did not significantly differ between groups (delirious: 36.7±6.7 vs nondelirious: 39.8±6.1, $p=0.1207$).

Conclusions: The BSEEG was shown to be an effective instrument at predicting delirium in older adults with low-energy femoral fractures. Patients who screen positive for delirium with the BSEEG should be provided with interventions to either prevent or treat their cognitive decline. However, further testing and development is required before the BSEEG can be properly implemented as a bedside tool. Factors associated with delirium include lower baseline cognitive scores, malnutrition, and low body fat. Prioritization of consistent screening for delirium in patients at highest risk could help to reduce the number of cases that go undiagnosed.

Cognitive Function in Long COVID and its Relationship with Lung Pathophysiology

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Background and Rationale: Long COVID or Post-COVID Conditions (PCC) involve new or continued symptoms lasting beyond the acute period of COVID-19 infection, with cognitive complaints and fatigue being among the most common symptoms reported. A few prior studies have examined symptoms of mood disturbance in relation to objective neuropsychological assessment with mixed results. The purpose of the current project was to characterize areas of subjective cognitive difficulty in everyday life, examine objective cognitive performance across domains, and explore the potential association between pulmonary physiology and cognition in Long-COVID. We hypothesized that patients with reduced efficiency of lung gas transfer and greater air trapping on lung CT would demonstrate higher self-reported rates of cognitive symptoms in daily life and reduced objective cognitive performance.

Methods: Participants included 46 patients (median age=48.5 yrs, 71.7% female) referred from the UIHC Long-COVID clinic for neuropsychological assessment who were participants in a local clinical research registry. Neuropsychological assessment data was integrated with medical and disease history, pulmonary function, and chest CT data. The BRIEF-A questionnaire measured subjective everyday cognitive symptoms. Normatively adjusted objective cognitive assessment scores were grouped into the following domains: perceptual reasoning, verbal comprehension, language, immediate memory, delayed memory executive function, processing speed, and attention. Impairment of subjective and objective cognitive scores was defined as ≥1.5 SD from the normative mean. The Beck Depression and Anxiety Inventories (BDI-II and BAI) were used as additional symptom measures. Pulmonary physiology measures included lung volumes (RV/TLC), diffusion capacity for carbon monoxide (DLCO), and percent of lung with gas trapping on lung CT. Associations between these pulmonary measures and cognitive scores were performed using bivariate Pearson correlations with significance set at p=.05.

Results: The Working Memory average t-score on the BRIEF-A was significantly elevated (T score=75.8), with 80.5% of participants falling in the impaired range. Group means on objective neuropsychological domain scores fell within normal limits, although 24% of patients had at least one cognitive domain fall in the impaired range. 59.1% of participants reported mild or greater depressive symptoms on the BDI-II and no significant associations were found between depressive symptoms and objective cognitive domains. There were no significant associations between RV/TLC or DLCO and objective cognitive performance. However, greater gas trapping on CT was associated with a lower perceptual reasoning domain score. There was also an association between worse performance on PFTs and higher reports of everyday cognitive difficulties on the BRIEF-A.

Conclusions: The data suggest that individuals with Long-COVID who are experiencing cognitive concerns report particular difficulty with working memory capacity in everyday life (e.g., holding information in mind to sequence steps). At the group level, participants' average cognitive domain scores were within normal limits. We observed few associations between pulmonary measures and objective neuropsychological testing. Though our small sample size limited statistical power in the current study, the results suggest that future work examining pulmonary physiology and cognition in Long-COVID is warranted.

Sociodemographic Variation in the Utilization of Minimally Invasive Surgical Approaches for Pancreatic Cancer

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Background: Minimally invasive pancreatic surgery (MIS), when selectively utilized, has been shown to hasten recovery with outcomes comparable to open approaches, but access to these techniques may not be equitable. This study explored factors associated with variation in utilization of MIS technologies for pancreatic cancer.

Methods: The National Cancer Database was queried to identify patients diagnosed with a primary pancreatic neoplasm from 2010-2020. Patients were included if diagnosed with clinical or pathologic stage 1-3 disease and received curative-intent surgery with known surgical approach data available. Multivariable analysis assessed the association between surgical approach and patient, facility, and oncologic factors.

Results: Inclusion criteria identified 73,137 patients; 51,408 underwent open surgery and 21,729 received MIS. Black race was associated with reduced odds of a MIS approach (OR 0.88; p=0.02), while older age (OR 1.17; p=0.01), later year of diagnosis (OR 1.57; p<0.001), and private insurance coverage (OR 1.30; p=0.05) were associated with increased odds. Neuroendocrine tumors (OR 1.47; p = <0.001) and body/tail tumors (OR 2.73; p = <0.001) were associated with increased odds of MIS, but tumor grade and clinical disease stage were not. When patients with adenocarcinoma were analyzed in isolation, disparities in MIS utilization persisted when controlling for disease stage, highlighting the association between sociodemographic factors and MIS.

Conclusion: Sociodemographic factors like age, race, and insurance coverage appear to vary in the utilization of MIS technologies for the treatment of pancreatic malignancy. Addressing variation with robust mixed methods approaches in future may incorporate prospective interventions and highly annotated outcomes.

Clinical Manifestations of Multiple Hereditary Exostoses: A Retrospective Study of 103 Patients in Iowa.

Authors: Jaden Troxel; Ignacio G. Fleury, M.D.; Joseph A. Buckwalter V, M.D., PhD

Abstract

BACKGROUND: Multiple Hereditary Exostoses (MHE) is an uncommon autosomal dominant disorder affecting approximately 1 in 50,000 individuals in Western populations. It is characterized by the development of benign bony tumors throughout the body called osteochondromas. These tumors typically originate from the metaphysis of long bones and cease to form with the closure of growth plates during the onset of puberty. Often, these exostoses impinge on surrounding nerves and muscles, leading to pain, functional impairment, and growth deformities. While primarily a pediatric disease, instances of adults undergoing treatment for either pre-existing or newly developed tumors are reported. MHE is recognized as a male predominant disorder, with a male-to-female ratio of 1.5:1, and various studies indicate that males generally present with more severe forms of the disease. Despite recent insights into the associated genes EXT1 and EXT2, the pathogenesis of the disease remains incompletely understood, and a definitive cure is yet to be identified. Consequently, surgical intervention and pain management represent the current standard for treatment in affected patients. While the existing literature contains numerous case studies, reviews, and treatment reports focusing on specific anatomical regions, larger retrospective studies are less common and very few studies have delved into the surgical statistics of MHE patients. In addition, there appears to be some conflicting evidence that suggests that the disease may not be as male-dominant as is generally accepted within the field. Hence, this paper aims to conduct a comprehensive retrospective review of MHE patients in Iowa, providing an in-depth analysis of the cohort's characteristics, surgical interventions, and sex differences, thereby advancing our understanding of the disease.

METHODS: This retrospective study included a cohort of patients of all ages who received treatment at the University of Iowa Hospitals and Clinics (UIHC) between June 2008 and March 2023, with a confirmed diagnosis of MHE based on ICD-10 codes and physician reports in the patient charts. The final cohort included 103 subjects after excluding three patients with localized multiple maxillary and mandibular exostoses unrelated to MHE. A manual investigation of each subject's medical chart was conducted to gather data on surgical intervention, with a focus on excision location. The analysis accounted for unilateral and bilateral procedures and subsequent interventions for the same location. Data extraction and manual chart review were utilized to collect demographic and clinical manifestation data. A one-sample z-test was used to assess differences in average height percentiles. Differences in average age between males and females were analyzed using a two-sample t-test, and differences in rates of excision between males and females were analyzed using a two-sample Poisson test.

RESULTS: The patient population consisted of 52 males and 51 females, showing no significant gender predominance in the incidence of MHE. A malignant transformation occurred in 5 individuals. The average height percentile was found to be slightly lower than the 50th percentile ($p=0.04$), and most patients had a family history of MHE (66.67%). Among the cohort, the most prevalent site of excision was the distal femur (21.01%), followed by the proximal tibia (19.33%), then the distal radius (9.24%). A total of 50 patients (48.54%) exhibited growth deformities, with knee deformities being the most common (39 patients, 37.86%). Significant differences were observed between males ($n=28$) and females ($n=27$) who underwent surgical intervention during the study. The average age of excisions for each patient was significantly higher for males (16.61 years) than females (12.48 years) (95% CI, 11.48-19.16; $p=0.03$). There was a significant difference in the rates of excisions between males and females (95% CI, 1.17-2.00; $p=0.001$), with females exhibiting a higher excision rate at a ratio of 1.53 (female/male). When considering specific excision sites, females showed a significantly higher excision rate at the foot/ankle (95% CI, 1.30-7.01; $p=0.038$) and the hand/wrist (95% CI, 1.29-4.77; $p=0.029$).

CONCLUSION: In contrast to prior reports of male predominance, we observed an equal distribution of males and females within the cohort of MHE patients. The prevalence of smaller height percentiles, malignant transformations, and family history were consistent with existing literature. The most common areas of excision were the distal femur and proximal tibia, corresponding to the regions with the highest prevalence of growth deformities. Males exhibited a higher average age of excisions compared to females, potentially attributed to the later closure of growth plates and subsequent development of exostoses at older ages. Females overall had a significantly higher excision rate, particularly at the foot/ankle and hand/wrist regions. Prior research claims that males have a higher lesion burden than females and that there is a positive correlation between lesion burden and surgical intervention. Our paper is the first to show that females have a significantly greater number of surgical interventions which diverges from previously established ideas. This suggests a greater complexity regarding sex differences within the disease and highlights a need for further investigation in this area.

Title: Similarities of FOXP2 Expression in the Brainstem of Rodents, Rhesus Monkeys, and Humans
Student: Eric Vallin
Mentor: Matthew Hoffman

ABSTRACT

Background: The Forkhead Box P2 gene encodes FOXP2, a transcription factor responsible for the development of neural structures involved in speech/language. Animal models have proven critical in the study of FOXP2 gene expression, though a lack emphasis on brainstem structures is noted. This study evaluates expression of FOXP2 within the brainstem of the rat, rhesus monkey, and human.

Methods: Brainstems of 2 rats, 1 rhesus monkey, and 1 human were harvested. Immunohistochemistry (IHC) for FOXP2 was performed followed by imaging and centroid analysis to identify regions of expression within the brainstem across the three species. Images of brainstem sections were examined with a Nikon Eclipse 80i microscope in conjunction with Neurolucida version 8 software to display FOXP2 expression in the 3-dimensional brainstem landscape in monkeys and rodents. Slices chosen for centroid analysis in all species contained the dorsal medulla along the floor of the 4th ventricle as well as the dorsal and dorsolateral pons in humans, areas which may play a role in FOXP2-related dyspraxia.

Results: Similarities in FOXP2-positive cell and centroid pattern across species were noted. A column-like, fingertip pattern which splits in the rostral centroids and reconvenes in the caudal medulla was found in all species. Similar centroid shape, column, and row patterning was observed with medial densities towards the caudal brainstem were identified in all species. Neural structures crucial for speech exhibited strong FOXP2 staining, encompassing the gigantocellular (Gi), parvocellular (PcR), and intermediate medullary nuclei (MdRt) nuclei as well as medullary and pontine respiratory columns.

Conclusions: Respiratory pattern generators in the dorsolateral pons and medulla which house critical pre-motor neurons for language generation show similar FOXP2 expression across the rat, rhesus monkey, and human. As FOXP2 expression is conserved across multiple species, animal models may be valuable resources in studying FOXP2-related disorders including dyspraxia.

Understanding the Role of EMT in Local Recurrence in Oral Cavity Squamous Cell Carcinoma

Mentee: Steven Van Meeteren
Mentor: Dr. Marisa Buchakjian

Background: The single greatest predictor of oral cavity squamous cell carcinoma (OCSCC) is a positive margin on the resection specimen. However, surprisingly, the risk of local recurrence does not significantly decrease with more surgery (6). This suggests that there is likely an underlying biologic cause for local recurrence in some settings – that recurrent OCSCC cancer cells have different baseline characteristics than nonrecurrent cells, resulting in unexpected positive margins, local recurrence, and overall more aggressive behavior and poor prognosis. Given that metastatic cancer cells undergo an epithelial-mesenchymal transition EMT, one way to characterize recurrent OCSCC cancer cells might be by their epithelial-mesenchymal properties. Better understanding of the epithelial-mesenchymal properties of OCSCC cancer cells could help predict prognosis and local recurrence.

Aims: The primary goal of the project was to identify differences in enzyme expression, metabolites, nutrient requirements, and ultimately the utilization of metabolic pathways between epithelial-like and mesenchymal-like OCSCC cells.

Materials and Methods: Prior to my SRF, the Buchakjian lab successfully sorted SCC9, a tongue squamous cell carcinoma line, into two non-fluctuating populations: SCC9E (epithelial) and SCC9M (mesenchymal). First, I used western blot technique to assay and compare the presence of enzymes between SCCE and SCC9M. Enzymes I assayed for included glucose-6-phosphate dehydrogenase (G6PD), fatty acid synthase (FASN), and pyruvate kinase 1 (PKM1). Additionally, I analyzed metabolomics data the lab had using MetaboAnalyst, identifying differences in metabolite concentrations between the two populations. Finally, I ran nutrient deprivation studies and drug treatment studies on the two populations, measuring their absorbance with a microplate reader at both 24 hours and at 48 hours. The drugs treatments were C75 and etomoxir.

Results: Our western blots demonstrated that the SCC9E population's lysate consistently had stronger staining of FASN than SCC9M. Conversely, the SCC9M population's lysate consistently had stronger staining of G6PD. The staining for PKM1 was not noticeably different between the two populations. Second, the metabolomics data showed that glycolysis and nucleic acid intermediates such as fructose 6-phosphate, glucose 6-phosphate, XMP, and hypoxanthine had more than two-fold greater concentrations in SCC9E than in SCC9M. Conversely, the data also showed that fatty acid intermediates, such as palmitate and malonate, were more concentrated in SCC9M than in SCC9E. Finally, the nutrient deprivation studies demonstrated that hypoxic conditions and treatment with C75 decreased the growth of SCC9E far more than SCC9M.

Conclusion: Using the Buchakjian lab's two non-fluctuating populations, SCC9E and SCC9M, I was able to identify differences in enzyme expression, metabolites, and nutrient requirements between the two populations. The western blots suggest that SCC9E synthesizes more fatty acids than SCC9M and that SCC9M utilizes the pentose phosphate pathway more than SCC9E. This is consistent with our nutrient deprivation and drug treatment results. Hypoxic conditions cause an increase in reactive oxygen species, which require reducing agents produced by the PPP to be reduced, and C75 is a fatty acid synthase inhibitor. While the metabolite data is interesting and worth consideration, it is the least indicative as to what metabolic pathways are being utilizes because the concentration of metabolites does not indicate anything regarding the flux of metabolic pathways. Nevertheless, I think it is noteworthy that the low concentration of fatty acid intermediates in SCC9E and low concentration of glycolysis intermediates is consistent with our conclusion.

DAIR for Periprosthetic Joint Infection in Primary versus Revision Knee Arthroplasty – A Comparison in Survival Rate

Matthew Van Engen, Christopher Carender, Natalie Glass, Nicolas Noiseux

Introduction: There is active debate regarding the effectiveness of Irrigation and Debridement, Antibiotic therapy, and component Retention (DAIR) as a treatment for acute periprosthetic joint infection (PJI) in total knee arthroplasty (TKA). Variable results have been published regarding the rate of infection eradication in addition to specific indications for DAIR to maximize success.

Objective: The purpose of this analysis was to evaluate DAIR's utility while considering the history of a primary TKA (pTKA) or revision TKA (rTKA) in place at the time of the index DAIR procedure. We hypothesized pTKAs that underwent DAIR would have a higher survival rate in comparison to revision cases.

Methods: A retrospective review of patients who underwent DAIR for treatment of acute PJI at the University of Iowa from 2008-2020 was performed. Patients met inclusion criteria if they underwent irrigation and debridement with polyethylene exchange along with chronic antibiotic therapy for treatment of an acutely infected total knee arthroplasty TKA. Chart review was further completed to separate patients as having a pTKA or rTKA in place at the time of the index DAIR procedure. Kaplan Meier survival analysis were performed. Failure was defined as a subsequent procedure performed for infection management.

Results: In total, 244 DAIR cases were reviewed. One hundred ninety-one of the index DAIR cases were performed in a pTKA while the additional 53 DAIR cases were in a knee with an existing rTKA. Median follow up time for the DAIR cases in the pTKA group was 4.4 years in comparison to 1.7 years for cases in rTKAs ($p=0.0046$). The rate of survival at 5 years in the pTKA group was 79.6% versus 56.6% in the rTKA cohort ($p=0.0005$). No significance in survival rate was found between acute post-operative versus acute hematogenous cases in either the pTKA (84% vs 79%, $p=0.604$) or rTKA (66% vs 54% $p=0.47$) cohorts.

Conclusion: Our data demonstrates a significantly decreased rate of survival in rTKA (56.6%) in comparison to pTKA (79.6%) irrespective of acute post operative or acute hematogenous classification. This difference of greater than 20% success rate may suggest DAIR has a more limited role as a treatment option for acute PJI in existing rTKA. Further investigation is warranted to identify individual factors which may be predisposing to the increased failure rates of rTKA specifically.

Title: Ultrasonic Fasciotomy for the Treatment of Refractory Plantar Fasciopathy- A Prospective Study
Student: Elena Volfsen
Mentor: Ryan Kruse

Background: Plantar fasciopathy is a chronic, degenerative condition affecting approximately 10% of the US population. Historically, patients with symptoms refractory to conservative treatments such as physical therapy and nonsteroidal anti-inflammatory medications were left with surgical intervention as their only remaining option. A newer, microinvasive procedure called an ultrasonic tenotomy/fasciotomy provides a safe and effective treatment option for these patients. However, the current literature is limited to case reports, case series, and small prospective studies.

Hypothesis: We hypothesized that an ultrasonic tenotomy/fasciotomy for chronic plantar fasciopathy would be a safe and effective treatment of plantar fasciopathy, with continued symptom improvement and high patient satisfaction up to 1 year post-procedure.

Study Design: Prospective cohort study

Methods: The primary outcomes were the change in Visual Analog Score (VAS) at 2, 6, 12, and 52 weeks as well as the Foot and Ankle Ability Measure (FAAM) and Patient Reported Outcome Measurement Information System (PROMIS) Physical Function Scores at 6, 12, and 52 weeks post-procedure compared to pre-procedure baseline. The secondary outcome measure was the patients' self-reported satisfaction with the procedure at 12 and 52 weeks post-procedure.

Results: 67 patients (59 female, 8 male) were included. There was a significant improvement in VAS and FAAM at all follow up time points, with an average overall improvement in VAS of 5.87. There was a significant improvement in PROMIS scores at 12 and 52 weeks but not at 6 weeks. 94% of patients reported satisfaction with the outcomes of their procedure at 12 and 52 weeks. No procedural complications were seen.

Conclusion: This prospective cohort study demonstrates that ultrasonic tenotomy/fasciotomy is a safe and effective treatment option for chronic plantar fasciopathy, producing both high patient satisfaction and sustained symptom improvement up to 52 weeks. Showing significant improvements in functional measures and pain scores, along with a lack of complications in the procedure, ultrasonic tenotomy/fasciotomy presents as a promising alternative for patients who are refractory to conservative therapies.

Comparison of Surgical Success Between Novel Prolapse Phenotypes

Student: Katie Weston, M2, Mentor: Joseph Kowalski, MD
Collaborators: Patrick Ten Eyck, PhD, Linder Wendt, MS

Introduction

Pelvic organ prolapse (POP) is a common condition in which the vaginal walls lose support and create a feeling of vaginal bulging. Since 1996, the Pelvic Organ Prolapse Quantification (POP-Q) system has been the accepted standard for describing POP. While the POP-Q system has greatly advanced understanding of POP and the ability to perform research, the staging system associated with the POP-Q has significant limitations.

Hypothesis/Purpose

We propose a novel classification system based on the POP-Q measurements that categorizes prolapse into potentially clinically meaningful "phenotypes". Given that varying prolapse subtypes (i.e., advanced anterior vaginal wall prolapse with apical prolapse as compared to isolated apical prolapse with preserved anterior and posterior vaginal wall support) may have heterogenous underlying pathophysiology, we hypothesized that the novel phenotypes may also have varying risk of recurrence after surgical treatment. Our primary aim was to determine the association between the POP phenotypes and the incidence of POP recurrence (bulge symptoms) twelve months following POP surgery. Secondary aims were to determine the association between the phenotypes and (1) anatomic recurrence, (2) POP recurrence following sacrospinous ligament fixation compared to uterosacral ligament fixation and (3) the incidence of new or worsened stress urinary incontinence (SUI) following POP surgery.

Methods

This was a secondary analysis of three trials previously evaluating various POP surgeries (OPTIMAL, OPUS, and SUPER trials). Participants from these trials who had a uterosacral ligament suspension (USLS) or sacrospinous ligament fixation (SSLF) were included and classified into one of seven phenotypes (isolated anterior wall, isolated posterior wall, isolated apical, anterior and posterior wall, anterior-predominant with apical, posterior-predominant with apical or anterior and posterior with apical). POP recurrence was defined as a response of yes to question 3 of the Pelvic Floor Distress Inventory (PDFI-20). Anatomic recurrence was defined as any prolapse beyond the hymen. New or worsened SUI was defined by question 17 of the PFDI-20. Demographics, relevant medical history, surgical history, and surgery details were compared between groups with appropriate statistical tests such as student's t-test and chi-square test. Primary and secondary outcomes were evaluated with univariate logistic regression. Multivariate models were fit using the best performing predictors for each outcome. Fisher's exact test was used to evaluate certain phenotypes with relatively low percentages of subjects.

Results

Of the 575 subjects available for inclusion, one was excluded who did not meet any phenotype definition of POP at baseline. 173 (30.1%) underwent SSLF and 401 (69.9%) USLS. Most (n=402, 70.0%) subjects were defined as having anterior-predominant with apical prolapse. 90 (15.7%) had anterior and posterior with apical, and 36 (6.3%) had isolated apical POP. The remaining 46 (8.0%) comprised the other 4 phenotypes. All comparisons were made to the anterior-predominant with apical prolapse phenotype since that was the largest group. With univariate logistic regression, only the anterior and posterior wall phenotype was significantly associated with POP recurrence (OR[95%CI] 7.55[0.89-64.2], p=0.046). However, this phenotype only had 4 subjects in total and was not significant in the multivariate model. Only smoking status (0.51[0.26-0.93], p=0.036) was significantly associated with POP recurrence in the multivariate model. Using Fisher's exact, the 36 subjects in the isolated apical phenotype had 0% recurrence (p=0.02). No significant associations were found between phenotypes and anatomic recurrence. However, the isolated apical phenotype was approaching-significance (0.28[0.05-0.96], p=0.089). POP-Q point Ba (1.32[1.20-1.46], p<0.01), private insurance (0.62[0.39-0.99], p=.047) and total vaginal length (0.81[0.66-1.00], p=0.049) were significant in the multivariate model. Similarly, no significant associations were found between phenotypes and new or worsened SUI. In the multivariate model, only genital hiatus remained significantly associated with SUI (1.37[1.02-1.83], p=.032).

Conclusions

We found that isolated apical prolapse is associated with less symptomatic POP recurrence than anterior-predominant and apical POP. Overall, our ability to draw conclusions about other prolapse phenotypes was limited by the relatively low numbers of phenotypes other than anterior-predominant and apical POP.

Investigating the Electrical Properties of a Zwitterionic Hydrogel Applied to Cochlear Implants

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Introduction

Permanently implantable devices are gaining popularity and are being utilized in a broad array of medical fields. While these devices are diverse in function, there is a common limitation found in many of them: the body's immune response to the foreign object. In the case of cochlear implants, the protein debris, fibrosis, and scar tissue encapsulate the implant and hinders its performance. In the presence of a fibrotic capsule, the impedance of the electrical stimulus is increased, dispersing the transfer of charge and reducing the specificity of neurons that are stimulated. Additionally, due to this increased electrical impedance, cochlear implants require a high amount of energy to function, and users are typically required to replenish the battery regularly. Recently, the application of a zwitterionic hydrogel coating has been shown to reduce the foreign body response. While the zwitterionic hydrogel's antifouling properties are beneficial to the performance and longevity of the implants, the hydrogel coating's effect on the electrical performance of the cochlear implant is not well understood. In order to optimize the electrical performance of cochlear implants coated with the zwitterionic hydrogel, we first need to understand the electrical properties of the hydrogel.

Purpose

The main objective of this study is to design a reliable method of assessing the electrical properties of the zwitterionic hydrogel, and to subsequently characterize these properties.

Methods

Our current method of assessing the electrical properties of the hydrogel centers around the use of a conductivity probe. We first create a monomer solution consisting of water, Irgacure, [2-(Methacryloyloxy)ethyl]dimethyl-(3-sulfopropyl)ammonium hydroxide (SBMA), and polyethylene glycol dimethacrylate (PEGDMA). We pipette 0.2 mL of this monomer solution onto the surface of the conductivity probe in a way that covers the electrode. The probe with the solution is then polymerized under UV light, yielding a hydrogel that is 400 micrometers thick. The probe coated with the hydrogel is then submerged into artificial perilymph for 20 hours, and conductivity and temperature measurements are automatically collected every hour for those 20 hours. In order to compare the conductivity measurements of the hydrogel to the conductivity of artificial perilymph by itself, we submerged an uncoated probe into artificial perilymph to measure its conductivity.

Results

The conductivity of artificial perilymph is 14.25 mS/cm at 20.4 °C, and in two trials the conductivity of the hydrogel in artificial perilymph has been 11.75 mS/cm and 11.98 mS/cm at 20.4 °C.

Conclusion

While we have developed a reliable and repeatable method of assessing the electrical properties of the hydrogel, the data collection phase has just begun. Early data show that the hydrogel soaked in artificial perilymph has a lower conductivity compared to artificial perilymph by itself. However, there is still much left to investigate. In the future, we will examine the conductivity of hydrogels of different properties, including different thickness and cross-link density. Additionally, we will compare the conductivities of zwitterionic versus non-zwitterionic hydrogels. Eventually, we plan to investigate possible additives and topographic changes that could provide a conductive advantage to the hydrogel, while also assessing how these changes affect the biological antifouling properties of the zwitterionic hydrogel. While we believe that our findings will be helpful in creating a hydrogel that maximizes the performance of cochlear implants, we also hope that our findings will have applications relevant to implantable devices elsewhere in the body as well.

SARS-CoV-2 Seropositivity Among Healthcare Professionals in a Rural State

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Background: Early in the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, healthcare professionals (HCP) were at risk of being exposed to the virus given the limited supply of personal protective equipment. In 2020 and 2021, numerous groups assessed seropositivity rates and risk factors associated with seroconversion among HCP. However, the results of published studies conflicted, and few studies assessed seropositivity rates among HCP in rural areas, as well as change in antibody titers over time. In addition, there are many cross-sectional surveys that evaluate healthcare professionals' knowledge and perceptions surrounding COVID-19, but prospective cohort studies are needed to analyze how viewpoints changed with the introduction of new variants and preventive measures.

Purpose: To address these gaps, the UIHC Healthcare Worker Serosurvey Study followed a cohort of 302 UIHC employees, with and without a history of COVID-19 at baseline, for one year. My project will identify healthcare professionals at an academic health center in a rural state who seroconverted, distinguish risk factors associated with seroconversion, and evaluate HCP perceptions towards COVID-19.

Methods: Healthcare professionals who were at least 18 years old were invited to complete a screening survey. All respondents who reported having COVID-19 were invited to participate; additional participants were selected randomly from the remaining respondents. Participants (n=302) completed surveys and provided blood samples at 3-month intervals (T0, T3, T6, T9). The laboratory used the Roche and Diasorin SARS-CoV-2 assays. We conducted a factor analysis to assess factors associated with seropositivity at baseline. To evaluate risk factors for SARS-CoV-2 seropositivity over the entire study period, we used generalized linear mixed models. The model selection process used Bayesian information criterion in a forward selection process, where time in months was assumed to be in the model and 18 pre-determined clinically meaningful variables (CMV) were used to build the final model.

Results: At T0, 86/302 (28.4%) HCP were seropositive. Of the seronegative HCP, 6/198 (3.0%), 6/183 (3.3%), 14/180 (7.8%) had seroconverted at T3, T6, and T9 respectively. Twenty one of 26 (80.8%) seroconversions occurred during the Omicron surge. Baseline model selection identified nurses, nursing assistants, and being within 6 feet of someone outside of work who did not live in their house as risk factors for seropositivity. Vaccination was a strong protective factor. After model selection for the entire study period, the study timepoint, having children in the household, and having been vaccinated stayed in the model.

Conclusion: This study investigated the risk of COVID-19 seropositivity among HCP at an academic healthcare center in a rural state over an approximately 19-month period. The study population primarily consisted of direct patient care givers who were 30-44 years old and white female nurses or nursing assistants. In addition to studying a population of HCP that had not been previously studied, factor analysis assessed risk factors for seropositivity at baseline and the entire study period. This approach allowed us to develop participant profiles that demonstrated the need for multiple basic public health and infection prevention measures to significantly decrease the risk of infection. Furthermore, these results support the public health and infection prevention measures that were implemented early in the pandemic.

Course of Carpal Tunnel Syndrome Management in Diabetic Patients

Sophia Xiao
Mentors: Dr. Joseph Buckwalter V, MD, PhD; Dr. Ignacio Garcia Fleury, MD; Dr. Natalie Glass, PhD, MHCDS

Introduction: Carpal Tunnel Syndrome (CTS) is the most prevalent compressive neuropathy, primarily resulting from external compression on the median nerve at the wrist. Its severity can intensify due to microvascular changes seen in diabetic neuropathy. Although diabetes mellitus (DM) patients experience a heightened risk of CTS, they are frequently underdiagnosed and undertreated. Carpal tunnel release (CTR) is a widely used treatment, yet DM patients often have suboptimal recovery post-CTR. This study aims to map the progression to CTS diagnosis and subsequent CTR in DM patients, eyeing better early detection and CTS prevention.

Methods: Data was extracted from 4,822 patient encounters with both CTS and DM from 2009-2022. Of these, 1,420 underwent CTR, which further narrowed to 304 patients (446 limbs) after filtering for DM diagnosis. Variables like age, HbA1c, and BMI were tracked. Analyses were conducted using SAS v9.4. For those undergoing bilateral CTR, only the initial CTR per limb was included. Time between CTS diagnosis to CTR was compared between patients diagnosed with DM prior to vs. after CTS using Wilcoxon rank sum tests. Spearman correlation examined relationships between age or A1c at diagnosis and the timeline between CTS to CTR or DM to CTS.

Results: 51% (n=154) of patients received a DM diagnosis post their CTS identification. Length of time between diagnoses was similar in patients diagnosed with DM after (24.3 (9.9 - 46.2) months) versus before (24.6 (8.0 - 41.8) months) CTS diagnosis ($p=0.604$). From CTS diagnosis to first CTR, the median time difference was 2.5 months (1.0 - 8.1) in all patients. This did not significantly differ by timing of DM diagnosis (before: 2.57 vs after: 2.20 months, $p=0.188$). There were small correlations between time from CTS to CTR and age ($rho=-0.24$, $p<0.001$) and A1c ($rho=-0.15$, $p=0.002$) at time of CTS diagnosis. No significant associations were observed with age and A1c at DM diagnosis (age: $rho=0.03$, $p=0.660$, A1c: $rho=0.00$, $p=1.00$).

Discussion: The revelation that over half of CTR patients were diagnosed with DM post their CTS detection underscores the urgency for a protocol that assesses newly diagnosed DM patients for CTS symptoms, ensuring timely interventions, promoting nerve recovery, and enhancing patient well-being. Future research should pivot to early CTS signs and the optimal timing for surgical interventions.

Title: Recognizing Rural Healthcare Disparities in Pain Assessment for Autoimmune Rheumatologic Diseases
Authors: Lydia Yang, M3; Bharat Kumar MD, MME
Keywords: Disparities, Access to Care, Disability, Pain, Quality of Care

Background/Purpose:
Pain is a common complaint seen in many autoimmune rheumatologic conditions, along with decreased function and decreased sense of well-being. Pain is a highly person-specific symptom without well-validated biomarkers, making it difficult to assess and use as a standardized metric in guiding immune modulatory therapy. Multiple lines of evidence suggest that rural-dwelling patients may conceptualize and relay pain differently than non-rural-dwelling patients, which may complicate the delivery of optimal care and further healthcare disparities. We aim to correlate rural-dwelling status with self-reported levels of pain, function, and sense of well-being in patients with autoimmune rheumatologic diseases. We additionally aim to determine if there is a statistically significant difference in functional activity, pain levels, and sense of well-being between rural-dwelling patients and non-rural-dwelling patients.

Methods:
We correlate rurality with elements of the RAPID-3 form. Rurality is determined by RUC (Rural-Urban Commuting) Codes based on the patient's home address. Using RUC, patients were classified into four categories: (1) urban, (2) large rural town, (3) small rural town, and (4) isolated small rural town. The RAPID-3 is a validated questionnaire consisting of three parts: (1) functional status, (2) pain level, and (3) global well-being. All items are self-reported by patients.

Results:
Among the 265 rheumatology patients seen between May 1, 2022, to November 1, 2022, 110 were urban-dwelling and 155 were rural-dwelling (large [82], small [27], or isolated [46]). Percentages of self-reported gender and ethnicity/race (Non-Hispanic White, Hispanic, Black) were comparable as well as average age. Isolated rural-dwelling patients had the highest degree of dysfunction (13.76/20) and sense of poor well-being (5.27/10) compared to small rural-dwelling patients (6.44/20 and 3.89/10, respectively), who had the lowest degree of dysfunction and poor sense of well-being, and urban-dwelling patients (7.07/20 and 4.31/10, respectively) [p-value<0.01). In contrast, dwellers of large rural towns report the highest levels of pain (4.84/10) compared to those in isolated rural communities, who had the lowest (4.16/10). However, differences in levels of pain were not statistically significant.

Conclusion:
There exist healthcare disparities in measuring pain, dysfunction, and sense of well-being among rural-dwelling patients with autoimmune rheumatologic diseases. Those that live in isolated rural communities tend to report lower amounts of pain despite having higher levels of poor well-being and dysfunction, compared to those living in larger rural and urban settings. This finding has important implications for 'treat-to-target' strategies, which may systematically underestimate the burden of pain in patients living in isolated rural communities. Recalibration of setpoints defining remission and the development of new instruments that account for this disparity may be productive approaches to address this issue.

Title: The Impact of 3D Printed vs 3D Virtual Congenital Heart Models on Patient and Family Knowledge

Presenting Author: Luke Zerwic

Mentor: Ravi Ashwath MD

Co-authors: Connor Byeman BS (M4), Ashray Mohan BS, MS (M3)

Background:

Pediatric patients and families face difficulties in grasping the intricacies of heart defects. Conventional 2D images fail to capture the complexities of these conditions. This study compared the effectiveness of 2D imaging with 3D virtual and 3D printed models in enhancing patient and family knowledge and ascertained their preferences.

Hypothesis: 3D heart models improve knowledge regarding the anatomy of congenital heart disease and normal heart anatomy compared to traditional 2D imaging. 3D virtual models lead to similar if not increased performance compared to 3D printed models.

Methods:
Family members of children with cyanotic heart defects were recruited, as well as patients aged over 15 years. Participants were presented with an echocardiogram illustrating the specific heart defect. To compare the effectiveness of different educational approaches, the subjects were then randomly divided into two groups. One group received a 3D printed model representing their unique heart defect, while the other group received a 3D virtual model. A questionnaire focused on knowledge of anatomy and congenital defects was administered: once after reviewing the echocardiogram and another following the examination of the 3D models. Additionally, participants' preferred method of education was assessed.

Results:

A total of 109 participants took part in the study, representing 73 individual patients. Subjects were more likely to rate themselves as understanding the cardiac condition ($p<.01$) and were more knowledgeable of normal cardiac anatomy ($p<.01$) after viewing either of the 3D images than after the 2D images. There was no difference between 3D groups on either subject's perceived understanding or knowledge of the cardiac condition. Initially, 74% of subjects reported the 2D images were very or extremely helpful, after viewing the 3D images, 93% found them very or extremely helpful.

Conclusions:

Most subjects displayed a distinct preference for the 3D models over the traditional 2D models, and they displayed a greater understanding. However, there was no significant difference in preference or knowledge between the 3D printed and 3D virtual model. Going forward, 3D models should be used in education of patients with congenital heart disease.

Title: Retroclival epidural hematoma in 7-year-old female after motor vehicle accident

Authors: Jimmy Zhang, Dr. Yutaka Sato, Dr. Mikhael G. Sebaaly, Dr. Lillian M. Lai

Introduction:

Pediatric retroclival epidural hematoma (REH) is hemorrhage confined between the clival periosteum and dura of the brain. Though a rare diagnosis, retroclival hematomas (RH) are more frequent in pediatrics than adults probably because of a larger head-body ratios alongside weaker muscles and ligaments; these make children more susceptible to shearing forces from high-energy impacts. Bleeding may come from the retroclival basilar venous network. Other RH subtypes include retroclival subdural hematomas and more rarely retroclival subarachnoid hematomas.

REH is a localized hematoma in the potential space created by the tectorial membrane (TM). There is most commonly stripping of the TM, lifting off the posterior clivus. Other co-ligamentous injuries include the anterior atlantooccipital membrane, apical, interspinous, and transverse ligaments. CT and MR imaging are critical for REH diagnoses as many pediatric patients are unable to verbalize symptoms. REH and other RH subtypes are most commonly associated with MVAs and then other traumatic brain injuries, including abusive head trauma. In adults, REH has been linked to clival fracture, but has not yet been reported in children.

Purpose:

For radiologists, this case adds to the limited literature and raises awareness for being aware of retroclival hematomas, especially where pediatric head and neck injuries are involved. Obtaining a cervical MRI alongside directed attention to the craniocervical junction will reduce missed injuries like retroclival hematomas.

Method:

After initial patient hospitalization, head and neck CT with soft tissue windowing of retroclival space led to further analysis with high resolution T1 and T2 MRI scanning. Written informed patient consent for educational use has been obtained.

Findings/Results:

Clinically, RH may also lead to brainstem compression, which may impact CN VI's course through Dorello's canal, causing CN VI palsy. After initial hospitalization, head and neck CT with soft tissue windowing of retroclival space in Figures 1-3 shows hyperdense hematoma formation in axial and sagittal orientations. Figure 3 further shows that the hematoma is limited to C2, indicating the possibility of retroclival epidural hematoma (REH). Figures 4-6 use MR to help confirm our diagnosis with clear views of an 8.8 mm thick REH in the prepontine space. Figure 5, in particular, demonstrates stripping of the thin tectorial membrane posterior to the REH. T2 hyperintense signal near the ligaments at C1 and C2 also indicates ligamentous injury. The hyperintense T2 signal in Figure 7 between C1 and C2 reflects transverse ligament of atlas rupture since it usually helps anchor dens to C1. Diagnosis of REH seen in Figure 8a warranted a cervical neck brace for management. 1.5 months later another axial MR shown in Figure 8b shows REH resolution.

Conclusion:

In this case, imaging prompted conservative treatment by cervical collar for ~ 3 weeks. Our patient used an eyepatch for CN VI palsy, with overall improvement in symptoms. The REH resolved 1.5 months post incident. However, there are no overall specific pediatric guidelines for treating REH. Treatment depends on the etiology, but in trauma settings, conservative treatment with a neck brace is first line therapy. However, in cases of brainstem or CN compression, surgical evacuation of the hematoma may be indicated. Stabilization of the craniocervical junction may also be needed given osseous injuries like clival or dens fractures.

REHs can be missed on initial CT due to posterior fossa beam-hardening artifacts and difficulty recognizing hematomas. Soft tissue windowing and attention to sagittal views on non-contrast CTs facilitate REH detection. C-spine MRI, including high resolution T2, is the modality of choice to diagnose both craniocervical junction ligamentous injury and RHs. This case adds to the growing awareness for radiologists to not forget the possibility of retroclival hematoma diagnoses.

A neural pathway for auditory stress

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The parabrachial region of the brainstem modulates behavior in response to sensory information. Neurons in this region have a diverse set of output connections and functions that can be differentiated based on their molecular identities. Transcription factors *Atoh1* and *Lmx1* delineate two macropopulations of parabrachial neurons which can be further divided into subpopulations. One subpopulation of neurons within the *Atoh1* macropopulation expresses the *Nps* gene. Prior pharmacological and genetic association studies have implicated neuropeptide S (NPS) and its receptor (NPSR1) in sleep/panic disorders, but the function of parabrachial *Nps*-expressing neurons remains unclear. Previously, we traced the output projections of these neurons and found they target brain regions responsible for modulating circadian behavior and threat response. However, the activity pattern and inputs to these neurons remain unknown. Here we map the inputs of these neurons and identify a possible role in auditory stress. Using Cre-dependent rabies retrograde tracing, we identify brain regions that send input to *Nps*-expressing neurons in the rostral parabrachial nucleus. Unlike any other neuron population in the parabrachial nucleus, Nps-expressing neurons receive input from auditory brainstem nuclei, and we found that audiogenic stress elevated c-Fos expression in these neurons. While most other neurons in the parabrachial nucleus relay interoceptive information, our findings suggest that NPS neurons play a role in auditory stress.