Abstracts

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SEMIAUTOMATIC AREA ANALYSYS OF THE DISTAL TIBIOFIBULAR SYNDESMOTIC INCISURA IN SUBTLE CHRONIC SYNDESMOTIC INSTABILITY. A PROSPECTIVE WEIGHTBEARING CT CASE-CONTROL STUDY.

Authors
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Background
Distal Tibiofibular Syndesmotic Instability (DTFSI) is usually caused by external rotation stress trauma to the foot and ankle, frequently as the result of an ankle sprain or fracture. Different biomechanical studies have demonstrated the devastating potential results of residual syndesmotic instability in the ankle joint, with ensuing progressive arthritic degeneration. The diagnosis of major DTFSI injuries is usually straightforward, with classical radiographic signs of increased space between the distal tibia and fibula (tibiofibular clear space), as well as possible widening of the space between medial malleolus and talus (medial clear space). However, diagnosis of subtle DTFSI remains a challenge, with high prevalence of false-negative results using conventional non-invasive clinical-radiographical diagnostic tools. Surgical arthroscopic assessment remains the gold-standard diagnostic method for subtle DTFSI. Recently, Weightbearing Computed-Tomography (WBCT) has emerged as a possible dynamic non-invasive alternative diagnostic option, with proved high diagnostic accuracy for syndesmotic incisura area measurements in the setting of major DTFSI. However, its role in diagnosing subtle injuries remains unknown.

Purpose of the Study
The aim of our study was to assess the accuracy of WBCT syndesmotic incisura area measurements in diagnosing subtle chronic DTFSI in patients with confirmed instability using the gold-standard arthroscopic assessment. Our hypothesis was that when compared to the contralateral uninjured control side, WBCT syndesmotic incisura area measurements would be significantly increased in the injured extremity of patients with arthroscopically positive DTFSI.

Methods
In this prospective diagnostic IRB-approved case-control study, patients with suspected unilateral chronic subtle DTFSI underwent bilateral standing weightbearing CT (WBCT) examination before being indicated for surgical treatment. All patients underwent surgical treatment with gold-standard arthroscopic assessment for DTFSI, using the introduction of a 3mm diameter arthroscopic sphere into the syndesmotic incisura as diagnostic for DTFSI. The syndesmotic incisura area (mm^2) was measured 10mm proximally to the apex of the distal tibia articular dome, using a semiautomatic measurement algorithm (Syndesmetrics®). The anterior and posterior borders of the syndesmotic incisura was marked by two tangent lines to the anterior and posterior borders of the distal tibia and fibula. Once the borders were marked, the incisura area was automatically calculated by the software based on a Hounsfield units (HU) contrast algorithm (Figure 1). For the calculation, a HU threshold of 200HU was utilized. Measurements were done independently by two fellowship-trained orthopedic foot and ankle surgeons. Normality of the measured syndesmotic area values was assessed using the Shapiro-Wilk Test. Comparisons between injured and control ankles were made using Student T-test or Wilcoxon, according to the normality pattern of the data. Interobserver reliability of the measurements was assessed with the Intraclass Correlation Coefficient (ICC). P-values of less than 0.05 were considered significant.

Results
A total of 10 patients with arthroscopically confirmed DTFSI were included in the study DTFSI (7 females/3males; mean BMI 31.7 kg/m^2, +/- 10.1 kg/m^2). Interobserver reliability of the syndesmotic incisura area measurements was excellent (ICC = 0.98). A parallelism plot of interobserver reliability between the two readers is presented in Figure 2. The average syndesmotic area and 95% Confidence interval (CI) for injured ankles was 87.4mm^2 (95% CI, 77.1 to 97.8mm^2) and 74.7 mm^2 (95% CI, 64.4 to 85.1mm^2) for uninjured control ankles (Figure 3), with a mean difference of 12.7mm^2 that was not statistically significant (p=0.087).

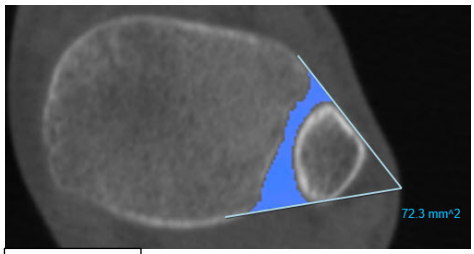

Figure 1

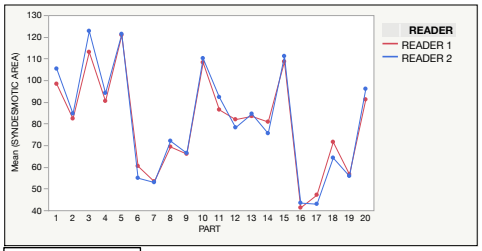

Figure 2

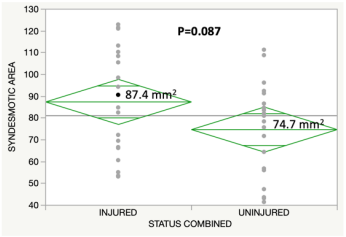

Figure 3

Conclusion
In this diagnostic prospective case-control study, we assessed the accuracy of semiautomatic WBCT syndesmotic incisura area measurements in diagnosing subtle chronic DTFSI. We found a trend toward increased syndesmotic area in injured ankles when compared to non-injured control ankles, with a mean difference of 12.7 mm^2. However, the difference was not statistically significant. Although this negative result can probably be related to the small sample size and lack of adequate power to demonstrate a possible real difference between the measurements, it also demonstrates how challenging it is to diagnose subtle DTFSI, with predicted small differences when comparing injured and control ankles. Larger cohorts and the addition of external rotation stress during the WBCT acquisitions could potentially increase the diagnostic accuracy of this non-invasive diagnostic tool.

Rural or Micropolitan Perceptions and Beliefs on Perinatal Mood Disorders, Maya Altemeier, Dr. Stephanie Radke, Dr. Kelli Ryckman, Nancy Weathers

Background:

Individuals living in rural areas who experience poor mental health are often more symptomatic than their urban counterparts. This is due to differential social and structural factors, health behaviors, significant health outcome disparities, and inaccessibility of appropriate and effective care. This rural-urban disparity permeates into maternity health and is particularly relevant in Iowa. Of the 37,585 Iowa residents who gave birth in 2019, 22% were rural residents and 15% were micropolitan residents. Rates of maternal morbidity and mortality are increasing, and pregnancy outcomes are consistently worse among rural communities. Rural residents experience higher rates of pregnancy complications (eclampsia, obstetric embolisms, and uterine ruptures/dehiscence), obstetrical interventions (Cesarean delivery), and overall higher rates of severe maternal morbidity and mortality. In 2018, it was found that 64% of mothers experienced psychological distress, an experience associated with low birthweight, preterm babies, and lower levels of parenting confidence. Further, poor maternal outcomes (pregnancy complications and obstetrical interventions) are associated with greater risk of poor postpartum mental health outcomes.

Much of the current literature on rural-urban health disparities is based on county-level records and fails to adequately explore the perspective of the community members. To effectively address geographic health disparities, it is critical to explore the intrapersonal and community-level contexts that contribute to attitudes, beliefs, and actions related to perinatal mental health. Rural maternal voices and values must be centered in the development of projects and for understanding the sociodemographic factors, clinical conditions, access to care, health behaviors, and other determinants of health that impact maternal care.

Purpose of Study:

Our overarching research question is to gain understanding of the perceptions (knowledge) and beliefs (values) about anxiety and depression during pregnancy and postpartum among residents of small towns and rural communities in Iowa.

Methods:

We are conducting a qualitative research study informed by community based participatory research practices. In preparation for research design, a literature review on rural maternal health was completed and a focus group of community advisors was recruited. Over the course of four meetings a research focus on perinatal mental health was selected, a research question was developed, and a focus group interview guide was drafted.

Next steps include determining a model or framework, further development of the focus group guide, and then conduction of the focus groups. At this time 6 focus groups, co-facilitated by the research team and community partners, are planned which will be situated within the physical communities of our community research partners. Each focus group will have between 5-7 participants who are currently pregnant or who have given birth within the past 3 years and reside in the community of interest. Participants will be recruited via convenience sampling using social media, advertisement in local businesses, churches, and public spaces.

Results:

While community input and data have been collected at each point of the research design process, the bulk of the data for this project has not yet been collected. The joint-developed focus group questions will be used to lead data collection this fall and winter. It is expected that the results will be improved understanding of the community factors that influence perceptions and decisions about mental health.

Conclusion/Discussion:

This study is a qualitative assessment of the knowledge and beliefs of rural and micropolitan residents about perinatal mood disorders and is conducted utilizing a community-based participatory approach. Mental health conditions during pregnancy and the postpartum are increasingly recognized as a major contributing factor towards excess maternal deaths in the United States and the state of Iowa. Unfortunately, there is a lack of literature on rural maternal mental health, and an even larger gap in the understanding of the patient perspective on this topic, despite community interest. Understanding the intrapersonal and community context in which rural and micropolitan mothers experience perinatal mood disorders is a critical step towards reducing the burden of mental health conditions. We anticipate the findings of this study to offer insight into opportunities to for prevention, early identification, and optimization of treatment for perinatal mood disorders for this population.

Hemodialysis and Surgical Applications of a Povidone-Iodine Nasal Decolonization Strategy

Student: Fiona Armstrong-Pavlik
Mentor: Marin Schweizer
Other collaborators: Ana-Monica Racila, Loreen Herwaldt, Linda Boyken, Jean Pottinger, Brennan Ayres, Rachel Quinn, Poorani Sekar, Melissa Ward, Priyadarshini Pennathur, Michael Willey

Background: Both surgical and dialysis patients are at elevated risk of developing infections, particularly *S. aureus*, which can cause bloodstream and surgical site infections. Around one third of people are nasal *S. aureus* carriers, which puts them at an even higher risk of infection. Nasal decolonization is an underused method of preventing infections in hemodialysis and trauma surgery patient populations. Povidone-iodine (PVI) is an attractive nasal decolonization method due to its low cost, ease of use, and inability to cause microbial resistance.

Aims: The PAINTS (Povidone-iodine to Stop Access-related Infections and Transmission of *Staphylococcus aureus*) study enrolled hemodialysis patients in a nasal decolonization program. Aims of this research rotation were to increase patient participation, understand facilitators and barriers to participation in the study, and gain perspectives on dialysis patients' views of their role in their own health and infection risks. Simultaneously, a study with orthopedic trauma surgery patients was completed including analyzing survey data to understand their perspectives using a similar povidone-iodine decolonization strategy.

Methods

PAINTS: Hemodialysis patients were recruited to the study at two Iowa sites of a national multi-center study. This is a real-world intervention, so adherence to the intervention was not closely monitored. Materials were developed to encourage patient and staff participation in the study. These included staff and patient education materials about the study and infection risks. Patient-friendly intervention facilitators included allowing patients to take PVI home if they chose, not enforcing use of PVI at every appointment, and allowing patients to start and stop the intervention as desired. Regular site visits were done to encourage dialysis center staff to help with the study, including by helping patients apply PVI to their noses and using labels to keep track of patients enrolled in the study. Surveys were administered to patients before starting the intervention and after participating for 1 and 4 months.

Trauma surgery: Patients were administered povidone-iodine intranasally the morning before and the evening after orthopedic trauma surgery. Surveys were conducted the day after surgery to understand patients' experiences with the decolonization intervention. Nasal swabs were also collected from surgical patients before and after povidone-iodine use to test for *S. aureus* presence.

Results

PAINTS: Many dialysis patients surveyed (66%, N=29) do not recognize they are at an elevated risk of developing a serious infection compared to an average person. Although most patients stated they would be willing to put forth at least some effort to prevent infections (93%, N=29), only 44% (N=16) of patients participating in the intervention said they would continue to use PVI at each dialysis appointment. Experience using a povidone-iodine nasal swab kit over time was variable. 81% of patients (N=16) found it pleasant or neutral. Half of surveyed participants (N=16) believed nasal povidone-iodine application to be somewhat or very helpful in lowering the risk of infection. Two patients reported mild side effects from using PVI. Staff barriers to participating in the study included time constraints and having a high number of patients to attend to. Facilitators of the intervention included identification of champions at intervention sites, staff willingness to help patients apply povidone-iodine, and allowing patients to decide whether to use the povidone-iodine at home or at the clinic.

Trauma Surgery: Patients were surveyed about their experience with a similar povidone-iodine nasal swab kit used over a short time period. Most patients (86%, N=51) found it neutral or pleasant to use. Many participants (31%) reported a minor side effect from PVI use. A subset of patients (16%, N=51) found the process annoying, but 94% (N=48) believed it to be beneficial.

Conclusions: Hemodialysis and surgical patients described nasal decolonization with povidone-iodine as pleasant or neutral at similar rates. However, a smaller proportion of dialysis patients viewed the povidone-iodine intervention as beneficial. Many dialysis patients also discontinued using PVI during the study. This may be due to the additional burden on patients and dialysis center staff of using povidone-iodine at multiple treatments. Results from these projects will help guide further infection prevention studies using nasal decolonization.

Title: Point of Care Gastric Antral Ultrasonography to Assess Gastric Content in Enterally Fed Patients.

Collaborators: Nabeel Baig, BS. Rakesh V. Sondekoppam, MD. Lucy Wibbenmyer, MD

Background: Regurgitation and pulmonary aspiration of gastric contents still remains a very serious complication following sedation. While the incidence of aspiration events occurring has decreased over time, the morbidity and risk of death still remains high when such events occur. A recent study analyzing anesthesia malpractice claims found that out of 115 cases involving aspiration of gastric contents, 66 (57%) of those cases resulted in patient death[1]. However, critically ill patients have increased caloric requirements and are often on enteral feeds. The current fasting guidelines at UIHC mandates that 8 hours is a sufficient amount of time for patients to have their enteral feeds shut off before surgery. Prolonged nutrient deprivation may precipitate a catabolic state in such patients which increases health risks so the duration for fasting in tube fed patients is currently unknown. Recently, gastric ultrasonographic evaluation of stomach contents using the cross-sectional area (CSA) of the antrum in the supine and right lateral decubitus position (RLD) can be used to calculate gastric volumes[2]. Volumes below 1.5 ml/kg present little risk for gastric content aspiration.

Purpose: The purpose of this study is to utilize the ultrasound (US) to assess the type and volume of gastric contents 4 hours after enteral feeds have been held and evaluate whether this would result in clinically relevant gastric volumes. Our primary outcomes include ultrasonographic qualitative assessment of gastric volumes at 4 hours in the RLD position using a grading scale (0-III) and a quantitative assessment of gastric volumes at 4 hours by measuring the CSA of the antrum in the RLD. Obtaining the CSA will allow calculation of gastric volume. Secondary outcomes include the same parameters as above but at baseline (<2 hours) with additional images in the supine position, and evidence of aspiration events during surgery/procedures.

Method: This is a prospective feasibility study. Any patient who is receiving enteral feeds and will be having them held for surgery/procedure is eligible for the study. Most patients were recruited from hospital intensive care units (ICU). Once consent was obtained, the study patient would receive a focused gastric US at baseline when tube feeds are stopped and again at 4 hours. The antrum will be captured as images using anatomical landmarks. Using the US machine, a measurement of the antral CSA can be determined and used to calculate gastric volume at the pre-specified time intervals.

Results: This is an ongoing study and we are presenting preliminary data on 14 study patients. Out of the 14 study patients, 4 had clinically-relevant gastric volumes at 4 hours on both quantitative (>1.5 ml/kg) and qualitative assessment (II or more) of gastric contents. A rescan of gastric contents was taken 1 hour later for these patients yielded clinically insignificant gastric volumes using the same measurements. The overall mean of calculated gastric volumes at 4 hours is 1.40ml/kg including the 4 study patients with clinically significant volumes.

Discussion/ Conclusion: Preliminary data analysis yields promising results regarding the utility and feasibility of gastric US to determine gastric content and volume in tube fed patients.While 4 hours was a sufficient amount of time for a majority of enterally fed patients to attain a fasting state, 4/14 patients had significant gastric volumes indicative of non-fasting status at the 4 hour time interval. However, the power of the study is severely limited by the sample size. Recruitment of patients was made difficult due to factors affecting the timing of surgeries, patient positioning in the ICU, and due to hospital Covid-19 guidelines impacting elective surgery volumes. This study will continue to recruit patients. Hopefully, data collected from this study can be used to modify NPO guidelines for tube-fed patients to find a better balance between lowering aspiration risk and depriving the patient of much needed nutrients.

[1.] Mark A. Warner, Karen L. Meyerhoff, Mary E. Warner, Karen L. Posner, Linda Stephens, Karen B. Domino; Pulmonary Aspiration of Gastric Contents: A Closed Claims Analysis. *Anesthesiology* 2021; 135:284–291

[2.] Susan Bragg, Richelle Kruisselbrink, Anahi Perlas; Gastric Ultrasonography for the Regional Anesthesiologist. *ASRANews* 2017; 7: 14-16

CCOM 2021 Medical Student Research Conference
Oral Presentation Abstract Submission

TITLE: Correlation of foveal cone density and retinal function in albinism
AUTHORS: Uma L. Balakrishnan, Arlene V. Drack

BACKGROUND & PURPOSE: Albinism is associated with poor visual acuity, foveal hypoplasia, and flattened slope of electrical response ("topography") from central to peripheral retina measured by multifocal electroretinogram (mfERG). With adaptive optics scanning laser ophthalmoscopy (AOSLO), individual photoreceptors at the fovea can be resolved. The contribution of retinal aberrations to poor vision in albinism is incompletely understood. This study is the first to correlate mfERG and AOSLO data, and to correlate foveal cone packing with retinal electrical topography and best corrected visual acuity (BCVA) to further investigate the causes of poor visual acuity in albinism.

METHODS: A prospective study of 14 subjects with albinism was performed. All subjects underwent mfERG to quantify electrical response and AOSLO to measure cone density at the fovea. Nine out of 14 patients had both interpretable AOSLO images and mfERG studies. Statistical analysis for these 9 subjects was performed using SAS, and one-tailed p values are reported.

RESULTS: All subjects had decreased central cone packing on AOSLO (average 59,921 ± 32,685 cones/mm^2; range 22,611 - 129,576 cones/mm^2 vs. 180,286 ± 25,436 cones/mm^2; range 122,710 - 247,710 cones/mm^2 in normal controls), decreased best corrected visual acuity (20/63 vs. 20/20 in normal controls), and flattened mfERG topography (rate of decline from Ring 1 to Ring 6: 0.266 vs. 0.322 in normal controls). BCVA did not correlate with mfERG topography ($p = 0.17$), however the subjects with BCVA > 20/70 ($n = 6$) had significantly flatter mfERG topography than those with BCVA < 20/70 ($n = 3$) (0.231 vs. 0.364, $p = 0.039$ using Mann Whitney U test). Interestingly, the only two subjects with two confirmed pathogenic mutations in *OCA1* have the steepest mfERG topography and poor BCVA, while the 6 patients with better BCVA all have one hypomorphic allele. Higher central cone packing correlated with higher amplitudes in the 4 peripheral mfERG peripheral rings (Rings 3 through 6: $p < 0.05$) and with mfERG topography ($p = 0.048$), but not with higher central mfERG amplitudes (Ring 1: $p = 0.33$). Denser central cone packing was significantly associated with better BCVA ($p = 0.031$).

DISCUSSION: This study is the first to demonstrate that, while normal central cone densities overlap between normal controls and albinism patients, within the albinism population higher cone density correlates with better visual acuity. Additionally, albinism patients with flatter mfERG topography have better visual acuity. mfERG central ring amplitudes do not correlate with denser central cone packing as expected, however the peripheral ring amplitudes do.

CONCLUSION: Central cone density and macular electrical topography are correlated in albinism in an unusual way with central cone packing related to peripheral macular electrical amplitudes. Measuring central cone density and mfERG electrical topography in children with albinism may help predict final visual acuity, and interventions aimed at the retinal anomalies may improve visual acuity.

1. Cava JA, Allphin MT, Mastey RR, Gaffney M, Linderman RE, Cooper RF, Carroll J: **Assessing Interocular Symmetry of the Foveal Cone Mosaic**. *Invest Ophthalmol Vis Sci* 2020, **61**(14):23.
2. Hu Z, Wang K, Bertsch M, Dunn T, Kehoe T, Kemerley AD, Helms M, Bhattarai S, Pfeifer W, Scheetz TE *et al*: **Correlation between electroretinography, foveal anatomy and visual acuity in albinism**. *Doc Ophthalmol* 2019, **139**(1):21-32.

Title
A Guided Near-Peer Mentorship Program for Transitioning into Clinical Clerkships at a Regional Medical Campus

Authors
Emma Barr, BS, BA, Steven R. Craig, MD, Hayden Smith, PhD, MPH

Background
Transitioning from preclinical to clinical medical education is a significant milestone in medical training; however, it is associated with anxiety and uncertainty about adapting to a new work and learning environment. These feelings can be additionally heightened when students are also transitioning to a branch or regional campus for their clerkship training. Moreover, mentorship has become an essential aspect of a career in medicine, yet there are few opportunities within medical training to learn how to mentor effectively. A guided, near-peer mentorship program was designed at a regional medical campus in hopes of reducing anxiety associated with transitioning into clinical rotations, as well as teach clinical medical students how to effectively mentor a fellow student.

Purpose
To describe the development and implementation of this new mentorship curriculum and examine participant feedback data on its perceived effectiveness.

Methods
This curricular improvement program was developed and implemented at the Des Moines Branch Campus of the University of Iowa Carver College of Medicine. A list of 14 topics for discussion was created from responses to reflection questions completed by students participating in the program. These topics were sorted into meeting guides that mentors could reference during their three individual meetings with their mentee. Mentors attended a workshop prior to the start of the program to learn more about effective mentorship in medicine. Participants completed feedback surveys after concluding their final required mentor-mentee meeting.

Results
Twenty-two of the 24 potential mentees participated in the program, with 20 of them completing the mentee feedback survey. Similarly, 21 of the 24 potential mentors participated, with 18 completing the mentor feedback survey. Ninety percent of mentees agreed that participating in the program decreased their stress and anxiety about transitioning into clerkships and 95% reported they would recommend the program to other students. Among the mentors, 94% reported they would recommend the program to other students and 78% agreed that the mentorship skills they practiced during the program are useful in their professional and academic development.

Discussion
With the introduction of this guided, near-peer mentorship program, mentees reported feeling supported in their transition into clinical clerkships and mentors reported feeling prepared to effectively mentor a fellow student. Though such one-on-one programs can be somewhat time-intensive to establish and execute, the skills gained by mentors can serve them for the rest of their careers and the individualized advice given to mentees markedly decreases anxiety in a high-stress transition.

Title:
Impact and Utilization of the ED Chest Pain Guideline*: Assessing provider attitudes regarding a newly implemented diagnostic algorithm for chest pain*

Student Author: Lisa Bell, MS4; Faculty Mentor: Paul Van Heukelom, MD; Collaborator: Kelli Wallace, MS

Background:
To expedite care of patients with chest pain, University of Iowa's (UIHC) emergency department (ED) implemented a new Chest Pain Guideline to assist with working up and managing patients who present with chest pain suggestive of acute coronary syndrome (ACS). This new Chest Pain Guideline was launched in March 2021, in conjunction with initiation of high sensitivity troponin testing. Although previous research suggests that instituting accelerated diagnostic pathways for management of chest pain alter patient care by reducing cost per patient and length of stay in patients with low-risk chest pain, it is still unknown how UIHC's providers feel about the use of the new diagnostic algorithm or how often it is utilized. This project seeks to obtain this information.

Purpose:
The purpose of this project is to obtain feedback from providers regarding a newly implemented protocol within UIHC. Information obtained from this project will be used to improve departmental operations.

Methods:
All data was obtained through an anonymous survey constructed in REDCap (Harris 2009, Harris 2019). Survey included queries on reported percent utilization of various clinical tools, assessment of attitudes using a Likert scale, multiple choice selections of strengths and weaknesses of Chest Pain Guideline, and free response. This survey was disseminated to 64 ED providers at UIHC during August 2021. Data collected from this survey was subsequently characterized by counts, percentages, and descriptive statistics. Free response answers were coded according to common themes.

Results:
There were 26 responses to the survey including those from: staff providers (n=15), advanced practice providers (APPs) (n=6), resident physicians (n=4), and participants who preferred not to answer who they were (n=2). Of the respondents, median reported utilization of the Chest Pain Guideline when working up patients with chest pain was 90% (interquartile range, 72-92). Median reported utilization of the HEART Score to guide management of patients was 89.5% (interquartile range, 77.5-98.75). Median reported utilization of the Epic HEART score tool in documentation of patients with chest pain was 50% (interquartile range, 22.75-61.5).

More than 2/3 of respondents stated that they feel confident that they have ruled out ACS and comfortable with discharging patients with low-risk chest pain without follow-up with the use of the Chest Pain Guideline. >75% of respondents believe that referral of low-risk chest pain patients to the cardiology clinic improves patient care, while only ~50% of respondents believe that patients will, in fact, attend their outpatient follow-up appointment. In addition, approximately 3/4 of respondents reported there is an insufficient number of cardiac observation beds available for chest-pain patient with medium cardiac risk. ~2/3 of participants find the new Chest Pain Guideline is easy to use and read, while ~1/3 reported that it is was confusing.

Most frequently reported strengths of the new tool included: impact on ED length of stay (n=14), organization (n=11), clarity of appropriate next steps (n=10), and ease of use (n=10). Meanwhile, the most frequently reported areas of improvement for the new tool included: impact on ED length of stay (n=8), font size (n=7), visual appearance (n=6), and ease of use (n=6).

Discussion and Conclusion:
The ED providers who participated in the study, in general, find the new Chest Pain Guideline to be useful for patient care, and they utilize it in management of chest pain patients most of the time. Attitudes vary in response to the efficacy of various components in the new pathway; however, most respondents endorse that the pathway has a positive impact on clinical operations and quality of care. Areas that may warrant an effort for improvement include availability of cardiac observation beds for further care of patients with medium cardiac risk and formatting of the pathway, most notably font size and clarity of instructions.

The association of exposure to hemodynamically significant PDA beyond the transitional period and growth failure over the first 6 postnatal weeks.

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[1]University of Iowa Carver College of Medicine, [2]University of Iowa Department of Pediatrics, [3]University of Iowa Department of Pediatrics, Division of Neonatology, [4]University of Iowa Hospitals and Clinics

Background: Persistent hemodynamically significant patent ductus arteriosus (hsPDA) shunt following preterm birth results in circulatory disturbance. Pre-ductal circulation, including the brain and heart, is hyperperfused and post-ductal circulation, including celiac and mesentery circulation, may be hypo-perfused. This may have an important impact on glucose utilization, lipid tolerance, acid/base balance, and growth. Previous studies have suggested that growth is impaired among patients with hsPDA, however, aggressive fluid restriction and diuretic use were common.

Objective: The aim of this study was to characterize the association between persistent hsPDA shunt beyond the transitional period (>3 days) and postnatal growth. We hypothesized that neonates with hsPDA will have similar growth parameters during the period of peak hsPDA exposure [0-6 weeks] in the absence of aggressive fluid restriction and diuretic use.

Methods: A retrospective cohort study was conducted of preterm neonates born <27 weeks gestation admitted to the Neonatal Intensive Care Unit (NICU) at the University of Iowa Stead Family Children's Hospital [11/2018-05/21]. Standard NICU care for patients with hsPDA includes: conservative feeding, optimal parenteral nutrition, diuretic therapy is uncommon and mild or no fluid restriction is practiced. Neonates were included if postnatal Targeted Neonatal Echocardiography (TnECHO) was performed in the first 24h. Patients with congenital anomalies or anatomic cardiac disease other than PDA, atrial communication, or small (<1 mm) muscular ventricular septal defect, those receiving chronic furosemide and those in whom weight at 42d was not reliable due to critical illness and anasarca were excluded. It is standard care to screen all patients <27 weeks for PDA within the first 24h, at day 5-7 and episodically thereafter. Patients were classified as hsPDA if the Iowa PDA score was ≥6 at any time after 3 days postnatal age and treatment for PDA was received [Figure 1]. Duration and magnitude [Mean PDA Score*days exposed] of hsPDA exposure was evaluated. The primary outcome was a composite of death or growth failure [defined as weight and/or head circumference (HC) for age loss of > 0.8 z-score] at 42 +/- 3 days. Weight (daily) and HC (weekly) are routinely measured. Demographics and antenatal factors were collected. Univariate analysis was performed and linear regression was used to compare metrics of hsPDA to growth.

Results: A cohort of 86 patients were screened of whom 81 met eligibility criteria [Figure 2]. hsPDA-exposed neonates (n=47) were younger and smaller at birth; however, their size was appropriate for gestation as indicated by birthweight percentile and z-score comparable to controls (n=34). Other demographic and antenatal factors were similar between groups. [Table 1] A total of 14 patients died before 42 days and the overall incidence of growth failure among survivors was n=13 (16%) for weight and n=27 (33%) for HC. HsPDA was associated with a 2-fold increase in the composite outcome (p=0.001) which was primarily driven by a greater risk of death. Growth failure was non-significantly higher for both weight and HC but the magnitude of growth failure was not different between the groups. [Table 1] On linear regression [Figure 3], there is no relationship between PDA duration or magnitude of exposure and postnatal growth metrics.

Conclusions: Extremely preterm patients exposed to hsPDA beyond the transitional period have a greater risk of death; however, survivors to 42 days are not more likely to have growth failure than un-exposed controls in an NICU which does not practice aggressive fluid restriction and diuresis. The 2x greater incidence of failure of head growth as compared to weight in this cohort merits further consideration.

Combining Superoxide Dismutase Mimetics and Pharmacological Ascorbate Enhances Efficacy of Radiation Treatment in Non-Small Cell Lung Cancer

Jayden Bisson, Dr. Douglas R. Spitz, Casey F. Pulliam, Dr. Melissa A. Fath, Amanda L. Kalen, Khaliunaa Bayanbold

Introduction: Lung cancer is currently implicated as being the top cause of cancer-related deaths in the United States and is expected to remain the top cancer-killer for at least another decade [1]. It is therefore necessary that advances in lung cancer treatment be deployed to reduce future cancer-related deaths. Radiation is a frequently utilized standard of care in the treatment of lung cancer, and for patients with contraindications to surgery, it is an especially promising alternative. However, it is limited in that it damages adjacent radiosensitive normal tissue. It is therefore necessary to evaluate potential treatments that, when used with radiation, limit the radiosensitivity of normal tissue, while simultaneously increasing the radiosensitivity of cancer cells. Vitamin C (P-AscH), when used intravenously at millimolar doses, and superoxide dismutase (SOD) mimetics, have both individually shown clinical potential in the protection of normal tissue, while enhancing radiation damage to cancer. By combining these compounds during radiation treatment, normal tissue protection and cancer cell sensitization could be enhanced.

Hypothesis: The combination of an SOD mimetic and high pharmacological doses of ascorbic acid will increase the radiosensitivity of tumor tissue and protect normal tissue from radiation-induced superoxide damage synergistically.

Aims: Evaluate the efficacy of the combination of SOD mimetics and P-AscH with radiation therapy in non-small cell lung cancer cells, normal human lung fibroblasts, and a mouse xenograft model.

Materials and Methods: Doxycycline inducible H1299T non-small cell lung cancer cell clones overexpressing catalase (CATc15), mitochondrial catalase (mCATc6), or ferritin heavy chain (FTHc11) were developed with lentiviral transduction. These H1299T cells were then treated with 10uM GC4711 (equivalent to GC4419), 2.5mM or 5mM ascorbic acid (P-AscH), and 2 Gy radiation (IR) alone or in combination. All three doxycycline inducible clones were assayed for clonogenic cell survival after treatment. H1299T cells were also utilized in flank xenograft models in which mice were given P-Asch (4 g/kg), GC4711 (15 mg/kg), and 12 Gy stereotactic body radiation therapy (SBRT) alone or in combination. Tumor growth and animal survival were assessed daily.

Results: Normalized survival fractions for H1299T cells were as follows: *control=100%, GC=93%, P-AscH=91%, IR=78.5%, GC+IR=82.9%, P-AscH+IR=62.4%, GC+P-AscH=5.67%, GC+P-AscH+IR=1.3%,* with significant differences detected in GC+P-AscH groups, with and without radiation. For the CAT, mCAT, and FTH clones, rescue of cell death occurred, with significant increases in survival when overexpression was induced. SBRT treatment trended toward longer survival in mice given GC, P-AscH, or both, and trended to slow tumor growth, with groups receiving either drug trending lower than SBRT alone, However no significant differences were detected *in vivo.*

Conclusion: GC4711 combined with P-AscH enhanced killing, with and without IR in non-small cell lung cancer cells *in vitro* relative to either drug alone. Over-expression of catalase protected cells from the GC+P-AscH-treatment with and without IR, suggesting peroxide flux as a mechanism of toxicity. Overexpression of mCAT also protected cells, but to a lesser extent then seen in CAT cells, suggesting cytosolic rather than mitochondrial hydrogen peroxide flux as a mechanism of toxicity. FTH overexpression also protected cells from P-AscH treatment suggesting involvement of labile iron metabolism in the toxicity observed in the T variant of H1299 NSCLC cells. No significant differences were detected in mouse survival or tumor growth, but tumor growth trended towards slowed tumor growth with GC+P-AscH+SBRT, and SBRT treatment trended toward longer survival in mice given GC, P-AscH, or both. Due to difficulties with anesthesia techniques the animal data needs to repeated prior to drawing firm conclusions.

Future studies: The ability of the combination treatment of P-AscH and SOD mimetics to protect normal cells from radiation damage during radiation therapy treatment for non-small cell lung cancer has yet to be established. Future studies will include treating normal human lung fibroblast cells with both drugs and IR and assessing survival to quantify the protective effects on normal tissue. Further animal studies assessing the efficacy of combined P-AscH, GC4711, and SBRT are also needed. Future studies examining the mechanism of protection against P-AscH toxicity observed in the FTH overexpressing cells are also needed and include conducting Western blots assessing for the presence of IRP2, FBXL5, and other components involved in iron metabolism and potentially linked to P-AscH.

Raising a child with intellectual and developmental disability: Impact on maternal stress and social support

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Introduction: Autism spectrum disorder (ASD) has lifelong implications for affected individuals, their families, and society. Research on how parents and caregivers are impacted by raising a child with ASD has been limited, and even less is known about families of children with non-ASD developmental delay. Greater than 80% of parents of a child with ASD report they feel “stressed beyond their limits” [1]. Parents of children with ASD are at greater risk for depression and other mental health concerns compared to the general population [2]. Therefore, we wanted to assess stress levels and social support in mothers of children with autism spectrum disorder (ASD), children with non-ASD developmental delay (DD), and typically developing (TD) children.

Hypothesis: Mothers of children with ASD will report higher levels of stress and have lower social support compared to mothers of non-ASD developmental delay and typically developing children.

Methods: Mothers of recently diagnosed children (13 mo-3 years) with autism and non-ASD developmental delay were recruited from the Center for Disabilities and Development. In addition, mothers of typically developing children were recruited from pediatric outpatient clinics. Once consented, mothers completed questionnaires about their child’s development and their own maternal wellbeing (measures of chronic stress, perceived stress, and social support). Demographic information was also collected. A generalized linear model was utilized to examine differences in measures of stress and social support.

Results: We recruited 30 mothers of children with ASD, 25 mothers of children with non-ASD developmental delay (DD), and 43 mothers of typically developing children (TD). Overall, mothers from the DD group scored significantly higher in measures of chronic stress ($p = 0.01$) and perceived stress ($p = 0.03$) compared to mothers of ASD and mothers of TD children. Mothers of DD children also reported a lower number of individuals that they could count on for social support ($p = 0.01$). These trends held after individually adjusting for marital status, race, ethnicity, maternal age, and Hollingshead score.

Discussion: Few studies have compared children with ASD, children with non-ASD developmental delay, and typically developing children, especially as a measure of maternal support. Much of the existing literature addresses the challenges of raising a child with ASD, with the assumption that parents of children with non-ASD developmental delay have similar experiences. Our study challenges this idea, by showing that mothers of developmentally delayed children have higher stress and lower social support compared to mothers of children with ASD and mothers of TD children. This may be due to higher levels of uncertainty and lack of direction surrounding a diagnosis of non-ASD developmental delay, especially if these children were initially evaluated for concerns of ASD. Future directions include increasing study recruitment, obtaining real-time measures of maternal wellbeing in the form of ecological momentary assessments, and measuring epigenetic change from birth to time of diagnosis in children with ASD, children with non-ASD developmental delay, and typically developing children.

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Intersectional labeling of CGRP receptor sites in the mouse brain

Claire Boettcher, Connor Castonguay, Levi Sowers, Brandon Rea, Mengya Wang, Andrew Russo

Background and rationale: Migraine is a painful and prevalent neurological condition, characterized by sensory abnormalities before, during, and following the headache stage. It is the 6th most common disease worldwide, with over one billion sufferers (Disease GBD, 2017). In the United States, 15% of Americans are affected by migraine, creating a total economic burden of $36 billion in 2016 (Burch et al., 2018; Bonafede et al., 2018). Additionally, migraine is listed as the fifth most common reason for emergency department visit (Burch et al., 2018). Patients with migraines are oftentimes overprescribed opioids for pain management, which increases risk of developing substance abuse and chronic migraines (Burch et al., 2018). Calcitonin gene-related peptide (CGRP) is a neuropeptide that has been a target for migraine treatment in the past decade (Russo, 2015). Studies have shown that CGRP is elevated in patients during a migraine (Juhasz et al, 2005; Van Dongen et al, 2016; Cady et al, 2009). Additionally, studies have shown that 70% of people with migraines develop a migraine-like headache after infusion with CGRP, compared to control patients who only developed mild headache (Lassen et al, 2002). Since 2018, six CGRP-based drugs have been FDA approved for prevention and acute treatment of migraine. However, only about 50% of patients sufficiently respond to these drugs, which supports the need to identify additional pharmacological targets (Loder & Robbins, 2018).

Recently, a second receptor for CGRP, AMY1 (CTR/ RAMP1) receptor, has been discovered. CGRP inhibitor treatment preferentially targets the original canonical receptor (CLR/RAMP1) for migraines. It is crucial to determine which receptor is important in migraine. The Russo lab collaborated on a recent study that showed that the amylin analog pramlintide, which recognizes AMY1, but not the canonical receptor, induced migraine-like attacks in patients with similar clinical characteristics as CGRP (Ghanizada et al, 2021). They also showed that injections led to cutaneous hypersensitivity and light aversion in mice (Ghanizada et al, 2021).

Purpose of the study: Hypothesis: The canonical CGRP and AMY1 receptors are expressed in distinct brain regions that contribute to migraine pathophysiology. The aim is to determine the expression pattern of the receptors by a strategy that should detect neurons that lie at the "intersection" of expression of both CTR & RAMP1 or CLR & RAMP1 receptor subunits in the mouse brain.

Methods: The FlpO and Cre recombinases were inserted into endogenous RAMP1, CTR or CLR genes to create fusion proteins (Fig.1). An ER inducible FlpO and Cre were used so that recombinases were active only in adult mice when treated with tamoxifen. A PA2 auto-cleavable element was used to separate receptor subunits from recombinase. Thus, FlpO or Cre should be expressed only in neurons that are actively expressing CGRP receptor subunits. A dual recombinase reporter could then be used to detect neurons expressing both FlpO and Cre (Fig.1). The first step was to measure FlpO and Cre expression by crossing with mice containing a Flp-dependent tdTomato reporter (FLTG) (Fig.1) or a Cre-dependent tdTomato reporter (not shown). Confocal microscopy was used to analyze brain slices of RAMP1-FlpO, CTR-Cre, & CLR-Cre mice.

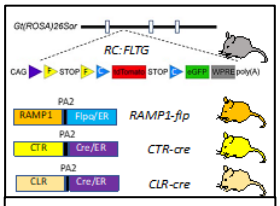

Fig. 1. Cre/Flp dependent reporter & CGRP receptor- Cre/Flp mice.

Results: Preliminary imaging of RAMP1-FlpO/FLTG reporter mice showed no expression of tdTomato fluorescence compared to control mice with reporter but lacking FlpO. Preliminary imaging of CLR-Cre/ tdTomato mice, showed no difference between images in the amygdala region; however, there were sporadic neurons positive for tdTomato throughout the brain. Preliminary imaging of CTR-Cre/tdTomato mice revealed weak tdTomato expression in neurons in the PVN of the hypothalamus as well as sporadic neurons in expected regions of the brain such as the DMX, compared to the control. Further images need to be analyzed.

Conclusion/Discussion: The goal was to create a genetic model that would allow us to identify neurons that express both subunits of the two CGRP receptors. Based on our preliminary results, the RAMP1-FlpO strategy is not working since there was no detectable reporter expression; whereas the CTR-Cre and CLR-Cre are showing some expression of the reporter in expected locations. However, expression was very sparse and not in many expected regions indicating that the protocol needs to be optimized. To increase reporter detection, we plan to increase the duration of tamoxifen induction and amplify the signal by staining with tdTomato antibodies. If reporter detection is still weak, we could switch to a viral vector encoding FlpO & Cre dependent reporters instead. Successful location of canonical CGRP and AMY1 receptors in the brain will allow us to move to the next step to determine which CGRP receptors cause migraine-like symptoms using FlpO & Cre dependent optogenetic and DREADD strategies. These results will determine the contribution of AMY1 in migraine will provide a new target for drug discovery and improve outcomes for migraine patients.

CORRELATIONS BETWEEN SLEEP AND COGNITIVE FUNCTIONING IN HEALTHY, OLDER ADULTS AT RISK OF DEVELOPING ALZHEIMER'S DISEASE

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Abstract

BACKGROUND: Alzheimer's disease (AD), a leading cause of dementia worldwide, affected an estimated 47 million people in 2015, placing a burden of over $1 trillion on health systems. Virtually all therapeutics aimed at slowing or halting the progression of AD have failed in clinical trials. However, subclinical and laboratory markers of AD pathology are seen many years before the clinical onset of dementia, suggesting that steps could be taken much earlier than the timing of current pharmacological interventions in the AD course to prevent progression of illness. Sleep optimizes cognition by creating a window of opportunity to consolidate memories, prune synaptic networks, and clear waste products. One of sleep's benefits that is of particular importance to AD pathology is the clearance of β-amyloid accumulation within the central nervous system (CNS). Although multiple hypotheses exist regarding the mechanism of AD pathology, β-amyloid accumulations within the CNS are thought to be a significant driver of AD development, because of their toxicity to neurons and their networks. Multiple meta-analyses over the past five years have demonstrated that sleep disturbances are associated with increased risk of dementia later in life. However, these reviews analyzed primary studies that have high heterogeneity, use short intervals of sleep data, and have yet to describe the relationship between objective sleep data and performance on tasks targeting specific cognitive domains. Studies that characterize the relationship between sleep and cognitive function prior to the onset of clinical AD could guide research into effective methods of delaying AD onset or preventing it altogether.

AIMS: The objective of our study is to describe how sleep quality and quantity affect performance on cognitive assessments within a healthy, aging population at risk of developing AD.

METHODS: Seventeen participants, between 62-82 years of age enrolled in a clinical trial assessing the effects of melatonin (5mg daily) versus placebo, were included in our study. The current study analyzed data obtained during the first two months of this 10-month trial. At study entry, participants underwent a neuropsychological evaluation to determine baseline performance across a broad range of cognitive abilities: attention, memory, speed of information processing, language, executive functioning, and mood. Then, all participants were asked to wear a watch that measured actigraphy and light data (Philips Actiwatch Spectrum Pro actigraphy monitor) for 8 weeks to evaluate their typical sleep habits. Pearson and Spearman partial correlations were used to evaluate relationships between objective sleep parameters and baseline cognitive function test scores.

RESULTS: Correlations reaching statistical significance were seen between age-adjusted measures of sleep activity and cognitive scores. Sleep wake after sleep onset (WASO) standard deviation, a measure of sleep fragmentation, correlated with HVLT delayed recall scores, an assessment of memory (r = 0.51, p = 0.037); and correlated with Boston Naming Test scores, an assessment of language (r = -0.49, p = 0.046). Sleep duration mean, which measures quantity of sleep, correlated with COWA, an assessment of language (r = -0.51, p = 0.038). Active wake time standard deviation, which measures the variability of time spent active during wake hours, correlated with Rey-Osterrieth Complex Figure Test Copy Scores (Rey-O CFT), an assessment of visuospatial ability (r = -0.62, p = 0.011); and correlated with SDMT written scores, an assessment of speed of information processing (r = -0.54, p = 0.027). Active duration standard deviation, which assesses variability in wake hours, correlated with Rey-O CFT (r = -0.58, p = 0.018). Sleep sleep-percent mean, which measures the average length of time spent sleeping in each sleep interval as a percent value, correlated with Rey-O CFT (r = 0.55, p = 0.027). Active sleep time standard deviation, which measures the variability of time spent sleeping during wake hours, correlated with SDMT written scores (r = -0.84, p = 0.012). Active duration standard deviation, which measures variability in the duration of wake hours, correlated with SDMT written scores (r = -0.59, p = 0.013).

DISCUSSION: The conceptual framework of this study - to assess whether sleep quality and quantity affect cognitive functioning in healthy, older adults at risk of developing AD - has been explored by prior studies in various ways. Our novel approach uses actigraphy data that is greater than 3 weeks, along with assessments that target specific domains of cognition. With a robust within-person dataset, we aim to describe subtler relationships between sleep and cognitive function that may be present in patients earlier in their AD progression. Making population-based deductions from the relationships described within this report is difficult, due to our small sample size. However, our findings suggest that increased variability of activity within wake and sleep hours correlates with poorer cognitive performance across multiple domains, and future studies should further explore this relationship. For future consideration, we plan on expanding our sample size, refining our validation methods of sleep monitoring, and incorporating circadian rhythm metrics and AD biomarker analyses to characterize sleep variability in a new light.

Bioimpedance for Revision Arthroplasty

Student Researcher: Eric Bracken

Mentor: Jacob Elkins MD, PhD

Background:

Total joint arthroplasty (TJA) is described as some of the most successful procedures in medicine. However, some patients still see poor results that in many cases lead to failure requiring surgical revision. Previous studies have identified significant changes related to body composition following TJA, likely related to changes in activity level during the prolonged post-surgical recovery period. Given the marked pain and dysfunction related to their osteoarthritis, intuitively, patients presenting for TJA have already sustained substantial body composition changes prior to their procedure as well. However, the changes in body composition due to pain and disability resulting from a failed prior TJA is currently unknown. As the degree of muscle wasting and other deleterious body composition changes prior to surgery is expected to affect the post-operative recovery period, identifying and quantifying pre-operative body composition parameters is an important objective. Therefore, the primary goal of this study was to utilize bioimpedance analysis to compare various body composition parameters between patients undergoing primary TJA and patients undergoing revision TJA.

Method:

Twenty patients undergoing revision total knee and total hip arthroplasty were recruited to participate in the study. Bioimpedance analysis (InBody 770, InBody USA, Cerritos CA) was performed prior to TJA. Pre-operative skeletal muscle mass, skeletal muscle mass index (SMI), lean body mass, fat mass/percent body fat (PBF), extra-cellular water to total body water (ECW:TBW) ratio and phase angle was assessed for each patient. These were compared to a historical cohort of 84 primary TJA patients.

Results:

There was no difference between the two groups regarding BMI (34.5 vs 34.3, p-value=0.462), weight ((239.7 vs 217.5, p-value=0.061), ECW:TBW ((0.399 vs 0.395, p-value=0.084) or phase angle ((4.740 vs 4.842, p-value=0.327). Revision patients demonstrated statistically greater SMI, (9.355 vs 8.427, p-value=0.014) and lower \PBF ((36.7 vs 40.9, p-value=0.031).

Conclusion:

This preliminary study does not support a difference in presenting body composition parameters between patients undergoing revision and primary TJA. This study was limited by the number of patients in the revision arm. Current and future studies will investigate the perioperative body composition changes seen in revision patients, and to identify if certain diagnoses (such as periprosthetic joint infection or periprosthetic fracture) incur greater changes compared to primary TJA patients.

Maternal and Neonatal Outcomes in a Rural Cohort During the Coronavirus Pandemic

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Faculty Mentor: Dr. Mary B. Rysavy, MD, University of Iowa Hospitals and Clinics

Introduction: Relative to previous coronavirus outbreaks such as Severe Acute Respiratory Syndrome Coronavirus (SARS) and Middle East Respiratory Syndrome Coronavirus (MERS), the impact of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) on pregnant populations was initially thought to be less severe. However, inherent changes in the maternal immune system during pregnancy often lead to a more severe and prolonged course of disease in respiratory infections, as observed in SARS and MERS. Recent studies have shown that risks of critical illness, admission to the intensive care unit, preterm labor, and unscheduled cesarean are indeed higher in patients with SARS-CoV-2 infection (COVID-19) during pregnancy than in the general population, with women in their third trimester at the most increased level of risk. Moreover, demographic factors such as race, rurality, and insurance status, and comorbidities including obesity, hypertension, and diabetes mellitus are associated with higher risk of severe disease. It is critical to determine the seroprevalence of SARS-CoV-2 among the rural, pregnant population, and to gain an understanding of the outcomes associated with infection during pregnancy and delivery.

Objective: In this study, we aimed to estimate the seroprevalence of SARS-CoV-2 in the obstetric population at the time of delivery and to examine demographics, clinical factors, and maternal and neonatal outcomes associated with COVID-19 during pregnancy over the course of one year of deliveries during the pandemic. In addition, we utilized residential zip code to map cases and outcomes in the study population in an effort to better understand the role of rurality in severe disease. Our hypothesis was that unfavorable maternal and neonatal outcomes resulting from COVID-19 in pregnancy are associated with certain demographics, specifically race, rurality, and insurance status.

Methods: This project was executed as a prospective cohort study, including all obstetric patients who delivered at the University of Iowa Hospitals and Clinics between May 1, 2020 and April 30, 2021. SARS-CoV-2 antibody testing was performed on leftover plasma collected from type and screen specimens obtained from every patient during the admission for delivery. Samples were tested using the LIAISON® SARS-CoV-2 S1/S2 IgG test (DiaSorin) and the Elecsys® Anti-SARS-CoV-2 (Roche) assays to determine the seroprevalence of SARS-CoV-2 antibodies. SARS-CoV-2 viral testing results, maternal and neonatal outcomes, and demographic information were obtained from the electronic medical record and entered into a REDCap database. Rurality was classified using the Rural-Urban Commuting Area (RUCA) coding system from the United States Department of Agriculture, where patients were assigned as metropolitan (RUCA codes 1-3), micropolitan (RUCA codes 4-6), or rural (RUCA codes 7-10). Data were analyzed using multivariate statistical methods.

Results: In a population of 1912 delivering patients, 14.0% (267) tested positive for SARS-CoV-2 IgG antibodies. There were demographic differences noted in the seroprevalence of SARS-CoV-2 by insurance status ($p < 0.001$[3]), race ($p < 0.001$[4]), rurality ($p = 0.034$[3]), and preferred language ($p < 0.001$[3]). COVID-19 was only correlated with higher risk of pre-eclampsia (OR 1.678, $p = 0.008$), among all of the maternal and neonatal outcomes assessed. Rural areas were associated with a higher seroprevalence of SARS-CoV-2 (OR 1.659, $p = 0.007$), lower rates of preterm labor (OR 0.543, $p = 0.003$), and a higher mean birth weight by 179.9 grams ($p = 0.001$) when compared to the metropolitan group. Micropolitan areas were associated with a higher seroprevalence of SARS-CoV-2 (OR 1.798, $p = 0.002$), higher rates of preterm birth (IRR 1.504, $p = 0.033$) and pre-eclampsia (OR 1.770, $p = 0.002$), but better Apgar scores at 1 minute (OR 1.155, $p = 0.043$) when compared to the metropolitan group. Distance of greater than 30 miles from the University of Iowa was associated with higher preterm labor (OR 2.086, $p < 0.001$), worse Apgar scores at 1 (OR 0.687, $p < 0.001$) and 5 minutes (OR 0.684, $p < 0.001$), and a lower mean birth weight by 219.0 grams ($p < 0.001$). Distance of 10-30 miles from the institution was also associated with worse Apgar scores at 1 (OR 0.788, $p = 0.003$) and 5 minutes (OR 0.803, $p = 0.008$).

Conclusion: 14.0% of delivering mothers at the University of Iowa between May 1, 2020 and April 30, 2021 were found to have SARS-CoV-2 antibodies. These data support previous studies suggesting that patients of racial/ethnic minorities, preferred languages other than English, and rural background were disproportionately impacted by the COVID-19 pandemic. In addition, maternal and neonatal outcomes such as pre-eclampsia, preterm labor, preterm birth, birth weight, and Apgar scores were found to be impacted by rurality and distance from the University of Iowa, underscoring the importance of access to care during pregnancy. Subsequent investigation considering the intersection of SARS-CoV-2 antibody status, rurality, and distance from the University of Iowa is needed to better characterize the implications of the COVID-19 pandemic on adverse maternal and neonatal outcomes.

Buprenorphine Induction in the UIHC Emergency Department

Conor Burke-Smith, Priyanka Vakkalanka, PhD, Joshua Radke, MD

Background

Opioid Use Disorder (OUD) is a substance use disorder relating to an opioid which affects over 2 million Americans each year. Buprenorphine, a μ-opioid receptor partial agonist, has been proven to be a safe and effective drug for reducing withdrawal symptoms and decreasing relapse rates in patients with OUD. Buprenorphine prescription and induction in emergency departments (EDs) have demonstrated increased subsequent engagement in OUD treatment programs. In June 2019, the University of Iowa Hospitals and Clinics (UIHC) ED initiated a protocol so patients presenting with OUD can be given buprenorphine in the ED and then scheduled for follow up and management with the UIHC Medication assisted treatment (MAT) clinic. Our primary goal was to assess whether patient characteristics and other pertinent medical information could predict continued opioid treatment in the MAT clinic after undergoing our protocol.

Methods

In this retrospective chart review, we identified patients presenting to the ED with OUD who followed our new protocol between 6/1/19 and 3/31/20. We characterized these patients by demographics (age, sex, race, living situation, insurance), clinical characteristics (medical and psychiatric comorbidities, concurrent medications), and medication and administrative characteristics (dosing of buprenorphine, whether or not a Chemical Dependency Service was consulted). The primary outcome was follow up with the MAT clinic within 90 days, and secondary outcomes included return to the ED for opioid-related reasons and urine toxicity screens in the MAT clinic and ED if administered.

Results

A total of 49 patients followed our new protocol in the ED during the study period. Overall, the median age of patients was 33 (IQR: 28-44), 61% were males, 76% were white, 82% had a family home as residence, and 74% had Medicaid. In the following 90 days, 31 (63%) of these patients followed up in our MAT clinic, and there appeared to be no differences in demographics, clinical characteristics, or medication use between those following up with the MAT clinic and those who did not. However, those who presented to the MAT clinic were more likely to have had previous MAT exposure outside of UIHC compared to those who did not follow up (74% and 44%, respectively; p=0.037). Approximately 18% of patients returned to the ED overall; however, the odds of returning to the ED were not significantly different between those who had MAT follow up compared to those who did not (OR: 1.20; 95%CI: 0.26-5.52).

Conclusions

We did not observe significant differences in characteristics between patients who presented to the MAT clinic and those who did not amongst a cohort of patients who followed our new protocol in our ED. While the absence of any findings may be due to a small sample size, the structure of this study may be able to serve as a framework for evaluation of similar programs in the future. Additionally, qualitative work might expand on findings pertaining to motivations for follow up with the MAT clinic and other relevant non-UIHC follow-up care, or limitations with successfully following patients within our care. Understanding what factors may impact these patient's ability to follow up is vital to amending these gaps of care.

Title: Use of 3-D Printing Technology to Assist and Formulate Surgical Plans in Complex Congenital Heart Disease Patients

Presenting Author, Other Collaborators, Mentor: Connor Byeman, BS; Eric Boeshart, MS; Dr. Ravi Ashwath, MD

Background: 3-D printing technology has grown rapidly across the globe and has infiltrated the medical field, prominently in the areas of surgery and education. In cardiothoracic surgery, 3-D models are most used to facilitate understanding of congenital heart disease anatomy. Gathering data from standard modalities like computed tomography, magnetic resonance imaging, and high-resolution ultrasound provides information necessary to extract a set of 3-D coordinates to create a model. Custom designed patches can then be created to allow surgical practice on exact anatomical representations in a more efficient fashion than designing a patch based on the surgeon's own intuition.

Purpose: The purpose of this study is to demonstrate that 3-D models can be used to augment knowledge beyond traditional 2-D imaging modalities in a fashion that helps surgeons feel more confident about performing the procedure on complex congenital heart disease patients. Another aim is to show that custom designed patches offer a new option to surgeons when contemplating the design of a patch during an operation.

Methods: For 5 different complex heart defects, models were generated via segmentation using Mimics software, then post processed in 3-Matic and Meshmixer softwares. Individual custom patches were designed using AutoCAD software. For each case, two identical models and a custom patch were 3-D printed. A cardiothoracic surgeon then performed virtual surgery on these 5 unique cases. First, they performed the procedure on one model creating their own patch using Gore-Tex patch material, then again, using the custom patch on the identical model, followed by a survey.

Results: Using the Likert-score based survey, we show that surgeons feel more prepared for surgery and are more knowledgeable about the anatomy of the patient after practicing on the 3-D models with a custom patch. In addition, geometric morphometric data shows major differences between patches created intra-operatively and the custom designed patches, indicating that sterilized custom patches could be useful as a template in the operating room. We predict that intra-operative orientation using the 3-D model and patch will help surgeons perform future operations more efficiently and safely.

Conclusions: Use of 3-D printing in complex congenital heart disease has the potential to change the standard surgical planning process. The ability to design a custom patch, practice on a case-specific model, and bring the sterilized prints into the operating room offers surgeons novel options to better prepare for the operation. Looking ahead, we hope to show this improves patient outcomes.

Cumulative live birth rate in women 37 years of age or less who utilize preimplantation genetic testing aneuploidy (PGT-A) versus untested embryos

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Background and Introduction

The use of preimplantation genetic testing for aneuploidy (PGT-A) has increased in recent years. As chromosomal abnormalities are assumed to be the major cause of implantation failure and early pregnancy loss, PGT-A has been touted as a method to select the best embryo for transfer in patients with age-related decline in fertility and recurrent pregnancy loss. However, even among younger patients, chromosomal abnormalities are common with aneuploid embryos encompassing 34% of the total embryo pool at age 35, and 43% of embryos by age 37. Because of this, PGT-A is increasingly used among all patients undergoing IVF regardless of age or diagnosis with some studies showing higher pregnancy and live birth rates when PGT-A is utilized. However, the utility of PGT-A for improvement in live birth rates is controversial, and a recent Cochran review found insufficient good-quality evidence that live birth rates after the first embryo transfer, cumulative live birth rates, or miscarriage rates are significantly different between IVF with and without PGT-A.

Hypothesis

There is no difference in cumulative live birth rates between cycles with and without PGT-A inpatients $\leq$ 37 years of age undergoing IVF.

Purpose

To determine the effect of PGT-A on the cumulative live birth rate (LBR) in women $\leq$ 37 years of age.

Methods

Data were collected from Society for Assisted Reproductive Technology (SART) reporting clinics on all 31,900 patients $\leq$ 37 years of age undergoing their first retrieval between Jan 2014 and Dec 2015. Subsequent transfer cycles utilizing embryos from the initial retrieval cycle were followed through December 2016. The women were grouped based on age, <35 and 35-37 years of age. Logistic regression was used to control for clinical and demographic variables. Factors included in the final model were selected by Bayesian Information Criterion. The primary outcome was cumulative live birth, defined as the occurrence of at least one delivery in the follow-up period. Secondary outcomes included multifetal births, miscarriage, and time to pregnancy resulting in live birth. Time to pregnancy resulting in live birth was calculated for cycles resulting in a live birth by adding 10 days (standard amount of time from embryo transfer to the pregnancy test) to the number of days between medication start in the retrieval cycle and the embryo transfer that resulted in the live birth.

Results

There were 29,362 patients using untested embryos (92.1%) and 2,535 patients using PGT-A embryos (7.9%) included. The average time from onset of the IVF cycle to a pregnancy resulting in live birth for patients <35 was 2.17 months (SD 2.86) for untested transfer cycles and 4.10 months (SD 3.12) for PGT-A transfer cycles. For patients 35-37, the average time to pregnancy utilizing untested embryos was 2.14 months (SD 2.86) and for PGT-A cycles was 4.44 months (SD 3.48). All odds ratios were adjusted for age, BMI, race, length of follow-up, and total 2PN embryos.

Cohort < 35 years old				
	PGT-A	**Untested**	**AOR (95% Cl)**	**p**
Cumulative Live Birth Rate	70.6%	71.1%	0.81 (0.71-0.92)	.001
Multifetal Births	8.6%	23.1%	0.61 (0.48-0.78)	<.001
Miscarriages	9.0%	8.9%	0.67 (0.37-1.19)	.168
Cohort 35 – 37 years old				
	PGT-A	**Untested**	**AOR (95% Cl)**	**p**
Cumulative Live Birth Rate	66.6%	62.5%	1.05 (0.91-1.21)	.548
Multifetal Births	10.5%	22.8%	1.04 (0.79-1.37)	.783
Miscarriages	10.5%	13.0%	0.83 (0.64-1.09)	.184

Odds Ratios adjusted for Age, Race, BMI, number of 2PN, number of embryos transferred, and length of follow-up.

Discussion and Conclusions

There was a decreased cumulative LBR in women <35 who utilized PGT-A compared to those who did not use PGT-A and no difference in LBR in women 35-37. A strategy utilizing PGT-A for these age groups does not appear to lead to improved LBR or reduced miscarriage rates compared to transferring untested embryos in this national data. Notably, PGT-A was associated with a marked reduction in multiple births although this strategy required a longer time to pregnancy compared to the transfer of untested embryos.

Title: Identifying Drivers of Cesarean Delivery Among Low-Risk Nulliparous Birthing People: A Foundation for Risk-Adjusted Improvement Targets

Name: Erica Carlson
Mentor's name: Stephanie Radke, MD
Other collaborators: Rachel Maassen, MD & Kelli Ryckman, PhD

Abstract

Background: Cesarean sections are a necessary and lifesaving procedure for many pregnant persons and their fetuses. This procedure is not without complications and risks - such as hemorrhage, wound infection, and increased risk of complications in future pregnancies. Pregnancies that are characterized by being nulliparous, term, singleton, vertex (NTSV) are considered low risk. Tracking the rate of NTSV pregnancies that end in Cesarean sections is a helpful tool in reducing the number of medically unnecessary Cesarean sections, and their complications. Healthy People 2030 set the national target NTSV Cesarean section rate at 23.6%[1]. While there is a target national rate, variation between healthcare facilities is robust due to numerous factors[2]. There is limited guidance regarding target NTSV Cesarean section rates for a particular facility.

Objective: To evaluate the NTSV Cesarean section (CS) rate at a Midwest tertiary care center by characterizing the maternal and neonatal sociodemographic context of this population, as well as their clinical, labor, and delivery courses.

Methods: This retrospective cohort study was conducted at a Midwest tertiary care facility over a three-year period, from July 1, 2016, to June 30, 2019. Deliveries that met NTSV criteria (n = 1,913) were identified and included in the study population. There were 471 deliveries within the study population that were conducted via a CS. Within the NTSV cohort, we examined outcome measures including maternal age, race, BMI, insurance status at delivery, presence of preeclampsia with severe features, diabetes, and labor induction.

Results: Of the NTSV population, 73.6% identified as non-Hispanic White, 8.4% identified as non-Hispanic Black and 8.4% identified as Asian. A majority, 77% of the cohort, had private insurance at the time of delivery. 53.8% of the birthing persons had a BMI $\geq$ 25.0, 9.2% had a diagnosis of diabetes, and 3.8% were diagnosed with preeclampsia with severe features. There were significant differences identified in the NTSV CS rate amongst various groups, including higher CS rates in those $\geq$ 35 years, persons with public insurance or who self-paid, persons with a BMI $\geq$ 25.0 kg/m^2, those with a diagnosis of preeclampsia with severe features and persons who underwent cervical ripening as a form of induction. Differences in the NTSV CS rate amongst racial/ethnic groups were initially significant, however were mediated by clinical characteristics.

Conclusion: Clinical characteristics of the NTSV birthing population at a given care center may aid in the creation of a risk-adjusted model to better estimate an appropriate NTSV CS rate for the specific facility.

Student: Alexander Choi
Mentor: David Hasan
Title: Atherosclerotic Proteins and Aneurysm Wall Enhancement in Unruptured Intracranial Aneurysms

Background and Purpose

Current MR-vessel wall imaging (VWI) of unruptured intracranial aneurysms (UIAs) permits visualization of wall structures. Aneurysm wall enhancement (AWE) was associated with atherosclerotic remodeling of the aneurysm wall accompanied by infiltration of inflammatory cells, potentially contributing to rupture. This study sought to investigate whether the luminal concentrations of atherosclerotic proteins in the aneurysm sac were associated with increased wall enhancement of UIAs in VWI.

Methods

Subjects undergoing endovascular treatment for UIAs were prospectively recruited. All subjects underwent evaluation using 3T-MRI including pre/post contrast VWI of the UIAs. Blood samples were collected from the aneurysm sac and the parent artery during endovascular procedures. The presence of AWE was correlated with the delta difference in concentration between the aneurysm sac and the parent artery for each atherosclerotic protein.

Results

-442.4±1676.3 mIU/mL, p=0.02, 114.8±397.7 versus -518.5±1344.4 μg/mL, p=0.04, and -5.6±11.3 versus -28.7±38.5 μg/mL, p=0.01, respectively).

A total of 45 patients with 50 UIAs were enrolled. The delta differences of anti-oxidized low-density lipoprotein (LDL) antibody, small dense LDL, and lipoprotein(a) were significantly higher in UIAs with AWE compared with those without AWE (767.6±1957.1 versus

Conclusions

Increased concentrations of atherogenic proteins in the aneurysm sac were significantly associated with wall enhancement of UIAs. Future studies examining the effect of medications for atherosclerosis on the atherogenic proteins within the aneurysm sac and hence the wall enhancement is warranted.

Predicting loss of ambulation in patients with muscular dystrophy due to *FKRP* variants

Lauren N. Coffey, Shelly R.H. Mockler, M. Bridget Zimmerman, Katherine D. Mathews

BACKGROUND: Dystroglycanopathies are muscular dystrophies characterized by hypoglycosylation of alpha-dystroglycan. The most common dystroglycanopathy results from variants in the Fukutin-Related Protein (*FKRP)* gene. Variants in *FKRP* are commonly associated with a limb-girdle muscular dystrophy phenotype (LGMDR9/LGMD2I). Here we examined results of standard motor function tests relative to time to loss of functional ambulation (LOA) in patients with LGMDR9.

METHODS: Participants in an ongoing dystroglycanopathy natural history study (NCT00313677) with *FKRP* variants were included (n=88). Participants who never achieved ambulation at time of data collection were excluded (n=2). Standardized motor function tests including 10-meter walk-run time (10MWT), 4-stair climb (4SC), and timed lying to standing (TLTS) were carried out by physical therapists annually. LOA was defined as self-reported full-time wheelchair use, weakness preventing 10MWT or 10MWT test time >30 seconds.

RESULTS: Among the 86 participants, 48 were homozygous for the c.826C>A founder variant. 57 retained ambulation throughout follow-up. Of the 29 who lost ambulation, 12 were homozygous for c.826C>A. Earliest age at LOA was 9 years (non-homozygous for c.826C>A). Median age at LOA for the cohort was 42.9 years. Kaplan-Meier analysis of age at LOA by genotype demonstrates that those with genotypes other than homozygous c.826C>A lost ambulation at a median age of 19.6 years, while 100% of those homozygous for c.826C>A were ambulatory at this age. Timed performance on functional tests were predictive of LOA with area under the ROC curve for LOA within 3 years of 0.88 for 10MWT, 0.91 for 4SC, and 0.83 for TLTS. Median time to LOA after losing ability to perform TLTS was 5.9 years (IQR: 2.8-8.6). Median time to LOA among those with 4SC time between 5 and 8 seconds was 8.6 years, and among those with 10MWT between 6 and 9 seconds was 9.5 years.

DISCUSSION: We show that age at LOA among patients with LGMDR9 varies by genotype, can occur in childhood, and is strongly predicted by results of timed function tests. These results can aid in anticipatory patient guidance and demonstrate real-world significance of these standard motor function tests.

Title: The Photic Blink Reflex As A Diagnostic Assessment Of Optic Neuropathy.

Student: Cyrus Colah
Mentor: Randy Kardon MD PhD
Collaborators: Nitsan Duvdevan-Strier MD, Pieter Poolman PhD, Emma Hartness

Abstract:

Background/Purpose:

The photic blink reflex has been studied in the past using electromyography (EMG). A video-based assessment of the PBR that quantifies the reflex based on degree of palpebral fissure narrowing could be useful as a non-invasive test of visual input in diseases affecting the retina or optic nerve. Our goal was to define normal physiology of the PBR in terms of PF (narrowing), including establishing normative ranges for the photic blink reflex's afferent-limb in response to light stimuli given to each eye and direct and consensual efferent-limb in normal subjects, compared to patients with optic nerve damage.

Methods:

Eyelid and pupil responses of each eye in response to flashes of light stimuli, increasing in intensity, were video-recorded in in 27 control subjects and 18 patients with optic neuropathy using a monocular hand-held device (RETeval). Direct (eyelid and pupil response of the stimulated eye) and consensual responses (eyelid and pupil responses of the eye not stimulated) to unilateral light stimuli were recorded with a binocular device (Neuroptics DP2000) in 22 control subjects. Percent-change of palpebral fissure width and pupil diameter from pre-stimulus baseline was measured from these video frames. Degree of inter-eye asymmetry was calculated using a contrast ratio.

Results:

In normal subjects, the inter-eye asymmetry of the direct photic blink reflex was greater than that of the direct pupil light reflex, and there was a greater degree of asymmetry attributed to the afferent limb than to the efferent limb of the photic blink reflex when assessed with palpebral fissure narrowing. ROC curves comparing optic neuropathy subjects and controls were established; when compared using photic blink reflex, the area under the ROC curve was 0.83±0.07, when compared using the pupil light reflex, the area under the ROC curve was 0.79±0.08.

Conclusion:

The photic blink reflex can be quantified with video-recording of the palpebral fissure narrowing. This has potential utility as an alternative to the pupil light reflex in diagnosing pathology affecting visual input, even in patients after pharmacologic pupil dilation or in pathology of the iris. The photic blink reflex and pupil light reflex had similar diagnostic accuracy in terms of area under the ROC curve in the optic neuropathy patients tested in this study.

Clinical Outcomes of Mixed-Grade Urothelial Carcinoma

George Cooper, MD Candidate, Class of 2024

Vignesh Packiam, MD

Background
The grade of non-muscle invasive bladder cancer (NMIBC) has an impact on the risk of tumor recurrence and progression. Mixed-grade (MG) urothelial carcinoma (UC) is poorly studied. Small retrospective studies have shown that MG urothelial carcinoma (UC) can have comparable outcomes to pure low-grade (LG) tumors, particularly with aggressive intravesical treatment. However, other series have conflictingly shown that MG UC, when treated with observation, has rates of recurrence and stage progression similar to or greater than high-grade (HG) UC.

Purpose
Our research seeks to analyze rates of recurrence, grade progression, and stage progression of MG UC. In addition, we provide new insight into recurrence patterns of MG UC to further understand optimal management of MG UC. We hypothesize that rates of recurrence, grade progression, and stage progression of MG UC will be similar to LG UC. We also hypothesize MG UC will primarily recur as LG UC.

Methods
Our retrospective cohort included all upper and lower tract MG UC cases treated at UIHC from Jan 2000-2020. Cases were identified by querying a database in the Department of Pathology. Full chart reviews were performed to confirm diagnosis and collect data. Any pathology report using the language "spectrum of low-grade to high-grade," "focal high-grade," or "mixed-grade," were included. Patients with less than 3 months of follow-up or tumor invasion beyond the lamina propria, were excluded.

Results
Eighteen patients with MG UC met the criteria for our study. Fourteen patients (78%) were male, and all 18 were non-Hispanic White. Median follow-up time was 22 months (Inter-quartile range (IQR) 8 – 37 months). There were 13 patients (72%) with at least one recurrence, with a median time to recurrence of 6 months (IQR 4 – 12 months). Of these, 5 (28%) had an initial LG recurrence, 2 (11%) recurred as MG, and 6 (33%) as HG. Overall, grade progression and stage progression occurred in 9 (50%) and 2 (11%) patients respectively. There were no deaths due to UC.

In a subset of 7 patients who had no prior UC, 5 (71%) had recurrent UC, while only 1 (14%) was treated with a full course of intravesical therapy.

Conclusion
Our results demonstrate that there are relatively high rates of recurrent UC in individuals with MG UC, suggesting potential benefit from intravesical treatment for these patients. Further studies are needed to determine the optimal management strategy for patients with MG UC.

Skin-to-skin contact and exclusive breastfeeding rates after cesarean birth at UIHC, before and during the COVID-19 pandemic.

Sarah Costello, BS; Alyssa Shelby, RN; Donna Santillan, PhD; Noelle Bowdler, MD

ABSTRACT

Background: Early mother-infant skin-to-skin contact (SSC) has been associated with increased rates and duration of breastfeeding independent of delivery method. This study was designed to test the hypothesis that recently implemented SSC practices after cesarean birth are associated with exclusive breastfeeding at University of Iowa Hospitals and Clinics (UIHC), and to compare rates before and during the COVID-19 pandemic.

Methods: We undertook a retrospective cohort study of women who underwent scheduled cesarean delivery at term (>=37 weeks gestation) at UIHC between April and October 2019 (before the COVID-19 pandemic) and between April and October 2020 (during the COVID-19 pandemic), 126 and 119 mother-infant dyads were identified, respectively. Subjects were grouped based on the location of SSC initiation after cesarean (operating room (OR), post-anesthesia care unit (PACU), mother-baby care unit (MBCU), or no SSC) and the mode of infant feeding (exclusive breastmilk, breastmilk and formula or formula only) at discharge and at 4-6 weeks postpartum was identified.

Results: Chi-squared analysis revealed an association between location of SSC and infant feeding type at discharge ($P<0.001$), and an association between SSC in any location and feeding type at discharge ($P<0.001$). Postpartum feeding type was associated with any SSC ($P=0.043$), however postpartum feeding type was not significantly associated with the location where the SSC was initiated ($P=0.089$). There was a strong trend towards association between time period (2019, pre-pandemic vs 2020, during pandemic) and location of SSC initiation ($P=0.051$), with increased SSC initiated in OR (16% vs. 25.2%) and PACU (12% vs. 19.33%), and decreased SSC initiated on the MBCU (30.4% vs. 20.2%). SSC in any location increased from 58.4% to 64.7% between 2019 and 2020, however, this trend was not significant ($P=0.593$).

Conclusions: SSC practices after cesarean birth at UIHC are associated with exclusive breastfeeding at discharge and 4-6 weeks postpartum. Knowledge of this relationship will be important for optimizing evidence-based practices surrounding SSC and breastfeeding support in the future.

Clinical outcomes in standard of care multiple sclerosis treatment: A case series

Landon Crippes, M2; Linda Rubenstein, PhD; Tyler Titcomb, PhD, RD; Erika Dorff, M4; Bridget Easler, BS; Mary Ehlinger, BS; Terry Wahls, MD, MBA

Background

There is growing evidence that a therapeutic diet and lifestyle may benefit people with multiple sclerosis (MS). Clinical trials are currently underway to assess the benefits of therapeutic diet and lifestyle. Review of current practices in MS care at University of Iowa Hospitals and Clinics (UIHC) will aid in better understanding trends in MS symptoms and disease progression when people with MS are given standard of care treatment.

Purpose

To describe the clinical course over time (relapse rate, severity of MS-related symptoms, number and size of enhancing lesions on MRI, utilization of disease-modifying drug treatments (DMT)) of persons newly diagnosed with clinically isolated syndrome (CIS) or relapsing-remitting MS (RRMS) between 2018 to 2020 who are treated at UIHC.

Methods

A list of medical records was generated for all newly diagnosed UIHC Neurology patients with MS from 1/1/2018 to 12/31/2020, yielding 2,500 patients. Patients were randomly selected and screened for eligibility. Inclusion criteria include age 18-56 years old and MS care at UIHC. All MS-relevant progress notes, laboratory results and radiology studies were reviewed to collect information regarding MS symptoms and disease course. Descriptive statistics were generated. Clinical course based on relapse rate was determined by reviewing each MS-related progress note for documentation of worsening of symptoms and statement of relapse occurrence. Treatment escalation was determined based on route of drug administration for DMT changes (i.e., escalating from oral to injection to infusion). MRI analysis included brain, cervical spine and thoracic spine imaging.

Results

A total of 40 patient records have been abstracted. The average age is 37 (SD 8.8). 30 participants are Female sex (75%). 34 self-identify as White (85%), 1 as African American/Black (2.5%), 1 as Asian (2.5%), 2 as Hispanic/Latino of any race (5%), 1 as Multiracial/Two or More Races (2.5%). There is an average of 5.7 progress notes recorded per patient (SD 2.8). There are 1.2 documented MS relapses per patient (SD 1.08). 10 patients have had an escalation in their DMT (25%). Of the 35 patients with more than 1 MRI (87.5%) 5 have improved (decreased lesion size/number), 23 show stable lesions and 7 have worsened (increased lesion size or number). A total of 5 patients have utilized a special diet (12.5%), including 5 different diet descriptions. All 5 of these patients utilize a DMT in conjunction with their diet.

Conclusion/Discussion

Due to the small sample size, statistical significance is not anticipated. Procedures for chart abstraction, definition of terms and data analyses will be refined in close collaboration with study biostatistician to establish the effect size of utilizing a special diet on MRI and clinical measures. Results and significance of findings will be presented.

Title: Analysis of peripheral CD4+ Vβ TCR repertoire expression in Bullous pemphigoid.

Authors: Tyler P Crowe, Samuel Connell, Mia Poleksic, Patrick Schlievert, Janet A Fairley, Kelly N Messingham.

Background: Bullous pemphigoid (BP) is an autoimmune blistering disease that primarily affects the elderly. BP is characterized by antibodies to collagen XVII and patients suffer from erosions and blistering of the skin. Since the immunologic mechanisms leading are unknown, standard therapy is high-dose immune suppression. Our research group has recently shown that ~90% of BP patients are colonized with *Staphylococcus aureus* that produces the toxic shock syndrome toxin-1 (TSST-1), a superantigen (SAg) toxin that is associated with autoimmunity. In addition to TSST-1, *S. aureus* produces up to 23 additional SAg toxins that modulate immunity through direct interaction with specific Vβ domains of the T cell receptor.

Purpose: The purpose of this study was to determine if cutaneous *S. aureus* colonization modulates systemic immunity through examination of Vβ TCR expression profiles.

Methods: Bacterial colonization was evaluated by sterile sampling of intact lesions and growth of catalase$^+$ and coagulase$^+$ Gram positive cocci. Vβ TCR expression was evaluated via RT-qPCR in CD4+ T cells purified from the peripheral blood of 11 BP patients and age- and sex-matched controls. Briefly, T cells were enriched from peripheral blood via magnetic sorting, RNA was extracted and cDNA libraries were generated. Expression of Vβ1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13c, 13d, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, and 24 mRNA was examined using published primer sets and RT-qPCR with housekeeping gene GAPDH and TCR Cβ as reference genes. In vitro T cell proliferation was evaluated in response to purified TSST-1 after 5 days.

Results: CD4+ T cells purified from BP patients exhibited significantly decreased expression of Vβ7, 9, 13c, and 17 compared to controls. All other Vβ showed similar variance in expression within disease groups, though Vβ3, 4, and 5 which are associated with other SAgs were increased and trending toward significance. Interestingly, Vβ2, known to bind TSST-1, expression by peripheral CD4+ T cells from BP patients and controls and Vβ2 expression was not significantly different or associated with lesional TSST-1+ *S. aureus* colonization. Proliferation of T-cells from BP patients in response to TSST-1 was elevated, compared to controls.

Conclusions: This study indicates that BP patients are characterized by a skewed Vβ TCR repertoire; however, TSST-1 does not appear to be a primary influence. It is possible that i) other *S. aureus* SAgs are driving systemic Vβ TCR changes; ii) the local (skin) effects of TSST-1 are not reflected in the periphery; iii) the primary TSST-1 in the skin is through modulation of keratinocytes, rather than T cells. Alternatively, it could be that the differences in Vβ TCR predispose individuals to developing autoimmunity and are independent of *S. aureus* colonization. Ongoing studies are aimed at understanding if *S. aureus* colonization is responsible for Vβ TCR repertoire skewing in BP patients.

Impact of Education and Self-Collection Kits on Extragenital Sexually Transmitted Infection Testing in the Urgent Care Setting

Victoria Cunningham, MS; Jonathan Hurdelbrink, PhD; Hayden Smith, PhD, MPH; Steven Craig, MD; Katherine Sittig, MD; Lisa Veach, MD

Background: According to Centers for Disease Control and Prevention 2019 data, sexually transmitted infections (STIs) in the United States have reached an all-time high. Extragenital sites such as the throat or rectum may serve as a reservoir for STIs and lead to increased transmission of infections if left untreated. Adequate screening and diagnosis of STIs can help prevent outcomes such as infertility, pelvic inflammatory disease, and an increased risk of contracting human immunodeficiency virus. The purpose of this study is threefold: to characterize the population of patients that present and test positive for STIs, to determine the proportion of patients that are receiving extragenital STI testing, and to observe the effect of an educational intervention and implementation of self-collected swabs on improving extragenital site testing and diagnosis of STIs.

Methods: Four urgent care clinics from the UnityPoint health system located within a metropolitan area in central Iowa participated in the study. Retrospective data was ascertained for all adults receiving STI testing for *Chlamydia trachomatis* (CT) and *Neisseria gonorrhea* (GC) at study clinics to serve as a historic comparison. Due to the impact of the COVID-19 pandemic on urgent care utilization, baseline data were taken from 2019. The prospective component of the study involved two interventions. All four clinics received an educational presentation regarding the importance of extragenital testing for STI detection. Two of these clinics also served as the pilot sites for utilization of patient self-collection kits. Information on demographics, testing type, and test results will be collected for adult patients undergoing STI testing at the four clinics from July 15 to December 31, 2021.

Results: Baseline data from 2019 are summarized in Table 1. Of note, during this period there were 1113 patient encounters across the four clinics related to CT and/or GC testing. Of these encounters, 708 (64%) were female patients and 182 (16%) were positive for CT or GC. Only 7 tests (1%) were obtained from extragenital sites (i.e., throat or rectum). The prospective portion of the study will review the same months and data fields after the educational intervention. A preliminary analysis using the first month of prospective data is planned and will be included on the study poster.

Discussion: The baseline data indicates that less than 1% of encounters for CT and/or GC testing involved extragenital site testing across the four participating clinics in 2019. Prospective data will examine the impact of both interventions on extragenital site testing. It is hypothesized that the two clinics that received education and self-collection kits will have more extragenital testing and potentially diagnosed STIs.

Table 1. Historic testing data at four urgent care clinics

Intervention Group*	Patient Encounters	Positive STI (CT/GC)	Extragenital Tests
Education and self-collection kits	582	100 (17%)	6 (1%)
Education only	531	82 (15%)	1 (<1%)
Total	**1113**	**182 (16%)**	**7 (1%)**

CT: *Chlamydia trachomatis*; GC: *Neisseria Gonorrhea*; STI: sexually transmitted infection.
*Intervention groups each consist of two urgent care clinics in central Iowa metropolitan areas

Renal sodium wasting in CF hemizygous mice

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Cystic Fibrosis (CF) is an autosomal recessive disorder caused by loss-of-function mutations in cystic fibrosis transmembrane conductance regulator gene (CFTR), which encodes a chloride channel expressed in multiple organs including the kidney renal tubule. Patients with CF may have a kidney defect leading to inappropriate loss of sodium chloride, and CF mutant heterozygotes ("carriers," 3% of the US population) were more likely to be diagnosed with hypovolemia in a large cohort study. The mechanism underlying renal sodium chloride loss remains unknown. We hypothesize that CFTR hemizygous mice, modeling CF carrier status in humans, have impaired chloride-dependent Na excretion, leading to volume contraction.

We observed that C57Bl/6J mice begin to retain Na when placed on a Na-replete, Cl-deficient diet, demonstrating kidney Na excretion is chloride-dependent. Compared to control littermates, CFTR hemizygous mice failed to retain Na when placed on the same diet, resulting in Na wasting. Membrane-enriched preparations of kidney lysates from these CFTR hemizygous mice also had increased abundance of activated phosphorylated Na-Cl cotransporter (pNCC), a sodium reabsorbing transporter which is a downstream target of sodium-retentive feedback systems (e.g. renin-angiotensin system). These results suggest that CF heterozygous patients may be more susceptible to hypovolemia, although further research is needed to understand why pNCC is increased despite evidence of reduced sodium retention.

Assessing the impact of nutritional intake on post-operative recovery following Orthopaedic Trauma

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Background: Poor nutrition is common in the general population. After musculoskeletal trauma there is an increased metabolic demand required for fracture and wound healing. Pain, nausea, narcotic use and required NPO status for operative procedures further decrease oral intake during the healing phase after trauma. The body compensates by entering a catabolic state, breaking down healthy, functional muscle mass leading to further disability in an already compromised host. By intervening on this pathologic process, nutrition supplementation has significant potential to prevent loss of functional muscle mass. This study aims to characterize specific perioperative macro- and micro-nutrient deficiencies and their association with loss of functional muscle mass and injury related complications in a high energy musculoskeletal trauma population.

Hypothesis: Nutrition deficiencies will be common among individuals sustaining high energy musculoskeletal trauma treated with operative fixation. Complications and loss of lean body mass will be common among musculoskeletal trauma patients experiencing malnutrition.

Methods: Adult patients ages 18-55 years with either an Isolated open fracture or $\geq$2 pelvic or extremity fractures indicated for surgical fixation were eligible for this study. Primary outcomes include nutrient intake and changes in lean body mass. Caloric and macro- and micro-nutrient intake and activity levels will be measured using a validated food frequency questionnaire and activity surveys (Vioscreen® & Vioactive®) (VioCare®) at baseline and 3 months. Changes in body composition (BMI, Body Fat %, Lean Body Mass) will assessed using Bioelectrical Impedance Analysis (BIA) at baseline, 6 weeks, and 3 and 6-months after surgery. Post-operative healing and complication rates up to 6 months post-operatively will be assessed via chart review.

Results: Currently 13 subjects (3 F, mean age 36 yrs.) have been enrolled. Two subjects have completed the 6-month follow-up visit. Statistical analysis comparing rates of change in body composition and descriptive analysis of post-operative nutrition deficiencies, as well as complication rates will be completed upon further prospective data collection.

Discussion: This study aims to characterize nutrition deficiencies during recovery from musculoskeletal trauma and their influence on fracture healing, muscle mass and complications. Study results will serve as preliminary data for application to high level funding for multicenter randomized controlled trials. Targeted interventions will aim to prevent malnutrition related complications and muscle loss after operative fixation of high-energy trauma.

Student: Jessica De Haan M3
Mentor: Dr. Franklin Dexter, Anesthesia

Title: Elements of Pregnancy and Parenthood Policies of Importance to Medical Students and Included in a Sample of Medical Schools' Websites and Student Handbooks

Background: Medical students who are parents or considering parenthood often want information about school policies. A survey of 194 medical students from one US school examined seven "elements that [students thought] should be included in a school policy on pregnancy/ maternity leave." For example, students want to know "how a student arranges for" such leave. We evaluated generalizability and usefulness of the survey results.

Methods: The survey included 35 demographic variables about individual students. We tested empirically for associations with the seven items, thereby evaluating generalizability of the survey results to different demographic groups. We then surveyed public websites of a sample of US medical schools to evaluate usefulness of the knowledge of the seven items. For the 33 surveyed schools, we generated PDF files documenting each of the seven items when present.

Results: The seven items had content validity as a necessary and sufficient set of items. In addition, there were no significant associations of the seven items with demographic variables. Therefore, there is little chance that demographic differences among medical schools in their averages would affect the items needed for their websites and student handbooks.
Among the surveyed medical school websites, one of 33 had all seven items (upper 95% confidence limit 14% of schools nationally would be expected to have all seven items). This being many fewer than half ($P < 0.0001$) shows usefulness to knowing the seven items (i.e., schools are not including the seven items on their own).

Conclusions: These findings show that it is known what information students want to know about in a school policy on pregnancy and parental leave. Adding these seven items to public websites is an easily actionable intervention to help current and future medical students.

Prognostic and therapeutic value of the Hippo pathway, RABL6A, and p53-MDM2 axes in sarcomas

Chandni Desai, Jon Thomason , Jordan L. Kohlmeyer , Anna C. Reisetter , Parmanand Ahirwar , Khadijeh Jahanseir , Mariah Leidinger , Georgina Ofori-Amanfo , Karen Fritchie , Sadanandan E. Velu , Patrick Breheny , Dawn E. Quelle , and Munir R. Tanas

Abstract: Additional prognostic and therapeutic biomarkers effective across different histological types of sarcoma are needed. Herein we evaluate expression of TAZ and YAP, the p53-MDM2 axis, and RABL6A, a novel oncoprotein with potential ties to both pathways, in sarcomas of different histological types. Immunohistochemical staining of a tissue microarray including 163 sarcomas and correlation with clinical data showed that elevated YAP and TAZ independently predict worse overall and progression-free survival, respectively. In the absence of p53 expression, combined TAZ and YAP expression adversely affect overall, progression free, and metastasis free survival more than TAZ or YAP activation alone. RABL6A independently predicted shorter time to metastasis and was positively correlated with p53, MDM2 and YAP expression, supporting a possible functional relationship between the biomarkers. Network analysis further showed that TAZ is positively correlated with MDM2 expression. The data implicate all five proteins as clinically relevant downstream players in the Hippo pathway. Finally, a novel inhibitor of MDM2 (MA242), effectively suppressed the survival of sarcoma cell lines from different histological types regardless of p53 status. These findings suggest both independent and cooperative roles for all five biomarkers across different histological types of sarcoma in predicting patient outcomes and potentially guiding future therapeutic approaches.

Mechanism of GRB2 Nuclear Localization in T Cells

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Background: Growth factor receptor bound protein-2, commonly known as GRB2, is an intracellular adaptor protein that is ubiquitously expressed throughout the human body. Comprised of a central SH2 domain adjoined by two SH3 domains, GRB2 functions to coordinate intracellular signaling events through SH2 binding with phosphorylated tyrosine residues and SH3 interactions with proline-rich regions across a broad repertoire of binding partners. Together, the multidomain structure of GRB2 orchestrates interactions between phosphorylated adaptors and receptors and their respective downstream effector proteins. In T cells, GRB2 interacts with multiple signaling molecules involved in T cell receptor (TCR) signaling. Our lab has recently described a novel role for GRB2 in facilitating the formation of Linker for Activation of T cells (LAT) clusters at the plasma membrane following TCR activation. Interestingly, although the majority of studies involving GRB2 have focused on the protein's roles at the plasma membrane and in the cytosol, recent research points to a preponderance of GRB2 within the T Cell nucleus.

Purpose: In the present study, we investigate subcellular localization and potential nuclear localization mechanisms of GRB2 through a combination of *in vitro* microscopic and biochemical approaches.

Hypothesis: We hypothesize that GRB2 is actively transported across the nuclear membrane through a karyopherin-mediated mechanism.

Methods and Results: We visualized intracellular GRB2 using Stimulated Emission Depletion (STED) Microscopy, where we found GRB2 distributed throughout the cytosol and nucleus. Surprisingly, when IMARIS software was used to generate a 3-dimensional rendering of the T-Cell nuclear membrane and areas of GRB2 signal intensity, we observed clear evidence of GRB2 localization and embedment within the nuclear membrane. Recognizing the potential for GRB2 active transport across the nuclear pore complex—a key regulatory checkpoint for nuclear entry—we then went on to investigate a possible association of GRB2 with the importin-β1/RanBP2 nuclear localization mechanism. Interestingly, while co-immunoprecipitation of wild type GRB2 in T Cells does not indicate interactions with RanBP2, our studies indicate an association of GRB2 with both cytosolic and nuclear importin-β1.

Discussion and Future Directions: Together, our findings support a novel model for GRB2 nuclear localization in T-Cells, in which GRB2 utilizes the importin-β1 pathway for nuclear entry. Future directions will focus on investigating potential functions of GRB2 within the nucleus, including in the regulation of gene transcription, DNA binding, chromatin remodeling, and differential roles of dimeric and monomeric GRB2.

Evaluating Airway Surface Epithelium in Chlorine Gas Exposed Ferret Lungs

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Introduction. Long-term survival after lung transplantation is limited largely by the development of obliterative bronchiolitis (OB). OB lesions are inflammatory and fibroproliferative occlusions that obstruct airways and lead to graft dysfunction. Half of patients who receive lung transplants will develop OB within five years of transplantation. OB lesions occur as a pathophysiologic response to the destruction of airway epithelium, which is caused by persistent or recurring injuries. These injuries can have myriad causes including gastroesophageal reflux, bacteria, viruses, immune-mediated injuries, as well as chemical toxin exposure. Multipotent airway basal cells have the capacity to fully regenerate the epithelium after loss of luminal cells and maintain it during homeostasis, but in OB, self-renewing basal stem cells are lost with disease progression. However, it is not yet clear what aberrant changes in basal stem cell properties lead to their loss in OB and what aspects of transplantation impose aberrant limitations on the capacity of basal stem cells to self-renew over time.

Purpose. In this pilot study our goal was to evaluate pathology in chlorine gas-exposed ferret airways to produce a model for interrogating how basal cell depletion leads to OB. Establishing a reproduceable model of OB-like lesions will allow further research into the pathological processes behind OB epithelial loss and stem cell depletion. Ultimately, leading to further research into treatment and preventative options for lung transplant recipients against chronic rejection and OB.

Methods. Chlorine gas was research grade, 400 or 600ppm balanced with nitrogen, then diluted to appropriate concentrations using medical grade oxygen or room air. A chlorine gas compatible regulator was purchased to verify concentration of chlorine gas delivered and the ferrets oxygen saturation was monitored for adequate oxygen intake. Ferrets were exposed to chlorine gas at 100ppm, 200ppm, or 300ppm for 30 minutes. During the procedure the ferrets were given a combination of an anesthetic plus pain medication. Body temperature was monitored during the procedure and initial recovery, and a heat lamp was used to help regulate appropriate temperature. Ferrets were euthanized 30 minutes (T30m cohort) post-chlorine gas exposure at concentrations of 100ppm, 200ppm and 300ppm and euthanized 48 hours (T48h cohort) post-exposure for 100ppm and 200ppm concentrations (n=1 for each chlorine gas concentration). The lung block was harvested and preserved in 10% neutral buffered formalin. The left lower lobe of the lung was isolated and tissue samples were processed by H&E staining and immunostained for specific cell type markers; surface epithelial basal cells (p63, K5, K14), goblet cells (Muc5AC), club cells (SCGB1A1), and ciliated cells (acetylated- α-tubulin). Tile-stained fluorescent images were quantified using ImageJ.

Results. Hematoxylin & eosin staining showed loss of ciliation of epithelial cells with chlorine exposure of 100ppm, 200ppm, and 300ppm for T30m cohort and in 100ppm and 200ppm for T48h cohort. Exposure to chlorine at 200ppm and 300ppm for T30m cohort and 100ppm and 200ppm for T48h cohort, showed increased loss of surface epithelial cells and cell debris within the airway lumen. The basal cell layer remained present within all groups and there was no histological evidence of fibrosis. Immunohistochemistry staining, represented as fold change of positive staining area relative to baseline control (no chlorine exposure), showed a decrease in acetylated- α-tubulin across the groups; 0.686x 100ppm T30m, 0.456x 200ppm T30m, 0.444x 300ppm T30m, 0.478x 100ppm T48h, and 0.160x 200ppm T48h. Muc5AC intensity showed a decrease across the groups; 0.690x 100ppm T30m, 0.594x 200 T30m, 0.523x 300ppm T30m, 0.438x 100ppm T48h, and 0.417x 200ppm T48hr. SCGB1A1 intensity showed a concentration dependent increase; 1.80x 100ppm T30m, 1.88x 200ppm T30m, 2.86x 300 T30m, 2.19x 100 T48h, and 2.41x 200 T48h. K5 intensity was strong and present across all conditions indicating no loss of the basal cell layer. K14 intensity increased; 1.90x 100ppm T30m, 1.65x 200ppm T30m, 2.61x 300ppm T30min, 2.70x 100ppm T48h, and 2.79x 200ppm T48h.

Conclusion. Basal stem cells remain viable at 48 hours following exposure to chlorine (200ppm). To see the loss of the multipotent airway basal stem cell layer and obliterative bronchiolitis like-lesions using this chlorine gas model in ferrets, longer timepoints and/or higher dose of chlorine gas need to be investigated. The next step in this experiment is to do an exposure 200ppm and 300ppm of chlorine gas and euthanize five days post-exposure, evaluating the tissue for basal cell depletion and fibrosis.

Dexamethasone Eluting Arrays suppress Foreign Body Response following Cochlear Implantation

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Introduction: Cochlear implants (CIs) provide auditory rehabilitation to patients with sensorineural hearing loss. CIs generally have low complication rates; however, implantation of the electrode array inevitably leads to fibrotic growth around the electrode within the cochlea. This is believed to be related to an inflammatory host-mediated foreign body response (FBR). Post-implant FBR has also been linked to the loss of residual acoustic hearing and diminished effectiveness of the CI due to elevated electrode impedances leading to a necessity for higher voltages, a decrease in the dynamic range of stimulation, and a decrease in battery life. In clinical practice, dexamethasone is applied perioperatively into the cochlea to reduce the FBR. To understand the underlying mechanism of the FBR and the role of dexamethasone in postimplant patients, dexamethasone eluting cochlear implants have been implanted in various animal models. These models suggests that macrophages, myofibroblasts, and lymphocytes are among the predominant cell types involved in the post-implant FBR and that dexamethasone eluting implants effectively suppress the FBR. It is further evident from models of implantation in other organs that the interaction among macrophages, lymphocytes, and myofibroblasts plays a critical role in the FBR. In the case of cochlear implantation, the presence or absence of such interaction and its significance are unknown. Mouse models offer specific advantages over other animal models in understanding the underlying mechanisms of FBR as: (1) much is known about the immune system of mice compared to most other animal models and (2) various genetic tools including knockouts and transgenic mice are available. We, therefore, developed a transgenic reporter mouse model for macrophages and neurons and implanted it with dexamethasone eluting cochlear implants.

Purpose: The goals of this study are to (1) evaluate the effect of a dexamethasone eluting CI on intracochlear FBR following surgical implantation in mice compared to a regular CI and (2) investigate the role of dexamethasone in suppression of immune activation after implantation.

Methods: 12-week-old CX3CR1-GFP, Thy1-YFP mice were implanted with either regular or dexamethasone eluting cochlear implants in the left ear with the contralateral ears acting as controls. The implants were stimulated for either 10, 28, or 56 days, after which they were euthanized. Cochlea were fixed with 4% PFA and cryosectioned at 30 micrometer thickness. In these reporter mice, macrophages were intrinsically labeled with green fluorescent protein (GFP) and neurons with yellow fluorescent protein (YFP). In addition, near mid-modiolar sections of the cochlea were labeled with dapi for nuclei and immunostained with antibodies against alpha-SMA for myofibroblasts to identify fibrosis and against MHC II to identify macrophages with antigen presentation capacity to lymphocytes. Images were taken using a Leica STELLARIS 5 confocal microscope. Quantitative image analyses were then performed using IMARIS 9.7.2 image analysis software. The analyses were completed for each cell type of interest in the spiral ganglia and lateral walls in the basal, middle, and apical turns of cochlea along with the scala tympani of the basal turn and the modiolus. The cochlear regions were manually traced, and the counting of nuclei, macrophages, and MHCII+ macrophages was automated using IMARIS. Volumetric analysis of fibrosis was done by measuring the relative volume of SMA+ cells in the scala tympani. The cochleae were compared with respect to their treatment condition, the number of days post-implantation (dPI), and the cochlear regions of interest. Differences in nuclei, macrophages, SMA+ cells, and MHC II+ macrophage densities were tested using one-way ANOVA with post-hoc Tukey analyses.

Results: Mice treated with a dexamethasone eluting CI had a significant reduction in cellular density, macrophage density, and fibrotic response in the scala tympani of the basal turn of the cochlea at all three time points. Significant reduction in the macrophage density for all other regions of interest was also observed at 10-dPI and 28-dPI. The dexamethasone eluting CI also yielded a significant reduction in the density of MHC II+ macrophages at all time points for all cochlear regions of interest.

Conclusions: (1) Dexamethasone eluting cochlear implants significantly reduce the intracochlear cellular infiltration, inflammation, fibrosis, and immune activation following surgical implantation. These results suggest this modified implant could potentially improve the long-term performance of the cochlear implant. (2) The expression of MHC II on infiltrating macrophages suggests antigen is presented to lymphocytes, further contributing to the foreign body response. More studies are needed to elucidate the role non-macrophage immune cells involved in the inflammatory response following surgical implantation.

Alexandra Eckburg

Mentor: Vincent Liu MD

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Frequency and Significance of Radiographic Findings Detected of Initial Staging for Mycosis Fungoides & Sezary Syndrome

Mycosis fungoides (MF) and Sezary Syndrome (SS) is the two common subtypes of cutaneous t cell lymphoma (CTCL). Depending upon the extend of cutaneous disease at initial presentation, a patient may undergo a staging workup that includes radiographic imaging. We sought to better understand how often patients were upstaged as a result of this imaging as well as how frequently unexpected (i.e. incidental) findings were detected. We found that 21/88 patients had lymphadenopathy related to CTCL, while 70/88 had incidental findings unrelated to CTCL. Of these 70 patients, 6 were eventually given significant diagnoses (i.e. requiring management by a non-dermatologist) as a result of their CTCL staging imaging. These findings contribute to our understanding of how frequently CTCL patients are upstaged as a result of imaging and demonstrates that clinicians should be aware of the potential for incidental findings when they image a patient for CTCL staging.

Title: Investigation of factors influencing antibiotic prescription decisions in the Veteran's Health Administration

Presenter: Evan Economos (M2) **Mentor:** Daniel Livorsi, MD

Introduction: Antibiotic resistance is a major public health concern. Reducing the overuse of antibiotics is an important strategy to combat the spread of antibiotic resistance. To do so, many healthcare institutions have implemented antibiotic stewardship programs to ensure effective and judicious antibiotic use. The implementation of antibiotic stewardship practices can be challenging, as it involves changing clinicians' knowledge, attitudes and emotionally-influenced behaviors around antibiotic-prescribing. Understanding these factors is an important pre-requisite to any effort to successfully implement a new stewardship practice.

Purpose: The goals of this project were to identify the factors that influence providers' antibiotic-prescribing decisions for common infections in hospitalized patients. Our findings may inform future work around both antibiotic decision-making and stewardship implementation.

Methods: We conducted 49 semi-structured interviews with healthcare workers at 15 Veterans Health Administration medical centers sites. The interviewees included the antibiotic stewardship program physician and pharmacist champion at each of the 15 sites, as well as other key stakeholders, including pharmacy administrators, hospitalists, ICU physicians, and Emergency Department providers at 5 of the sites. The interviews were designed to elicit perspectives on barriers and facilitators to the adoption of management policies for fluoroquinolones and extended-spectrum cephalosporins and factors that influenced the use of these antibiotics.

All interviews were audio-recorded and transcribed. Transcripts were uploaded into MAXQDA, a qualitative data management and analysis software program. An interdisciplinary team of physicians with antibiotic stewardship expertise and qualitative analysts analyzed the transcripts using thematic analysis with a focus on 1) barriers and facilitators to stewardship implementation and 2) decision-factors surrounding antibiotic-prescribing. Decisional factors were then coded for interview segments regarding pneumonia, urinary tract infections, intra-abdominal infections, and skin/soft tissue infections. One team member completed preliminary coding for decisional factors, then consulted with another team member to ensure that consensus was reached.

Results: Each decisional factor that had been identified by at least 2 participants was sorted into one of five categories: type of infection, patient-specific factors, contextual factors, provider-specific factors, and drug-specific factors.

Participants frequently commented on the complexity of antibiotic-prescribing decisions and occasionally balked at the idea of answering a question about antibiotic-prescribing without additional information. There was emphasis on the individuality of each patient situation. One stewardship pharmacy champion highlighted the individuality of each patient's situation and the difficulty of speaking in generalities about antibiotic-prescribing: "the value of us [the stewardship team] reviewing all these antibiotics is that every single patient is slightly different and there's lots of gray area and nuance."

Many decisional factors that participants cited (e.g. allergies, guidelines, or spectrum of coverage) were relatively straightforward. However, there were also decisional factors that were more vague, such as "complicated infection," "healthcare exposure," or "septic." Many different participants used these terms in describing factors present in their decision-making process, but no specific definition was provided.

Discussion: Our investigation revealed that participants consider many different aspects of each patient's case when prescribing an antibiotic. These factors may differ slightly across participants, but there was a strong consensus that these prescription decisions are complex and cannot be easily reduced to a few simple rules. In addition, we learned that some phrases used in the decision-making process are poorly defined and may differ across providers. Investigating the scope of these differences, and how divergent understanding of these phrases affects prescription practices could be valuable.

This investigation provides a strong foundation for further work on antibiotic decision-making, which could leverage surveys or more in-depth semi-structured interviews of providers. Understanding what exactly providers are considering when making prescription decisions will be beneficial to current stewardship efforts. Future work should explore how important each of these factors are relative to one another.

Maternal antioxidants prevent cortical microglial morphology changes in offspring after prenatal stress

Student: Hannah Erlbacher, Mentor: Dr. Hanna Stevens, MD, PhD – Department of Psychiatry
Collaborators: Dr. Sara Maurer, PhD and Dr. Jada Bittle, PhD

Introduction: Previous research has established an association between prenatal stress and an increased risk of offspring psychopathology, including autism spectrum disorder, depression, and schizophrenia. Past research has also established that prenatal stress affects offspring brain microglia morphology. Because microglia are essential for synaptic development, connectivity, and regulation of proliferating neural progenitors in the developing brain, more research is needed to explore how prenatal stress impacts offspring microglia and how negative changes can be prevented. One mechanism underlying these changes at the cellular level is redox dysregulation. Redox dysregulation due to prenatal stress has been shown to disrupt the development of inhibitory neural circuitry, including GABAergic forebrain systems, and delay the migration of embryonic cortical interneurons. Because the administration of antioxidants to pregnant mice prior to stress has been shown to normalize these migration delays, which are also linked to offspring psychopathology, the role of antioxidants in rescuing microglia from redox-related effects should be explored. The purpose of this project was to examine the effects of prenatal stress on adult offspring microglia morphology and to determine whether the administration of antioxidants, N-acetylcysteine (NAC) or astaxanthin (AST), to pregnant mothers would mitigate morphology changes. I hypothesized that consistent with past research, microglia morphology would be significantly different in the stress conditions. I also hypothesized that maternal antioxidant administration during prenatal stress would rescue offspring microglia from these changes.

Method: In these experiments, half of the pregnant CD1 mice were non-stressed while half were stressed using 45-minute bright light sessions, three times daily from embryonic day 12 until delivery. Pregnant females were intraperitoneally injected with either NAC (200 mg/kg daily in phosphate buffered saline (PBS)), AST (30 mg/kg [first daily injection] or 10 mg/kg [second and third daily injections] in PBS), or PBS (200 µl daily) prior to stress sessions or at equivalent times in non-stressed females. Adult offspring were euthanized at five months of age, and the brain tissue fixed, sectioned and immunostained using a primary antibody specific for microglia (Iba-1) and a secondary antibody (Goat x Anti-Rabbit 594) as a florescent tag. Using Stereo Investigator software (Microbrightfield) and a Zeiss epifluorescent microscope, a blinded optical fractionator approach and unbiased counting rules estimated the total microglia population and population of each morphological category in the cortex. The morphology classification rules were as follows: (1) amoeboid: 0-1 process, (2) lowly ramified: 2 or 3 thicker processes, (3) moderately ramified: 4 processes or those with multiple thin, spindly processes and a small soma, (4) highly ramified: 5 or more processes and a large soma. To compare microglia density across conditions, total microglia population was divided by total cortical volume. The percent of each morphology was calculated and later combined into two morphology types for analysis due to similar results in the morphology outcomes that were combined: those with fewer processes (ameboid + lowly ramified) and those with many processes (moderately + highly ramified). 3-way ANOVAs calculated with Graphpad Prism determined how each factor—prenatal stress, treatment, and offspring sex—affected the outcomes of interest.

Results: Prenatal stress significantly decreased the percent of ameboid + lowly ramified microglia and increased the percent of moderately + highly ramified microglia in the cortex of both males and females. Percent ameboid + lowly ramified microglia was also affected by an interaction between treatment and stress for both NAC ($p=0.0006$) and AST ($p=0.0022$): antioxidant administration restored the percent ameboid + lowly ramified microglia in the male and female offspring of stressed mothers to levels similar to non-stressed offspring. Similarly, percent moderately + highly ramified microglia was affected by an interaction between treatment and stress for both NAC ($p=0.0223$) and AST ($p=0.0341$): maternal antioxidant administration prevented the increase in percent moderately + highly ramified microglia in male and female offspring of stressed mothers. For total cortical microglia density, there was an interaction between sex and prenatal stress with no effects of antioxidant administration. Male offspring of non-stressed mothers had trend lower overall microglia density than those of stressed mothers whereas females of non-stressed mothers had trend higher densities than those of stressed mothers.

Discussion: Adult offspring of prenatally stressed mothers had microglia morphology changes consistent with past research: increases in the more highly ramified types and decreases in the more lowly ramified types. Maternal treatment with either antioxidant before stress sessions rescued offspring microglia from these changes. In addition, while stress effects on morphology were similar across males and females, there was a significant interaction of prenatal stress and offspring sex on total cortical microglia density. Combined with past research, this project suggests that insults during early brain development have a lasting impact on microglia. The normal distribution of morphology types becomes skewed after early stress. More research is needed to understand how changes in morphology reflect microglia and neuropsychiatric functioning and to elucidate how antioxidants could be used as a possible means to protect against the negative effects of prenatal stress on development.

Pathophysiology of Sodium-Dependent Glucose Transporter 1 in Diabetic Cardiomyopathy

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Mentor: Ferhaan Ahmad, M.D., PhD, Division of Cardiovascular Medicine, Department of Internal Medicine

Abstract

Background. There are two kinds of heart failure: systolic and diastolic. Systolic heart failure is characterized by an inability of the heart to contract efficiently, whereas diastolic heart failure is characterized by impaired relaxations. There are numerous pathologies that may lead to heart failure, including inherited and acquired cardiomyopathies. Diabetic cardiomyopathy occurs in patients with type 1 and 2 diabetes in the absence of other causes for heart failure, such as coronary artery disease. Although this disorder has a prevalence of 1.1%, its pathophysiology remains poorly understood, resulting in it currently having no specific treatment[1]. However, it has been demonstrated that when cardiac stress occurs, glucose becomes the primary energy metabolite over free fatty acids[2]. Chronic glucose uptake has been shown to lead to heart failure[3]. Therefore, the mechanism of glucose uptake into cardiac tissue is vital to understand. Traditionally, it was thought that the five GLUT transporters played the largest role in the facilitated diffusion of glucose. However, my mentor's laboratory previously discovered that sodium-dependent glucose cotransporter 1 (SGLT1) was expressed and upregulated in cardiac tissue in several pathologies. My mentor's laboratory has also shown that SGLT1 is upregulated by AMPK, insulin, and leptin[2,4]. AMPK and insulin do not directly interact with SGLT1, rather, both activate ERK which then upregulates SGLT1 by several putative mechanisms[5]. When activated, ERK is phosphorylated, and P-ERK may stimulate increased SGLT1 expression via direct phosphorylation of SGLT1, activating transcription factors that promote transcription of SGLT1, or by activating SGLT1 stabilizing factors.

Hypothesis. The purpose of this study is to examine the effect of diabetic cardiomyopathy on ERK and P-ERK content. We hypothesize that hyperinsulinemia and hyperglycemia present in type 2 diabetes increases activation of ERK, which results in increased downstream SGLT1 expression.

Methods and Results. To test this hypothesis, wild type (WT) and SGLT1 knockdown mice were fed control and high fat diets (HFD) to induce type 2 diabetes mellitus. Transgenic mice with cardiomyocyte-specific knockdown of SGLT1 ($TG^{SGLT1\text{-}DOWN}$) were created using RNAi technology. Western blots were used to determine the relative amounts of P-ERK, ERK, and ratio of PERK:ERK in heart tissue of sacrificed mice, utilizing beta-tubulin as a loading control. An ANOVA with Bonferroni correction was used to compare results. There was significantly less ERK present in WT and $TG^{SGLT1\text{-}DOWN}$ mice on a control diet compared to the down HFD mice. There was no significant difference noted between the P-ERK levels or the ratio of P-ERK:ERK between any of the mice models, although the HFD mice appeared to have less expression. The increased expression of ERK in HFD mice compared to control diet mice supports the hypothesis, suggesting that hyperinsulemia increases expression. The lack of difference within diets also supports our hypothesis, suggesting that ERK is indeed upstream of SGLT1. However, the P-ERK and P-ERK:ERK data does not support our hypothesis, as we expected there to be increased expression of activated P-ERK. This can likely be attributed to the low sample size and differences in protein loading.

Conclusions. Our results are not consistent with previous studies, which indicate that ERK and P-ERK levels are elevated during diabetes. This disconnect is likely the result of such a small sample size. Moving forward, more data should be collected evaluating ERK and P-ERK levels. Additionally, determining whether taking mice off the HFD changes the P-ERK and ERK content may be relevant for determining if this pathway may be used as a therapeutic target.

Frailty as a predictor of negative outcomes in trauma patients with isolated rib fractures

Lawrence Feng, BA; Colette Galet, PhD; Dionne Skeete, MD

Background. In trauma, older patients typically experience worse outcomes. Age alone is not an adequate marker of physiologic fitness and reserve. To better guide our clinical decisions, metrics are needed that can accurately assess the health status of older patients. Frailty has emerged as one metric that may help providers identify which older patients are at risk of poor outcomes. Rib fractures account for a significant portion of injuries following blunt trauma. In patients with isolated rib fractures, the number of rib fractures has been linked as a risk factor for adverse outcomes whilst other studies suggest that pre-existing conditions are more associated with these outcomes. The Canadian Study of Health and Aging clinical frailty scale (CSHA CFS), which takes into account the effect of comorbidities on functional status pre-injury, has the potential to better define which patients are at increased risk for adverse outcomes.

Methods. We retrospectively reviewed the medical records of patients age 50 and older admitted for isolated rib fractures from July 2015 to June 2020 at UIHC Trauma Center. Patients with other body region abbreviated injury scores (AIS) ≥3 were excluded. Patients who were immediately transferred, only visited the Emergency Department, presented with chronic rib fractures, or for whom we did not have sufficient information to score frailty were excluded. Demographics, comorbidities, injury information, hospital course, and complications were collected. Patients were scored for frailty using the CSHA-CFS. Our primary endpoints were in-hospital mortality, the development of pneumonia and/or respiratory failure, requiring a ventilator or supplemental oxygen. Secondary outcomes were hospital length of stay, ICU admission, other complications (respiratory distress, pulmonary embolism, renal failure, deep vein thromboembolism, septic shock, delirium, etc.), and discharge to higher level of care. Univariate analysis was performed to assess the impact of frailty and number of rib fractures on outcomes. Multivariate analysis guided by our univariate analysis findings was performed to assess the association between number of rib fractures and frailty with poor outcomes. The interaction between frailty and number of rib fractures and its impact on outcomes were also determined.

Results. Of the 1406 trauma patients admitted for chest wall trauma from July 2015 to June 2020, 627 patients met inclusion criteria; 102 (16.3%) were not frail (CSHA-CFS scores 1 to 3), 407 (64.9%) were pre-frail (CSHA-CFS score = 4), and 118 (18.8%) were frail (CSHA-CFS scores 5 to 7). On univariate analysis, frail and prefrail patients were significantly older than non-frail patients (76.9 ± 11.4 vs. 66.2 ± 10.4 vs. 60.3 ± 7.1; $p < 0.001$). Frail patients were more likely to be female (42.4% vs. 25.8% vs. 20.6%, $p = 0.003$), to have 1 to 3 rib fractures (53.4% vs. 41.8% vs. 42.2%, $p = 0.002$), to have a lower injury severity score [ISS] (9.8 ± 5.1 vs. 11.4 ± 4.9 vs. 11.7 ± 3.8, $p = 0.002$), and to suffer a ground level fall (67.8% vs. 15.2% vs. 3.9%; $p <0.001$). Frail patients were also more likely to be on anti-thrombotics pre-injury and have chronic health conditions like diabetes, heart disease, kidney disease, and dementia. On univariate analysis, frail patients were more likely to stay longer in hospital (7.9 ± 10.1 vs. 6.8 ± 6.5 vs. 5.1 ± 4.6; $p = 0.011$), to develop other complications outside of pneumonia or respiratory failure (37.3% vs. 27.1 vs. 16.7%; $p = 0.003$), and to be discharged to skilled nursing facilities (SNF) (45.8% vs. 19.2% vs. 4.9%; $p <0.001$). In multivariate analysis, controlling for age, gender, ISS, injury mechanism, and any of the comorbidities that showed significant differences, number of rib fractures was associated with developing pneumonia (OR = 1.206 [1.088-1.338]; $p < 0.001$), respiratory failure (OR = 1.237 [1.143-1.339], $p < 0.001$), requiring O2 during hospitalization (OR = 1.171 [1.087-1.262], $p < 0.001$), other complications (OR = 1.120 [1.052-1.193], $p < 0.001$), hospital length of stay (OR = 1.682 [1.389-2.038], $p < 0.001$), number of days in the ICU (OR = 1.552 [1.290-1.867], $p < 0.001$), on a ventilator (OR = 1.476 [1.105-1.972], $p = 0.008$), mortality (OR = 1.184 [1.057-1.326], $p = 0.004$), and discharge to long term acute care facilities (OR = 1.335 [1.119-1.594], $p = 0.001$). Frailty was associated with hospital length of stay (OR = 1.599 [1.082-2.362], $p = 0.019$), the development of other complications (OR = 2.596 [1.152-5.833], $p = 0.021$), and discharge to SNF (OR = 4.680 [1.487-14.730], $p = 0.008$). Interaction analysis indicated that frail patients who presented with 4 or 5 rib fractures were more at risk of developing other complications (OR = 3.910 [1.426-10.722], $p = 0.008$). No interaction between frailty and number of rib fractures was observed regarding discharge to SNF or hospital length of stay.

Conclusion. In our population, the number of rib fractures is associated with poor outcomes (longer length of stay, mortality, and other complications) in patients 50 and older. Contrary to our initial hypothesis, frailty is not associated with increased mortality or respiratory complications but was associated with other complications. Yet, despite a lower number of rib fractures and a lower energy mechanism of injury, frail patients had a longer hospital length of stay and were more likely to discharge to a facility requiring greater healthcare resources at discharge.

Title: Predicting High-Risk Spinopelvic Relationships Using Anteroposterior Pelvic Radiographs

Primary Author: Bennett Feuchtenberger, BS

Mentor: Nicholas Bedard, MD

Collaborator: Christopher Carender, MD

Introduction: Abnormal spinopelvic relationship, imbalance and/or stiffness, is known to be high-risk for dislocation in patients that undergo total hip arthroplasty (THA). Identifying these patients is important, but not all providers have the capabilities or the time to perform the necessary radiographs on every patient. Detecting these patients requires standing and sitting lateral radiographs with a proper radiograph machine. Once identified, patients can be properly informed and given post-surgical precautions and/or unique surgical interventions to reduce the probability of dislocation.

Purpose: This study aimed to determine if high-risk spinopelvic relationships could be predicted with anteroposterior (AP) pelvis radiographs, which are routinely performed in many clinics.

Methods: Patients from the University of Iowa Healthcare who underwent THA with both an AP pelvis and standing/sitting lateral radiographs were tracked. The standing/sitting lateral radiographs were assessed for lumbar lordosis (LL), pelvic incidence (PI), pelvic tilt (PT), and sacral slope (SS). Utilizing those measurement, patients with spinopelvic stiffness (SSstand-SSsit<10°) and spinopelvic imbalance (PI-LL>10°) were identified. AP pelvic radiographs were evaluated for each of the following characteristics: scoliosis>5°, pelvic obliquity>5°, overlap of the sacrococcygeal junction/pubic symphysis (OL-SC/PS), disc space narrowing, lumbosacral hardware (LS-HW), and spine osteophytes. Univariate and multivariate analyses were performed. Each parameter was calculated by area under receiver operating characteristic curves (AUC) for diagnostic performance. Inter- and intra-reliability analyses were conducted for LL, PI, PT, and SS using intraclass correlation coefficient (ICC).

Results: 486 patients were included, 54% had normal spinopelvic relationship, 33% had spinopelvic imbalance or stiffness, and 13% had both spinopelvic imbalance and stiffness present. ICC for intra- and inter-reliability were >0.75 for LL, PI, PT, and SS. Univariate analyses demonstrated a significant correlation ($p< 0.05$) with both spinopelvic imbalance and stiffness for the following variables: presence of LS-HW, history of any lumbosacral surgery, lumbosacral fusion to the sacrum/pelvis, spine osteophytes, disc space narrowing, scoliosis>5°, and OL-SC/PS. Multivariate modeling demonstrated presence of OL-SC/PS (Odds Ratio [OR] 10.2 [5.3-19.8], $p<0.0001$), LS-HW (OR 4.4 [2.0-9.4]; $p=0.0002$), and scoliosis >5° (OR 3.1 [1.4-6.8], $p=0.006$) to be predictors of spinopelvic imbalance and stiffness. AUC of OL-SC/PS was 0.778; LS-HW, AUC was 0.624; and scoliosis >5°, AUC was 0.551.

Conclusion: Patients with AP radiographs that demonstrate OL-SC/PS, LS-HW, and/or scoliosis>5° are significantly more likely to have high-risk spinopelvic relationships. Any patients with one or more of the previously stated findings should be worked up for abnormal spinopelvic relationships prior to scheduling a THA.

Impact of Interfacing Near Point of Care Clinical Chemistry and Hematology Analyzers at Urgent Care Clinics at an Academic Health System

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Background and Purpose: Point-of-care (POC) testing equipment is commonly utilized in outpatient clinics. Our institution recently interfaced POC chemistry and hematology devices at two outpatient clinics via middleware software to the central electronic health record (EHR), facilitating a comparison of manual transcription versus automatic reporting via interface. This allowed for estimation of serious/obvious error rates and manual time savings. Additional goals were to develop autoverification rules and analyze broad trends of results in response to common clinician complaints on the POC testing.

Material and Methods: Data was obtained from two satellite clinic sites providing both primary and urgent care within an academic medical center health system. Interface of devices was accomplished via Instrument Manager middleware software and occurred approximately halfway through the 38 month retrospective analysis period. Laboratory results for three testing POC chemistry and hematology panels were extracted with EHR reporting tools.

Results: Nearly 100,000 lab values were analyzed and revealed that the rate of laboratory values outside reference range was essentially unchanged before and after interface of POC testing devices (2.0-2.1%). However, 12 (0.03%) serious/obvious errors such as negative numbers or physiologically implausible values were noted in total before interface. None were recorded after the interface with automatic reporting alone, and only 3 after the interface related to manual edits of results that failed autoverification. Fewer duplicated test results were identified after interface. Anion gap values of less than zero were observed more frequently in POC device tests when compared to central laboratory tests and are attributed to a higher proportion of Cl values greater than 110 mEq/L and CO_2 values greater than 30 mEq/L with POC results. Time savings of eliminating manual data entry were calculated to be 21.6 employee hours per month.

Conclusions: Data entry errors were overall low with both manual entry and interfaced devices. The most notable change was a reduction of a low frequency serious/obvious errors such as missing values. Significant time employee time savings highlight an additional benefit of instrument interfacing. Lastly, a notable difference between POC and central laboratory instruments is a higher rate of Cl and CO_2 values relative to the central laboratory.

Key Messages: Overall error rates in recording of POC test results are low and do not change significantly when POC equipment is interfaced with the EMR

Return to Sport after Knee Injuries in Collegiate Wrestling

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Background: Wrestling is known to be a sport of relatively high injury incidence, and knee injuries account for a large percentage of those injuries. Treatment of these injuries varies considerably depending on injury and wrestler characteristics, leading to differences in complete recovery and return-to-sport (RTS).

Purpose: The purpose of this study was to evaluate injury trends, treatment strategies, and RTS characteristics after knee injuries in competitive collegiate wrestling.

Methods: NCAA Division I collegiate wrestlers who sustained knee injuries between January 2010 and May 2020 were identified using an institutional Sports Injury Management System (SIMS). Wrestling-related knee, meniscus, and patella injuries were identified, and treatment strategies were documented to investigate potential recurrent injury trends. Descriptive statistics were used to quantify the number of days, practices, and games missed, RTS times, and recurrent injuries among wrestlers.

Results: Overall, 184 knee injuries were identified. After excluding non-wrestling injuries (n=11), 173 injuries remained (77 wrestlers). The mean age at time of injury was 20.8 ± 1.4 years, and the mean BMI was 25.9 ± 3.8 kg/m^2. There were 135 primary injuries (74 wrestlers), which consisted of 72 (53%) ligamentous injuries, 30 (22%) meniscus injuries, 14 patellar injuries (10%), and 19 other injuries (14%). The majority of ligamentous injuries (93%) and patellar injuries (79%) were treated non-operatively, while the majority of meniscus tears (60%) underwent surgery. Twenty-three wrestlers (22%) sustained recurrent knee injuries, of which 76% were treated non-operatively after their initial injury. Recurrent injuries consisted of 12 (32%) ligamentous injuries, 14 (37%) meniscus injuries, 8 (21%) patellar injuries, and 4 (11%) other injuries. Fifty percent of recurrent injuries were treated operatively. When comparing recurrent injuries to primary injuries, recurrent injuries had a significantly longer RTS time (Recurrent 68.3 ± 96.0 days vs. Primary 26.0 ± 56.4 days, p=0.01).

Conclusions: The majority of NCAA Division I collegiate wrestlers who sustained knee injuries were initially treated non-operatively, and approximately one in five wrestlers sustained recurrent injuries. Return to sport time was significantly increased after a recurrent injury.

The Factors Associated with Tissue Infarction Following Thrombectomy for Acute Ischemic Stroke:

Emily Fuller; Nick Fain, MD.; Cynthia Zevallos, MD.; Colin Derdeyn, MD.

Endovascular thrombectomy following an acute ischemic stroke has been shown to be beneficial but leaves behind distal emboli in about 2 out of 5 cases. There is reduced efficacy and increased risk with attempting to retrieve distal emboli. Furthermore, it is possible that distal emboli do not cause any infarction on 24-hour imaging due to autolysis and collaterals to the distal territory. The aim of this study is to determine the frequency of infarct from distal emboli and potential factors associated with infarction post-thrombectomy.

We reviewed 358 patients with large vessel occlusions (LVOs) who underwent thrombectomies from 2015-2018. From those, we selected 96 patients with internal carotid artery or middle cerebral artery occlusions, Thrombolysis in Cerebral Infarction (TICI) score of 2b, and follow-up MRI. We identified distal emboli on angiography and infarct presence in the area at risk on MRI.

The median age was 69 (IQR 59-78) and 54% were female. The most common preexisting condition was hypertension (60.8%) followed by hyperlipidemia (33.3%). 59 patients (61.5%) received intravenous tissue plasminogen activator (IV tPA). 39 patients (40.6%) had good collaterals, greater than 50% filling, as assessed on CT angiography. The median difference between initial and discharge NIH Stroke Scale (NIHSS) was 10 (4-13). The median 3 month modified Rankin Scale (mRS) was 3 (1-4).

An additional 23 patients were excluded due to an initial infarct seen on head CT or CT angiography in the overlapping territory of the distal embolus. Two patients were excluded for inaccessible imaging and vasospasm. Of the remaining 71 patients, 46% developed infarct at the location of the distal embolus on MRI. Factors including age, mean arterial pressure, body mass index, anesthesiology type, and diameter of the occluded vessel did not predict the presence or absence of infarction. Behavioral habits such as smoking, alcohol, and cocaine use were not associated with infarction. Chronic hypertension ($p = 0.004$) and pial collaterals ($p = 2.5 \times 10^{-8}$) were significantly associated with infarct presence and absence respectively.

Chronic hypertension was significantly associated with distal embolus infarct. This suggests that of all the variables we looked at, hypertension was the most likely underlying condition to project a significant corresponding infarct in the eventuality of a distal embolus. Of note, transiently elevated blood pressure, as a function of the Mean Arterial Pressure (MAP) was not significantly associated with infarct presence or absence. This disconnect can be explained by the underlying effect of hypertension on autoregulation. If central vasculature is already close to maximally constricted there is little room for the required increase in tension necessary in the setting of ischemia. Collateral flow is less likely to reach at-risk tissue, and infarct is more likely to develop. As expected in this context, the development of robust pial collaterals was significantly associated with the absence of distal emboli infarction.

Of additional interest, we found that patient age was not associated with development of infarct at the site of the distal embolus. This was surprising considering that vessel age is correlated with increased risk of developing hypertension, which was significantly associated with infarct. As an independent variable, we did not demonstrate any association in our study, but whether this was due to insufficient power cannot be determined yet. However, with the same sample size, our correlation with pial collaterals demonstrated very low p value, suggesting any lack of power is not endemic to the study itself. We did not find evidence of any upper limit within our inherently elderly population of those in need of thrombectomy. At least for now, we conclude that thrombectomies may continue to be performed without concern that elevated age may yield greater stroke burden at the site of a possible distal embolus.

Future studies include obtaining quantitative measurements of areas at risk and infarct volumes and designing clinical trials to test the safety and efficacy of different devices, lytic agents, and techniques for revascularization in a subset of patients with distal emboli that are likely to benefit from revascularization

Cardiomyocyte-specific deletion of Med13 and Med13L leads to dysregulated gene expression, heart failure, and subsequent death

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The Mediator co-activation complex is an important component in RNA Pol-II-dependent gene expression that functions to integrate intracellular signals, allowing for optimized cellular response to (patho)physiological states. The Mediator kinase submodule functions to fine-tune these molecular transitions. The kinase submodule consists of four proteins, including Med13, Med12, Cdk8, and Cyclin C. Also involved is Med13's paralog, Med13-like (Med13L), which is both mutually exclusive in the submodule and redundant. Humans with mutations in Med13 and Med13L have congenital heart defects. As such, we hypothesize that the acute loss of Med13 and Med13L in cardiomyocytes results in disrupted Mediator kinase submodule formation leading to altered gene expression and subsequent pathogenesis of heart failure. To investigate this, we created a Tamoxifen-inducible cardiomyocyte specific Med13/Med13L double knockout mouse model and treated mice for two-weeks with Tamoxifen beginning at 8-weeks old. One-week post treatment, we observed significantly decreased ejection fraction consistent with severe heart failure. Post-mortem analysis showed increased heart weight and heart-weight-to-body-weight ratio as well as histological findings consistent with dilated hypertrophy. To begin elucidating the mechanistic processes underlying these findings, mRNA sequencing was performed and showed basal transcription was not altered; however, heart failure response pathways were dysregulated. Taken together, Med13 and Med13L are critical for normal Mediator-regulated RNA-Pol II-dependent transcription and subsequent cardiac physiology. Therefore, disruptions cause significant cardiac dysfunction and death as sequelae of heart failure.

Weightbearing CT: Does Joint Loading Improve Evaluation of Hip Instability/Dysplasia

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Background/Intro: Hip dysplasia is under-coverage of the femoral head by the acetabulum resulting in poor mechanics and instabilty of the hip joint. The resulting incongruency causes increased stress and mechanical forces applied to the outer rim of the acetabulum and surrounding soft tissues including the cartilage and labrum. Left untreated, progressive degeneration of the joint can result in osteoarthritis. Currently, preoperative CT scans for patients with hip dysplasia are taken supine. Weight Bearing Computed Tomography (WBCT) is a novel imaging technique which allows for improved interpretation of joint morphology compared to standard CT, by orienting the patient in a dynamic-weight bearing position. This is the first study that will look at the effectiveness of WBCT in diagnosing hip dysplasia and instability of the hip in dysplastic patients and controls.

Purpose of Study: To assess the effectiveness of WBCT in measuring instability in patients with hip dysplasia and to compare these measures to controls. To identify if WBCT demonstrates significant differences in measures of instability when compared to supine CT scans for patients with hip dysplasia. Discover correlates between WBCT measurements and physical exam findings.

Methods: 11 Patients with hip dysplasia indicated for PAO surgery and 11 healthy controls were recruited to participate in the study. Each control subject underwent 2 WBCT images, one in neutral position and one with the hip stressed in external rotation to 0 degrees. The pre-operative supine CTs for dysplastic patients were obtained via chart review. A novel measurement technique, developed by the senior investigator was used to evaluate congruency of the joint space on all subjects and widening of the joint space with external rotation among controls. Images were evaluated using RadiAnt DICOM Viewer 2020.2.3. Data analyses comparing neutral, stressed, and supine views were done for the dysplastic patients while analyses comparing neutral and stressed views were done for the control group. The dysplastic neutral and stressed measurements were compared to the control groups and the deltas between neutral and stressed measurements were compared between these groups as well. Radiographic and physical exam measurements such as lateral center edge angle and internal rotation in flexion were used for correlations between these measurements and the measurements taken from the CT scans.

Results: There was a significant difference in distance from the center of the femoral head to the wall line of the acetabulum when comparing the neutral WBCT vs stressed in dysplastic patients (P=.0420) while there was not in controls (.5918). There was no significant difference in distance from center of head to wall line of acetabulum when comparing supine vs stressed for dysplastic patients (P=.9766). There was a significant difference in superior joint space when comparing neutral vs stressed in controls (P=.0029) while there was not in dysplastic patients (P=.5195). A difference also existed in the distance from the medial wall of the acetabulum to the femoral head when comparing dysplastic patient's vs controls in the stressed view (P=.0488). However, when comparing the differences between neutral and stressed views for controls and dysplastic patients there were no statistically significant differences. There was a positive linear relationship between anterior wall joint space in the stressed view and LCEA of dysplastic patients (r=.79044, P=.0065) and hip flexion and IRF (r=.66347, P=.026). There was a negative linear relationship found between IRF and center head to wall line in the stressed position (r=-.71352, P=.0137) and ERF and center head anterior or posterior in the stressed position (-.62747, P=.0388).

Conclusion/Discussion: A significant difference existed in distance from center of head to wall line when comparing neutral WBCT to stressed in dysplastic patients but not in controls. The position of the stressed view appears to be effective at eliciting changes in the hip that allow for detection of instability in dysplastic patients when compared against controls. No significant difference existed in the center of head to wall line for the supine vs stressed views, demonstrating that WBCT may be able to visualize changes in measures of instability in the hip not detected by supine views. There were no significant differences in any measurement when comparing neutral vs supine views, meaning that the neutral WBCT view provides an accurate and similar view of the hip when compared to the supine CT scan. This study is limited by a small sample size, n=11 in each group, and differences in age between controls and patients (P=.0254). This study provides evidence for the use for WBCT in hip dysplasia imaging and provides merit for a larger study looking at the effectiveness of this technology for evaluating instability in the hip.

Optimizing Gene Therapy in a Mouse Model of Juvenile X-linked Retinoschisis

Ella Gehrke, Arlene Drack, MD

Introduction and Purpose: Juvenile X-linked Retinoschisis (JXLR) causes genetic vision loss in XY males, affecting up to 1/20,000 XY males globally. Intraretinal cysts and schisis cavities impair retinal signal transduction and cause bilateral vision loss from scotomas due to schisis, progressive macular atrophy, retinal detachment, and/or amblyopia[1]. Carbonic anhydrase II inhibitors reduce intraretinal cyst formation, however they do not cure the disorder and do not prevent progression. JXLR is a good candidate for gene therapy due to its etiology in mutations within a single gene and the lack of curative therapies. Sieving at al. showed promising results with intravitreal gene therapy using an AAV8 vector in An *Rs1* Knockout (*Rs1-KO*) mouse model model, but the subsequent human trials were disappointing[2]. The Drack lab achieved short term rescue with either intravitreal or subretinal AAV2/4-*RS1* -CMV promoter, but rescue was not durable[3]. My summer research project studied treatment of this model with two novel vectors for gene therapy – AAV2/4-*RS1*-Rho kinase promoter which selects for expression in photoreceptors, and AAV2/4-*RS1*-Ef1α promoter which drives expression in all retinal layers. In addition, we investigated whether the immune axis modulates response to treatment via the creation of a double knock out mouse line between *Rs1-KO* and Caspase1/11 knockout. Caspase-1, also known as interleukin-1β (IL-1β)-converting enzyme (ICE), regulates antimicrobial host defense and additional proinflammatory immune actions. We hypothesized that we could rescue the *Rs1* phenotype using novel vectors and could improve durability by suppressing part of the immune axis.

Methods: A Knock-out mouse model of JXLR *(Rs1-KO)* was obtained from Paul Seiving, MD, PhD, at the NEI. An immunomodulated mouse model of JXLR (*Rs1-KO; Cas1$^{-/-}$)* was created by crossing the *Rs1KO* with the Cas1/11 KO obtained from the Prajwal Gurung lab, University of Iowa. AAV2/4-RhoKinase (Rho kinase), and AAV2/4-Ef1α (Ef1α) vectors were delivered by subretinal 2 ul injections of 2E9/ml in *Rs1-KO;Cas$^{-/-}$* and *Rs1-KO* mice. Electroretinogram (ERG) and a visually guided swim assay (VGSA), were chosen as endpoints to assess efficacy. One and two months after treatment all animals had ERGs performed using ISCEV protocols. Five months after treatment mice underwent a VGSA performed in light and dark conditions to asses functional vision.

Results: ERG: At one-month post injection, Rho kinase treated eyes showed significantly higher b-waves (p=0.00050) than untreated eyes on light adapted (3.0 flash: predominately cone) testing. EF1α treated eyes were also significantly different from untreated eyes at one-month post injection (p<0.0001). By 2 months post injection, Rho kinase treated eyes had lost significance from controls for the 3.0 flash (p= 0.5428), while the EF1α treated eyes continued to show significance over controls (p<0.0001). For the 5 Hz flicker, a pure cone response, EF1α showed significance at one and two months (p<0.0001 and p<0.0001), whereas the rho kinase was significant but showed a trend for lower amplitudes at two months (p=0.0016 and p=0.0265). There was no difference between treated and untreated eyes with either vector in the *Rs1-KO;Cas$^{-/-}$* mice 3.0 flash (p=0.5140 and p=0.7947), or 5 Hz flicker (p=0.341 and p=0.2401). VGSA: At five months after treatment under dark and light adapted conditions, we observed that Rho kinase was not significantly better than controls in either dark (p=0.9093) or light (p=0.4472) conditions. However, the EF1α cohort was significantly different from untreated controls under light adapted conditions (p=0.0024). The observed significance was lost in EF1α treated *Rs1-KO;Cas$^{-/-}$* mice (p=0.4823). The EF1α group was not significantly different from untreated controls in dark adapted conditions (p=0.755.).

Discussion and Conclusion: Subretinal gene therapy using AAV2/4-*RS1*-EF1α promoter showed a longer lasting and more robust improvement in cone ERG and functional vision than the same construct under the Rho kinase promoter. EF1α broadly transfects all layers of the retina whereas the Rho kinase promoter specifically targets photoreceptors but drives lower expression than CMV. This suggests rescue relies on a therapy that can target diffuse layers of the retina. We also observed that in our immune modulated mouse, the effect of the therapy was lost, suggesting an intact immune response is necessary for beneficial effects. Longer studies of EF1α and investigation into the role of the immune system in retinal survival and rescue is imperative to identify factors necessary to develop effective gene therapy for individuals with JXLR.

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Medical Applications of Extended Reality

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Background/Introduction: Technologies that utilize virtual and augmented reality (collectively referred to as extended reality or XR) are becoming increasingly common. In medicine, XR is used to teach students anatomy, simulate surgical environments, and visualize patient-specific defects. Students using XR and 3D visualization technology have reported better understanding of complex spatial anatomy with further evidence suggesting improved student performance. In cardiology, XR has been shown to improve diagnosis and was useful in preparing surgeons to perform operations. In 2020, a Korean group of researchers reviewed the utility of XR in teaching congenital heart disease (CHD) and concluded, "A digital library of 3D images and 3D printed models embracing the entire spectrum of CHD should be established and would be tremendously beneficial for medical education."

Despite improvements in hardware and more affordable prices, the use of XR in medicine is limited by high initial investment costs and perceived lack of utility due to limited applications. Although these devices are already being employed at schools like Stanford and Case Western Reserve University, the use of XR at small/medium sized institutions is uncommon.

Purpose: Demonstrate simple but effective uses for XR technology, including a library of congenital heart defects, to encourage Iowan medical institutions to incorporate XR systems into their curriculum and practice to improve both education and patient care while providing valuable resources for trainees from various specialties at UIHC.

Method: Heart models were generated via segmentation from CT scans or MRA, processed to remove noise, add color, and reduce the file size, and uploaded to software packages like Unity that are used for video game development. The models were used in conjunction with other interactive elements (diagrams, videos, echocardiogram clips) to create virtual reality (VR) modules as well as educational, augmented reality-based smartphone applications. After the one-time purchase of VR equipment to engage with the model, every step in this process could be performed at little to no cost. The effectiveness of the VR modules as opposed to more traditional learning techniques was evaluated in a randomized, controlled study on medical students at the Carver College of Medicine. Student performance on a quiz over a CHD was assessed before and after the student interacted with either the VR module or a paper study guide. Members of the control group were also given time to test the VR software. All participants were asked to give feedback about their experience in order to obtain an evaluation of engagement, ease-of-use, and the ability of the VR equipment to aid the understanding of anatomic structures.

Results: The average quiz scores of the virtual reality and traditional learning groups when being tested on the heart defects (Transposition of the Great Arteries/Tetralogy of Fallot) were 91.66/93.75% and 93.75/90.625% respectively ($p = 0.619/0.398$;$n=16$) with an average improvement of 41.66/30.21% and 48.96/42.71% ($p=0.578/0.126$;$n=16$). Despite being unable to show any significant difference in performance, the collected survey results demonstrated that 29/32 participants somewhat or strongly agreed that "The use of VR training modules would be a beneficial addition to my medical education" while 30/32 somewhat or strongly agreed that "Interacting with the 3D heart models enabled me to understand the anatomy better than an equivalent 2D diagram would". Of the participants who engaged with both the traditional learning materials and virtual reality modules, 14/16 agreed that "The anatomy was easier to understand by interacting with the 3D models than from the 2D diagrams" and 11/16 agreed that "Using the VR headset helped clarify things that were confusing to me from the study guide alone".

Conclusion: XR tools can provide a welcome and beneficial supplement to the education of medical trainees for topics involving complex anatomy. Medical professionals interested in incorporating XR technology into their workflow will find the described method leaves much room for customization and versatility in the creation of additional XR applications. As costs continue to decrease and technology improves, we foresee the adoption of XR by medical institutions around the globe. By implementing XR tools and techniques now, medical institutions will continue to enjoy the benefits of this exciting technology for years to come.

A Mixed Methods Approach to Advancing Health Equity for Patients at Risk for Diabetes-Related Foot Conditions

Carolina Gonzalez Bravo, BS; John Barsotti, MS; Martha L. Carvour MD, PhD

Introduction:

Diabetes mellitus (types 1 and 2) is a prevalent chronic condition in Iowa and across the United States. The Iowa Department of Public Health reports that the prevalence of diabetes has been steadily increasing over time; diabetes now affects approximately 10% of Iowa adults.[1] Diabetes-related foot conditions (DFC)—including peripheral neuropathy, peripheral vascular disease, foot ulceration, and infection—are a significant cause of morbidity, hospitalization, and amputation among patients with diabetes. Although multiple social and structural determinants of health may impact diabetes care and DFC risk, there are no established, systematic methods for detecting and depicting structural inequities on a population level.[2]

Purpose:

The objectives of this study were to (1) assess for gaps or disparities in DFC-related care among a de-identified cohort of patients with diabetes from the University of Iowa Health Care (UIHC) system; (2) develop and refine circular data visualization methods for representing the structural basis of any observed disparities; and (3) design a complementary qualitative research study to provide patient-level and community-level context to these research findings.

Methods:

A UIHC cohort of adult patients with one or more International Classification of Diseases code corresponding to diabetes mellitus was identified using TriNetX. A set of 16 clinical outcomes related to diabetes and DFC care were defined. These ranged from primary measures of diabetes care (e.g., insulin use, metformin use) through interventions indicative of severe DFC (e.g., diagnosis of osteomyelitis, surgical record of amputation). Distributions of race, ethnicity, and sex were compared for each outcome. Preliminary methods for depicting structural disparities using circular visualization tools were developed in R.[3]

Results:

Race, ethnicity, and sex distributions were calculated for each of the 16 clinical outcomes. Circular plots depicting the distribution of these outcomes differed across subgroups. Race and ethnicity data were incomplete or unknown for a significant share of the TriNetX-based cohort. Unknown race was the second most common racial category in the overall TriNetX cohort and the third most common in the last 10 years (10-year cohort n= 73,450). A sensitivity analysis is underway to assess the potential impacts of the unknown race and ethnicity data on clinical and epidemiological analyses using TriNetX. Results of this research will be used to inform ongoing efforts to enhance the completeness and quality of health equity-related data at UIHC. A qualitative, semi-structured interview study to provide further context about these findings was also designed and approved.

Conclusion:

Enhancing the completeness and quality of health equity-related data in clinical databases will augment future efforts to promote health equity among patients who are at risk for DFC. Qualitative, community-based studies may also provide important context for these efforts. Circular visualization methods may be useful tools for visualizing structural inequities in health care.

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Prolapse, Pelvic Pain and Pelvic Floor Muscle Dysfunction

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Background
Pelvic organ prolapse (POP), the descent of the vaginal walls and/or uterus into the vaginal space, is associated with bothersome vaginal bulge, bladder, and bowel symptoms. POP is not traditionally associated with pelvic pain, but recent studies suggest pain may occur in conjunction with POP more often than originally thought. Results from these studies find pelvic floor myofascial pain (pelvic floor muscle dysfunction (PFMD)) may occur in some women with POP. PFMD, a cause of pelvic pain, is an understudied condition, and its associations with prolapse and prolapse treatment outcomes are poorly understood.

Hypothesis and Aims
We hypothesize that among patients with POP, those with PFMD are more likely to report pelvic pain and less likely to have their pain resolve after POP treatment. Our aims were to characterize pelvic pain symptoms in women with POP, determine if pain is associated with PFMD in women presenting for POP treatment, and identify whether pelvic pain symptoms persist after POP treatment in women with and without PFMD.

Methods
We conducted a retrospective, longitudinal study of women enrolled at the Iowa site of the Pelvic Floor Disorders Registry (PFDR). PFDR data were collected prospectively (including clinical information and patient-reported outcomes). Data specific to pelvic pain symptoms, comorbid pain conditions, pain treatments, and pelvic floor muscle examination findings were obtained via retrospective chart review and merged with the PFDR dataset. A standardized pelvic floor muscle examination was used in assessing all patients prior to POP treatment, and PFMD was identified if tenderness was documented. The primary outcome was the PFDR Pain questionnaire that asks about pain in the past 24 hours in 7 locations (each rated 0-10) in the pelvic region and lower extremities (range 0-70). Secondary pain outcomes included symptom assessment using individual items from the Pelvic Floor Distress Inventory Short Form (PFDI-20) that inquire about symptoms of pelvic “pressure”, pelvic “heaviness or dullness” and “pain or discomfort in the lower abdomen or genital region” (an item score ≥ 3 suggests symptom is present and at least moderately bothersome) and an assessment of total body pain (Global Health (GH) item 7, range 0-10). Change in outcomes was calculated as 6-12 month post-treatment score minus baseline score. Bivariable comparisons were made using chi squared, Fisher’s exact, student t and Wilcoxon ranksum tests.

Results
158 women were included who planned surgery (138 (88%)) or pessary (20 (12%)) treatment, and 134 (84.8%) had 6-12 month post-treatment follow-up. Twenty (12.6%) had PFMD at baseline. Those with PFMD (vs. no PFMD) were younger (mean (SD) 55.7 (14.2) vs. 64.5 (11.0) years, p=0.002) and more likely to have prior diagnosis of chronic pain (15.0% vs. 3.6%, p=0.07). Patients in the PFMD group were also more likely to present with pelvic pain symptoms at baseline (80.0% vs. 30.4%, p<0.001). Women with PFMD vs no PFMD had greater baseline pain outcomes (Pain score median (IQR), 9.7 (4-23) vs. 3 (0-7), p=0.0008); had at least moderately bothersome lower abdomen/genital pain (11 (55%) vs. 27 (19.6%), p=0.004); and had greater overall pain (GH 7, 4 (3-6) vs. 2 (0-3), p=0.0002). Pelvic pressure and heaviness symptoms did not differ by group. Pelvic pain specific outcomes improved after treatment overall, and women with PFMD at baseline had greater improvement in Pain scores compared to those without PFMD (-6.5 (-15.2-0) vs. 0 (-3-0), p=0.03). Post-treatment Pain scores were not significantly different in the PFMD group compared to those without PFMD (3 (0-12) vs. 0 (0-4), p=0.18). Overall body pain did not improve after treatment in either group.

Conclusion
Patients with POP and PFMD report more pelvic pain than those without PFMD. Contrary to our hypothesis, pain scores improved in patients with POP and PFMD 6 to 12 months after POP treatment. These findings are important to help counsel patients about likely changes in pain symptoms after POP treatment.

The Impact of Point-of-Care HbA1C Testing on HbA1C Levels and Medication Management in a Community-Based, Free Clinic Setting

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Introduction: Hemoglobin A1C (HbA1C) tests play an indispensable role in care for patients with type 2 diabetes (T2DM). The test allows for a medical provider to assess a patient's level of glycemic control over the past 3 months. The American Diabetes Association (ADA) recommends HbA1C tests to be run every 3 months for T2DM patients with HbA1C values above their goal. To aid in management of diabetes, point-of-care (POC) HbA1C tests have grown in popularity; these allow a provider to instantly assess a patient's glycemic control and provide face-to-face counseling to patients on how to best manage their T2DM. Previous studies have showed that access to POC HbA1C testing improves glycemic control, results in more frequent medication intensification, and improves provider compliance with ordering HbA1C tests in accordance with ADA guidelines. In October 2020, the Iowa City Free Medical Clinic gained access to POC HbA1C testing. The clinic provides comprehensive medical care to uninsured patients who are disparately affected by numerous social determinants of health and sees over 150 T2DM patients each year. To our knowledge, no studies have assessed the efficacy of POC HbA1C testing in a clinic that serves such a patient population. We sought to answer the following research questions:

1. Do patients have lowered HbA1C levels 3 months after the implementation of POC HbA1C testing protocols?
2. Do providers make more frequent changes to patients' diabetic medications when they have access to POC HbA1C testing?

Methods: We reviewed the charts of 50 T2DM patients who had been seen in the clinic for at least 3 months before the introduction of POC HbA1C testing and had at least 2 POC tests run. We recorded patient demographics including age, sex, race, ability to speak English, preferred language, and BMI. We then recorded patient's HbA1C levels from both the first visit a POC HbA1C test was run and from their 3-month follow-up appointment, as well as the number of medication changes made at the visit 3 months prior to implementation of POC HbA1C testing, and the changes made at the first visit with POC HbA1C testing. Each patient served as their own control, and the differences in HbA1C values and medication changes per visit were analyzed with paired student t tests.

Results: We found no significant decrease in patients' HbA1C values after 3 months of POC HbA1C testing, nor did we find a significant increase in the number of medication changes made per visit after implementation of POC HbA1C testing. Patients had an average HbA1C level of 8.42 when POC testing was first introduced, and an average of 8.31 3 months later ($p = 0.462$, *n.s.*). The average number of diabetic medication changes made per visit was 0.64 3 months prior to POC HbA1C testing and 0.62 at the first visit POC HbA1C testing was used ($p = 0.835$, *n.s.*).

Discussion: Our finding that POC HbA1C testing does not result in significantly improved glycemic control or a greater number of diabetic medication changes made per visit differs from the existing literature. It is possible that the clinic acquired their POC HbA1C analyzer recently enough that its long-term effects have yet to be seen, as management of T2DM is a lifelong process and we only considered a 3-month timeframe. Alternatively, it may be that POC HbA1C testing confers no benefit to a clinic that serves an uninsured and disadvantaged patient population. Potential reasons for this could be difficulty intensifying pharmacotherapy regimens due to the limited availability of generic diabetic medications, significant communication barriers between patients and clinic providers, as well as the patient population's comparatively limited ability to make necessary dietary modifications.

The impact of genital psoriasis among psoriatic patients

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Abstract: Genital dermatoses can severely affect patients' quality of life, including their sexual life.[1] We sought to examine the impact of genital psoriasis among psoriatic patients, their response to treatments, and how often genital psoriasis is evaluated by dermatologists. A cross-sectional qualitative study was completed. Patients 18 years or older seen for psoriasis by one of the attending dermatologists or those receiving phototherapy from the Massachusetts General Hospital Outpatient Dermatologic Clinic were recruited. Fifty-five subjects were enrolled in the study and completed a 23-item questionnaire.

The average age of participants was 56 years. Only 23.6% of participants had ever been asked if they had a genital rash by a dermatologist. 60% of participants indicated a dermatologist had never examined the genital area. When asked if they currently had a rash in the genital areas, 29.1% of participants answered affirmatively. However, 43.6% of participants indicated they had had at some point some form of itching, burning, pain, or involvement in the genital areas. There was no statistically significant difference found for gender or race, however we cannot tell if a larger study may. Of these, 45.8% indicated that their dermatologist did not ask/diagnose the genital rash. These patients ranked genital itching 4.61/10, pain 4.09/10, and stinging/burning 3.86/10. Of areas affected in females, 62.5% indicated involvement of the labia majora. Of male patients, 56.3% (9/16) indicated involvement of the penile shaft and perineum. The most common and helpful treatment tried for their genital psoriasis were topical steroids. 80% of participants indicated that they were self-conscious or experienced some form of embarrassment because of their skin psoriasis. 29.1% of participants described that their overall psoriasis has caused some form of sexual difficulty for them. 50% of participants with involvement in their genital area indicated experiencing some form of sexual difficulty. When looking at the gender breakdown of sexual difficulty, 62.5% of female patients indicated significant sexual difficulty compared to just 25% of male patients.

This qualitative study of patients with psoriasis showed that even though almost half of the patients enrolled in the study had a rash or some form of symptoms in their genital regions, a majority of patients had never had their genital area examined by a dermatologist for psoriasis nor had they ever been asked if they had a genital rash. For those patients with symptoms in the genital areas, there was mild to moderate discomfort experienced by patients in regards to pain, stinging, and itching in the genital regions. A majority of these patients, specifically female patients, experienced significant sexual difficulty due to their genital psoriasis. In the future, providers should regularly examine and ask patients with psoriasis about potential genital involvement. Given the significant sexual difficulty and embarrassment patients felt from their skin psoriasis, providers should also ask about the psycho-social burden patients may experience from their psoriasis.

References:

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Title: Identifying Social Needs Among Gynecologic Oncology Patients Receiving Acute Inpatient Care
Authors: Anna Greenwood (M3), Caroline Hartman (P4)
Mentor: Michael Haugsdal MD

Background: Social determinants of health (SDoH) are the conditions in which patients are born, grow, work, and live that positively or negatively affect their health.[1] Seventy-percent of health quality and outcomes is thought to be derived from the these social factors, while only the remaining 30% or less is owed to effects of routine clinical care.[2] The clinical course for patients with chronic diseases such as cancer are especially vulnerable to negative influence of social needs gaps—low income, low health literacy, and poor understanding of cancer symptom knowledge contributes to delays in cancer patients' presentation to care and timeliness of treatment.[3] Furthermore, the financial burden of long-term cancer care is associated with lower health-related quality of life and increased risk of mental illness among cancer survivors.[4] Despite abundant literature supporting these relationships, many—if not most—healthcare systems lack the resources, strategies, and processes to effectively assess and address SDoH for each unique patient population and there is a paucity of research seeking to identify the specific social factors that impact patients with gynecologic cancers. [1,5,6] An upstream approach to oncologic healthcare aims to identify and address these specific social needs that may be affecting a unique patient population and even each individual patient.[7]

Hypothesis: Building upon previous work focused on a specific outpatient gynecologic oncology patient population, this study aims to identify the incidence of social needs among a gynecologic oncology population receiving acute inpatient cares and assess for trends that may arise based on acuity of care, demographics, and diagnosis.

Methods: This prospective cohort study of a gynecologic oncology inpatient population at the University of Iowa was completed from November 2020 to March 2021. During this period 141 patients were invited, and 101 patients participated (72% response rate). Participants completed a needs assessment survey comprised of previously validated questions screening for common social needs including food and housing security, transportation means, financial stability, health literacy, and social support. Responses were considered positive if any degree of need was reported. Participants also consented to chart review to collect demographic and cancer diagnosis data.

Results: Responses demonstrated diversity of demographic traits and pathologic diagnoses (ovarian, uterine, vulvar/vaginal, cervical, and other metastatic cancer as well as benign neoplasms and premalignancies). The most substantial reported needs across all gynecologic malignancies in this cohort were social support (65%), health literacy (37%), and financial need (22%). Less need was reported in the categories of food insecurity (11%), housing (7%), and transportation (4%).

Conclusion: There are unmet needs, most notably in social support and health literacy, within this gynecologic oncology population receiving acute inpatient care. SDoH have been studied in the outpatient gynecologic population and the needs seen in this study are similar to the needs of that population.[7] However, it remains to be determined if different challenges and frequencies of unmet need exist among various gynecologic cancers with potential to affect the stage at which their cancer is diagnosed as well as the number of hospital admissions related to cancer care.

UI Poster Presentation
Abstract
Student: Sarah Gross
Mentor: Sarah Shaffer, MD

United States Abortion Policy During the COVID-19 Pandemic: A summary of state and federal policy responses to a public health crisis

Abortion is a vital component of comprehensive reproductive healthcare and family planning. Delays in abortion care increase the risk of procedural complications, mortality, and financial hardship. At the beginning of the COVID-19 pandemic, access to regular healthcare services decreased drastically in an effort to redistribute and ration services needed for COVID-related care. These disruptions have disproportionately affected people's access to sexual and reproductive health services. In response to the first wave of COVID-19 in the United States, a number of experts recommended swift policy change to ensure continuity of abortion care; however, states adopted varying regulations on abortion care in the pandemic – from the postponement of procedures to extended access. This lack of a unified response may reinforce already-existing inequities and a more detailed exploration of abortion policies implemented during the COVID-19 pandemic is necessary to understand the barriers to abortion access and identify effective policy response to improve sexual and reproductive health services during public health crises.

Title: Electroretinogram abnormalities in patients with dystroglycanopathies

Authors and Affiliations: Joshua L. Hagedorn MS, Taylor M. Dunn, COMT, Sajag Bhattarai MS, Carrie Stephan, MA, RN, Katherine Matthews MD, Wanda Pfeifer OC (C)#, Arlene V. Drack MD#

Background:
Dystroglycanopathies are a heterogeneous group of membrane-related muscle dystrophies. The dystroglycanopathy phenotype may include neurodevelopmental anomalies. Previous studies have characterized abnormal ocular electroretinograms in mice engineered to display the dystroglycanopathy phenotype, but have not been tested in human subjects.

Purpose:
The current study set out to characterize the ocular electrophysiology in patients with dystroglycanopathies due to mutations in *FKRT* and *POMT2* to determine its potential as a biomarker and endpoint for developing gene therapies.

Method:
Subjects were recruited in clinical practice at the University of Iowa. Inclusion criteria were children aged 6-17 and adults 18-90 with molecular confirmation of dystroglycanopathies and limb girdle muscular dystrophy. Subjects underwent penlight anterior segment ophthalmic examination, best corrected near visual acuity, intraocular pressure measurement, and full field electroretinogram (ERG). Full-field electroretinograms were recorded using ISCEV standard protocols.

Results:
Seven patients were recruited, six male and one female, average age thirty-five years old (range eighteen to fifty-six). Five patients had mutations in FKRT and one in POMT2 with four patients having the same genotype in FKRT. The most remarkable differences between the ffERG of study participants and age matched controls were that dystroglycanopathy patients had statistically significantly lower a-wave amplitudes on 3.0 and 10.0 dark adapted flashes ($p=0.0024$; $p=0.0093$) and had an unusual sawtooth pattern in the 30 Hz flicker with faster rise than descent. Additionally, our patients showed a decreased b-wave amplitude using On/Off response protocols ($p=0.0076$).

Conclusion:
The electronegative electroretinogram, which has been reported in humans with Duchenne and Becker muscular dystrophy[1], and in mouse models with a dystroglycan deficiency[2], were not found in this study's human population with dystroglycanopathies. Decreased b-wave amplitude during On/Off testing reflects dysfunction of the cone On- (depolarizing) bipolar cells. We believe that the abnormal "sawtooth" light adapted 30 Hz flicker is also specific for a bipolar cell defect in patients with dystroglycanopathies. Decreased b-wave amplitude during On/Off testing and the abnormal 30 Hz flicker are both specific for cone On- bipolar cell dysfunction in dystroglycanopathies and have not previously been described. As genetic therapies continue to develop, these could be used as potential biomarkers to establish therapeutic effectiveness.

References:

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Gathering Contact Network Data to Inform Interventions Designed to Decrease the Spread of COVID-19 in Healthcare Facilities

Hanson A, Evans N, Polgreen P

Background: COVID-19, a respiratory-droplet infectious disease of global pandemic status, is frequently transmitted between healthcare workers (HCWs) before symptom onset. Electronic medical records (EMR) force HCWs to spend large amounts of time together documenting patient charts, and after following COVID-19 protocol with patients, HCWs may be less likely to wear personal protective equipment (PPE) upon returning to their workroom. If workrooms were constructed prior to the introduction of the EMR, they may not be designed to handle today's need for social distancing while charting. Crowding can increase the frequency and duration of close contact between HCWs, increasing their risk of disease transmission.

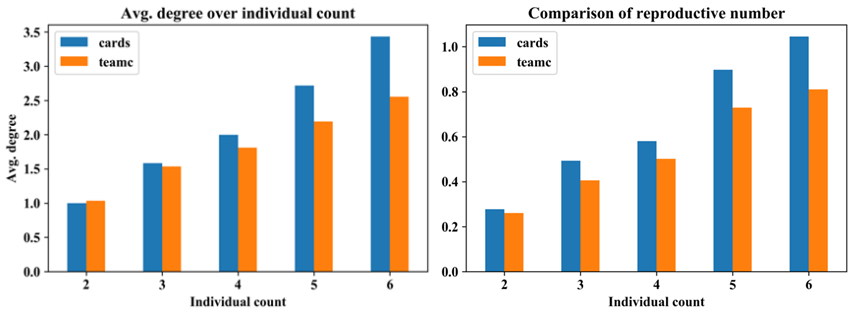
Purpose: We built a badge-based system to measure fine-grained interactions between a workroom's HCWs. The purpose of this study was (1) to demonstrate that a mobile-sensor network can measure HCW interactions in hospital workrooms, and (2) describe how the size and layout of workrooms influence the contact patterns among the rooms' occupants, and thus the potential spread of diseases.

Methods: This study utilized mobile sensors, or motes, worn in a badge holder on a HCW's collar. These motes are battery-powered, programmable devices containing a processor, flash memory, and an IEEE 802.15.4-compliant wireless radio. The mote broadcasts a time-stamped radio wave every 8 seconds in a unique band of the WiFi spectrum to not interfere with other electronics. Each mote has a unique identification number and was distributed daily to track HCWs' movements and distances relative to each other or to stationary motes (beacons). Prior to deployment in clinical settings, the motes were calibrated to accurately correlate their signal strength output (RSSI) with distance.

Motes were distributed to HCWs upon their arrival to two hospital workrooms: General Medicine (larger room) and Cardiology Teaching (smaller room). Architectural drawings of each room were collected, and the number of HCWs and the duration of their shift depended on the team's on-call schedule. The badges were worn throughout the course of 18 days and collected at the end of each shift.

After deployments were completed, the average degree (the average number of contacts for each HCW) was calculated for both rooms. Furthermore, simulations were performed to compare the two rooms if, hypothetically, one HCW had come to work infected. The probability that the infected HCW infects another was computed as the reproductive number, R_0; R_0 represents the number of other HCWs that would be infected by the end of the day.

Results: Mote calibration achieved a sensitivity of 97% and specificity of 100% in identifying a 6 ft distance between subjects.



The data showed an increase in HCWs' degree of contact with an increase in the workroom's occupancy (see figure). In addition, the degree of contact rose more quickly in Cardiology Teaching ("CARDS", the smaller of the two rooms) than in the General Medicine room ("Team C").

Simulations showed that R_0 rose with the number of HCWs in the room. R_0, like the average degree of contact, was also higher in Cardiology Teaching than General Medicine (See figure).

Discussion: We have demonstrated an approach to compare workroom safety in preventing disease spread. Workroom safety appears to be a function of the number of HCWs it is assigned and the amount of space it allots for them to work. This approach was generally acceptable and minimally intrusive on the HCWs' workdays, and we believe these results can inform interventions to improve workroom safety.

Title: Computerized Evaluation of Double Vision Caused by Ocular Misalignment
Name and collaborators: Emma Hartness; Randy Kardon, MD, PhD (mentor); Alina Dumitrescu, MD (PI); Julie Nellis, RN; Andrew Solsrud; Maddy Kroeger

Introduction: Veterans and civilians experience misalignment of the eyes that results in double vision. The resulting visual and social impairment can have negative implications for employment and independent daily living activities. Strabismus can be treated, optically with prism or surgically to achieve single binocular vision. Double vision requires extensive clinical evaluation to determine the pattern of misalignment in different fields of gaze, to localize the location of anatomical dysfunction, (e.g. extra-ocular muscle, neuromuscular junction, cranial nerve), and to prescribe appropriate treatment. This evaluation currently requires manual expertise to measure the pattern of misalignment in different gaze positions, which is time consuming and not widely available in most clinical practices. As a solution, this project seeks to develop novel software that uses head-mounted, infrared video cameras to quantify and track right and left eye positions in different gaze positions. The goal of this study is to provide automated, objective measurements of strabismus and motility that are reproducible and will provide greater accessibility for diagnosis, appropriate work-up, and treatment.

Purpose: This study aims to improve care quality, portability, and accessibility for patients experiencing ocular misalignment (strabismus) and double vision (diplopia). Novel eye-tracking software will be used to provide automated measurements of ocular misalignment and will be validated by comparison with the current standard of care manual measurements, which use alternating cross-cover testing of each eye combined with neutralization of misalignment with prisms of various strength placed over one eye.

Methods: Patients with double vision and normal subjects eligible for the study were identified from within the ophthalmology clinics at Iowa City VA and from those at the University of Iowa Hospital and Clinics adult strabismus clinic. Patients wishing to participate signed informed consent and were enrolled. With supervision from the PI, the student research intern tested patients with recently developed head-mounted virtual reality display containing infrared video cameras that recorded the right and left eye position in conjunction with automated software. The software presented visual targets to each eye that moved to different locations using an outward spiraling target (smooth pursuit movement) and targets that jumped from the center to eight different clock-hour locations at 20 degrees in the periphery (saccade eye movement). Determination of horizontal and vertical components of ocular misalignment were determined as a function of target location. The automated measurements are compared with standard of care manual measurements using prisms.

Results: To date, 51 patients with double vision and strabismus and 6 normal subjects have been tested.

Discussion: Automated computerized assessment of eye misalignment and dynamic eye movements shows promise for precise quantification of abnormal eye movements, accurate diagnosis, and monitoring of treatment over time. The automated software's portability can potentially provide rapid and remote testing when prompt triage is necessary. The testing of patients with various causes and manifestations of double vision is ongoing and shows promise in providing new and more accurate information used for evaluation and treatment of double vision.

Title:
Factors Influencing High Adolescent Pregnancy Rate in Riobamba, Ecuador

Collaborators:
- Kaleigh Haus, M2, Carver College of Medicine
- Hans House, MD, Clinical Professor of Emergency Medicine at UIHC
- Pablo Martínez, Specialist in Applied Linguistics and Translation
- Allison Schuette, GRA, Department of Biostatistics

Background:
The country of Ecuador has the highest rate of adolescent pregnancy in Latin America and the Caribbean. The local government in Riobamba, Ecuador has implemented educational youth programs aimed at reducing adolescent pregnancy. To most effectively implement these governmental programs, the root causes of this high rate need to be explored.

Purpose:
The purpose of this study is to identify factors contributing to adolescent pregnancy in Riobamba, Ecuador. Early sexual initiation, poor reproductive health knowledge, and disruption of family structure are hypothesized to be the major risk factors contributing to the high rate of adolescent pregnancy in Riobamba, Ecuador.

Methods:
We conducted a case-control study during June and July of 2021 for six weeks in five separate clinics (three urban and two rural) within the city of Riobamba, Ecuador. The study included a 21-question survey about age, education, home life, menstruation, contraception, sexual activity, and association with the law. The survey was given to 99 women who had adolescent (<20 years) first pregnancy and 99 women who were not adolescents (>=20 years) for their first pregnancy. The stated factors were analyzed using Welch's two-sample t-tests and Fisher's Exact tests, for continuous and binary variables, respectively.

Results:
The mean age at first sexual initiation was significantly lower in those who had an adolescent first pregnancy compared to those who were adults at the time of first pregnancy (16.4 and 20.2 years, respectively; p=<.0001), and the mean age of their partner was significantly lower for women who were adolescents at the time of first pregnancy compared to women who were adults at the time of first pregnancy (19.3 and 22.4 years, respectively; p=<.0001). Not knowing about contraception was associated with adolescent pregnancy (crude OR=6.6; p=<.0001), as well as not using contraception (crude OR=3.2; p=.002). Also, not living with both parents had a significant association with adolescent pregnancy (crude OR=2.2; p=.04). Those that lived rurally, did not want first pregnancy, did not have prenatal care, and did not experience domestic violence were, in addition, significantly associated with adolescent pregnancy.

Conclusion:
The present study shows that adolescent mothers were significantly younger at the time of first sexual encounter and had partners that were significantly younger than adult mothers. Adolescent mothers were also more likely to have poor reproductive health knowledge and a disruption in family structure. Early education about sexual health and use of contraception should be an initial goal of programs to reduce adolescent pregnancy.

First Trimester Human Plasma and Urine Endothelin-1 Predicts Development of Hypertensive Diseases of Pregnancy

Devin Hedlund MS4, Emma Lewis MS2, Ashlyn Mulcahy BS, Debra Brandt PhD, Donna Santillan PhD and Mark Santillan MD PhD

Background: Hypertensive diseases of pregnancy (HDP), including gestational hypertension, preeclampsia (with and without severe features)/eclampsia/HELLP syndrome, chronic hypertension, and chronic hypertension with superimposed preeclampsia/eclampsia, have a lifetime incidence of 15% and are increasing in prevalence. HDP results in morbidity and mortality for both mother and child both during the pregnancy and afterwards. Studies have identified elevated levels of the vasoconstrictor endothelin-1 (ET-1) in plasma in the third trimester in patients with HDP. However, it remains unknown if ET-1 is elevated in the first trimester and could predict the clinical development of HDP later in pregnancy.

Objective: Our study aimed to evaluate if elevated first trimester maternal plasma and urine ET-1 are predictive of HDP.

Method: This study was a nested case-control study of banked samples from the AHA-PREDICTV study cohort, a prospective cohort study aimed to investigate early biomarkers of HDP. This study included women treated in practices across the state of Iowa and determined by their clinician to be at elevated risk for developing preeclampsia. Maternal plasma and urine ET-1 concentrations from 121 participants (79 controls and 42 participants with hypertensive disease of pregnancy) were measured using an enzyme-linked immunosorbent assay specific for human ET-1.

Results: First trimester plasma ET-1 was higher in patients who developed HDP (2.2 ± 0.7 vs 1.9 ± 0.6 pg/mL, $p=0.0248$). Elevated plasma ET-1 was significantly associated with HDP even after controlling for BMI, history of diabetes mellitus, and systolic blood pressure with an odds ratio of 2.1 (95% CI 1.1-4.0, $p=0.024$). First trimester plasma ET-1 is moderately predictive of HDP (ROC AUC=0.63, $p=0.02$, sensitivity 60% and specificity 53% at 1.9 pg/mL cutoff). Further, first trimester plasma/urine ET-1 ratio was significantly elevated in HDP vs. controls (28 ± 13 vs 1.7 ± 0.3, $p=0.0120$). The plasma/urine ET-1 ratio was also significantly associated with HDP even after controlling for BMI, history of diabetes mellitus, and systolic blood pressure with odds ratio 1.7 (95% CI 1.1=2.6, $p=0.016$). First trimester plasma/urine ET-1 ratio is robustly predictive of HDP (ROC AUC=0.83, $p<0.0001$, sensitivity 73% and specificity 75% at a 1.8 pg/mL cutoff).

Conclusion/Discussion: These data support the concept that elevated ET-1 in HDP begins as early as the first trimester and may play an important role as a biomarker for first trimester prediction of patients at risk for the development of HDP. The significant elevation of plasma ET-1 in the first trimester suggests that ET-1 is involved in early pathogenesis of HDP. These data demonstrate that ET-1 may prove to be a potential novel tool for the early prediction and prevention of HDP.

NSCLC Patients' Therapeutic Response to Pharmacological Ascorbate is Correlated with Markers of Oxidative Stress

John Henrich, Melissa Fath, Casey Pulliam, Khaliunaa Bayanbold, Charles Searby, Taher AbuHejleh, Muhammad Furqan, Kristin Plichta, John Keech, Kalpaj Parekh, Joseph Cullen, Dan Berg, Emyleigh Opat, Kellie Bodeker, Nancy Hollenbeck, Sandy Vollstedt, Meghan Chandler, Heather Brown, Bryan Allen, Douglas R. Spitz

Lung cancer is the most lethal and second most prevalent cancer in the United States, with non-small-cell lung cancer accounting for approximately 85% of cases [4]. Despite recent advancements in lung cancer therapy, the five-year survival rate for lung cancer patients has remained relatively unchanged over the past 40 years. One such potential treatment, pharmacological ascorbate, has demonstrated radio-chemo-sensitization in cancer cells while acting as an antioxidant to normal tissue. Clinical trials, conducted at the University of Iowa, further demonstrate that ascorbate therapy is both safe and tolerable when used concomitantly with the standard of care therapy in NSCLC and that it increases the objective response rate when compared to the standard of care alone [1-3]. It is proposed that ascorbate's specific toxicity for cancer cells is a result of their increased levels of redox active labile iron. With the hypothesis being that ascorbate's reaction with labile iron leads to the production of critical levels of reactive oxygen species causing cell death.

The purpose of this study was to 1) determine if conditional overexpression of ferritin heavy chain can inhibit the radio-chemo-sensitization induced by pharmacologic ascorbate in H1299 (NSCLC) cell lines and; 2) to quantify markers of oxidative stress (lipid peroxidation marker: 4HNE and protein marker: protein carbonyls) in the plasma of patients in both the ongoing (NCT02905591) and completed (NCT02420314) NSCLC phase 2 clinical trials where subjects receive infusions of ascorbate in addition to the standard of care paclitaxel and carboplatin. The first purpose was accomplished by transfecting H1299 cells with a lentivirus that conditionally overexpressed ferritin heavy chain in the presence of doxycycline. Calcein flow cytometry was then performed and revealed that conditional overexpression of ferritin heavy chain after 24 hours of doxycycline lead to significantly decreased levels of labile iron. Clonogenic assays with this cell line demonstrated that ferritin heavy chain overexpression rescues the NSCLC cells from ascorbate toxicity after 24 hours of doxycycline induction, supporting the above hypothesis.

The second purpose was accomplished by performing dot blot analysis of subject plasma from the two phase 2 clinical trials. The results from the ongoing clinical trial (NCT02905591) revealed a significant increase in plasma protein carbonyl levels as well as an increase in 4HNE plasma levels that trended towards significance in the subjects receiving ascorbate therapy when compared to subjects receiving only the standard of care. We speculate that this is due to ascorbate producing critical levels of ROS in cancer cells, thus causing cell death and lysis. The results from the completed clinical trial (NCT02420314) revealed that subjects who clinically responded best to pharmacologic ascorbate therapy had a significantly higher level of protein carbonyls at the start of therapy and then a significantly lower level of carbonyls towards the end of therapy. We speculate that this trend is caused by the initial death and lysis of NSCLC cells from ascorbate which then leads to a decrease in tumor burden. The resultant reduction in active cancer cells could potentially shift ascorbates effect from causing oxidative stress to acting as a systemic antioxidant, explaining the pattern of carbonyl levels seen in the subjects.

Validation of Visual Field Results of a new Open-Source Virtual Reality Headset

Zachary Heinzman; Karam Alawa, MD; Iván Marín Franch, PhD; and Michael Wall, MD

Background

Visual field testing is extensively used in the diagnosis and surveillance of many ocular diseases. Glaucoma, the leading cause of irreversible blindness not just in the United States but throughout the world, is a classic example of this where visual field testing is used to diagnose, assess disease severity, and monitor treatment efficacy. In practice, projection-based perimeters are most commonly used and can cost upwards of $30,000. This high price point restricts access to visual field testing, particularly for individuals in low-income areas, such as third-world countries. An open-source virtual reality (VR) headset programmed for visual field testing has been developed at the University of Iowa Hospitals & Clinics. With hardware costs of $100 for the VR headset plus the cost of a capable Android smartphone, this system is more affordable and accessible than current perimeters in use today.

Purpose and Hypothesis

The purpose of this study is to assess the validity of a newly developed VR headset for visual field testing. We explored the test-retest repeatability of the system and compared results obtained from the VR headset to those obtained using an Octopus 900 (O900) projection-based perimeter in both control subjects and glaucoma patients. We then tested the hypothesis that visual thresholds and visual field defect detection is similar between the O900 perimeter and the open-source VR headset.

Methods

19 ocular healthy subjects were initially tested twice on both an Octopus 900 and Google Daydream VR headset. Subjects alternated between each system, and the test eye and test order were randomized. 18 subjects then went on to complete 3 more tests on the VR headset for a total of 5 tests to assess the repeatability of the VR headset. With respect to glaucoma patients, 3 subjects were tested 5 times on the VR headset and their previous results on an O900 perimeter from a previous study were obtained. For all visual field tests, both the O900 and VR headset were controlled through the Open Perimetry Interface—an open-source software for controlling perimetric devices—and all tests utilized a P-Central 26 grid pattern with size V stimuli. Finally, results from 2 previous studies (VIPI and VIPII) using a Humphrey Field Analyzer 2 perimeter were obtained and analyzed for test repeatability. Test-retest repeatability was assessed using the Bland-Altman repeatability coefficient (RC). RCs, using mean test values, were calculated for each pair of sequential measurements on each device and an average RC was then calculated for each system.

Results

Initially, a Bland-Altman plot using repeated measurements was created to compare the VR headset and Octopus 900 results. The mean difference between these systems was 6.4db and was relatively homogeneous across the visual field. Average RCs were 1.03 ± 0.23db and 1.16db for the VR headset and Octopus 900, respectively. The average RC from control patients on the Humphrey Field Analyzer 2 (VIPI study; size V stimuli; SITA testing algorithm; 24-2 testing grid) was 1.25 ± 0.07db. Finally, gray-scale visual field graphics were created, and it was qualitatively shown that the VR headset was able to successfully map glaucomatous visual field patterns when compared to the Octopus 900 in all 3 glaucoma patients tested.

Conclusions

Qualitatively, visual field defect detection was similar between the Octopus 900 perimeter and VR headset in all 3 glaucoma patients illustrating the potential capability of the headset to map glaucomatous visual field patterns. Importantly, while severe loss was mapped well on the VR headset, mild loss was also able to be identified. Along with this, the repeatability coefficient was shown to be statistically similar between the Octopus 900 and VR headset highlighting the excellent repeatability of the system. These results were also comparable to the more popular 24-2 SITA test conducted on a Humphrey Field Analyzer 2. Overall, the VR headset has been shown to be able to produce repeatable visual field results and successfully map glaucomatous visual field changes. This opens up the possibility that the VR headset, running the Open Perimetry Interface, may be able to provide more affordable and accessible visual field testing than what is currently available today.

Dependence on canonical MAPK and RAC signaling in drug-resistant melanoma

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Background: Melanoma is the most aggressive form of skin cancer. Understanding key cellular pathways is important for improving patient outcomes with metastatic melanoma. The RAS/RAF/MEK/ERK pathway, or canonical MAPK signaling, is a key driver of cell proliferation that has been targeted by multiple drug therapies. Mutations in BRAF and NRAS are the most common drivers in cutaneous melanoma, and BRAF inhibitors produce profound clinical responses in BRAF mutant melanoma. However, resistance to BRAF inhibitors frequently develops. We have focused on the role of RAC, a monomeric GTPase in the RAS superfamily, in BRAF inhibitor-resistant melanoma cell lines. Last summer we performed a dropout screen using CRISPR to target over 700 kinases in VRPP3 cells, a subline of A375 melanoma cells that can proliferate in the presence of BRAF inhibitors because it harbors an activating mutation in RAC. The results of this dropout screen revealed candidate kinases that may be important in the survival and proliferation of drug resistant melanoma. From this list of potential candidates, we chose three kinases for further study: MAP2K3, MAP3K4, and RSP6KA1. MAP2K3 and MAP3K4 were selected because they are known to be downstream targets of RAC signaling in an alternative MAPK pathway that operates in parallel to the canonical MAPK pathway. RPS6KA1 was selected because it is an important target of ERK in the canonical pathway. We previously showed that the RAC-mutant VRPP3 cells continue to depend on a basal level of ERK activity for proliferation, and that ERK inhibitors blocked both VRPP3 cell proliferation and RPS6KA1 phosphorylation. Moreover, ERK1 was also on our list of candidates from the dropout screen. Lastly, because RAC signaling can also regulate cell adhesion, we also investigated how the cell substrate influenced drug resistance in VRPP3 cells.

Methods & Results: We performed RNAi to knockdown expression of these three kinases in VRPP3, with 2 constructs for each kinase, using retroviral RNAi vectors to construct cells with stable knockdown. Knockdown was assessed by Western blot. MAP3K4 and RSP6KA1 had 62% and 72% knockdown, respectively, while MAP2K3 had 18% knockdown. We then assessed cell proliferation using an Alamar blue assay. Alamar blue assays of MAP2K3 and MAP3K4 knockdown cells failed to suggest a role in drug resistance. RSP6KA1 knockdown cells in the presence of the BRAF inhibitor, vemurafenib, showed a 38% decrease in proliferation after 6 days compared to cells in DMSO. To investigate the role of the extracellular matrix in drug resistance, we grew VRPP3 cells on rigid tissue culture plastic versus soft, 0.8% collagen gels in DMSO and vemurafenib. Cells growing on soft 3D collagen appeared partially resensitized to vemurafenib treatment compared to tissue culture plastic.

Conclusions & Future Directions: Our data suggest that RSP6KA1 can contribute to RAC-driven resistance to BRAF inhibitors in BRAF-mutant melanoma. Since ERK1 was also on our candidate list from the dropout screen, we plan on further investigating its role in drug resistance. In addition, the collagen growth assay provided preliminary data that extracellular matrix can markedly affect the drug resistant phenotype of RAC-mutant melanoma cells.

Determining the Relationship Between TRAF3 Protein Levels and Phenotypic/Functional Characteristics of B Lymphocytes with Aging

Nicole Hines, Kyp Oxley, Gail Bishop

Introduction: B lymphocytes are the cell of origin in the majority of hematologic malignancies, and most human B cell cancers occur in individuals > 60 years of age. This age group also displays a greater propensity for various types of immune dysfunction, including both chronic inflammation, as well as suboptimal immune responses. Understanding how chronic immune-activating signals in aging lymphocytes contribute to both compromised immunity and increased risk of immune-cell malignancies is critical to developing effective strategies for interventions to increase 'healthspan' of the growing population of humans of older ages.

Prior reports on the impact of the signaling adapter protein TNF receptor associated factor 3 (TRAF3) deficiency on B cells primarily studied cells completely lacking TRAF3 genes and protein. However, germline biallelic mutation of Traf3 is lethal in mice, and no humans with complete lack of TRAF3 have been reported. It is thus important to assess the impact of reduced TRAF3 protein on B cell biology, to distinguish between gradient and 'threshold' effects on TRAF3-regulated functions.

Hypothesis: Using B cells from laboratory mice with varying levels of TRAF3, we tested the working hypothesis that reduced TRAF3 protein will result in abnormal B cell survival and increased activation mediated by multiple TRAF3-regulated pathways.

Methods: We isolated B cells from spleens of WT parent, B-*Traf3*$^{-/+}$, and B-*Traf3*$^{-/-}$ mice. Samples were processed into whole cell lysates, and proteins separated by SDS-PAGE, to determine relative amounts of survival and signaling proteins by Western Blot: TRAF3, NF-κB2, CREB, Mcl-1, Glut1, c-Myc. To assess IL-6 receptor signaling, cells were stimulated with IL-6 for varying amounts of time (0, 5, 15, 30, and 60 minutes, then samples were processed into whole cell lysates, proteins separated by SDS-PAGE, and amounts of STAT3 and pSTAT3^{Y705} were determined by Western Blot. Additionally, cells from each *Traf3* phenotype were plated in 24-well plates in BCM10 without additives. Cell survival was measured by trypan blue exclusion assay for up to 2 weeks.

Results: Measurements of protein expression were most consistent for Mcl-1, c-Myc, and NF-κB2. We found that expression of these 3 proteins in B-*Traf3* $^{-/+}$ samples resembled the WT phenotype more than that of B-*Traf3* $^{-/-}$ samples. However, levels of STAT3 phosphorylation via IL-6 stimulation did show and intermediate phenotype in *TRAF3*$^{-/+}$. B cell survival in partially deficient TRAF3 *in vitro* experiments did not express increased longevity as seen in cells completely lacking TRAF3.

Conclusion: Here we saw in Mcl-1, c-Myc, and NF-κB2 that even partial TRAF3 expression was sufficient to maintain normal signaling compared to WT and KO. However, in IL6 signaling, an important inflammatory modulator, we saw that partially decreased TRAF3 protein levels could have important biological outcomes. Studies of B cells with partial depletion of TRAF3 will be important and a more faithful representation of the natural aging process in humans.

Arthroscopic Irrigation Fluids and their Effect on Articular Chondrocyte Health

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Background: Arthroscopy is a commonly used, minimally invasive surgical technique for the diagnosis and treatment of articular cartilage injuries. While arthroscopy allows patients to benefit from reduced postoperative swelling, lower risk of complications, and faster recovery compared to open arthrotomy, arthroscopic procedures can cause joint damage due to sub-optimal joint irrigation and lubricin washing. The most commonly used irrigation fluid, normal saline, is notably hypotonic with respect to the cartilage matrix, creating an unfavorable environment for chondrocyte viability and function. Joint irrigation during arthroscopy additionally causes flushing of synovial fluid (404 mOsm/L) and washing of lubricin, a critical glycoprotein and boundary lubricant synthesized by superficial chondrocytes, from the cartilage surface. Because lubricin is the primary cartilage lubricant, its depletion causes increased coefficients of friction between cartilage surfaces, thus accelerating cartilage wear. The loss and metabolic impairment of chondrocytes from osmotic variation and saline exposure likely hinders de novo lubricin synthesis needed to restore this vital coating. Despite these apparent risks and the ubiquitous nature of these techniques in orthopedic practice, little work has been done to characterize or prevent such injuries from occurring.

Purpose: The goal of this study is to characterize the effects of normal saline, a common irrigation fluid used during arthroscopy, on articular cartilage health. We also plan to assess whether the addition of metabolic or osmotic agents to saline serves a chondroprotective role during arthroscopic irrigation.

Methods: Bovine stifle joints were collected from a local abattoir and used in two separate experimental designs: chondrocyte culture in agarose and osteochondral explant culture. A high cell density (5 x 10^6 cells/ml) agarose gel culture was produced using harvested bovine chondrocytes and was used to generate 3-dimensional agarose scaffolds. Constructed samples were incubated in culture media, saline (308 mOsm/L), glucose (340 mOsm/L), or mannitol (340 mOsm/L) for 24 hours and placed into culture media for recovery for 0 or 24 hours (n= 3-4 per treatment group). Following incubation, samples were collected and stained with dihydroethidium (DHE), a probe for cellular oxidant production, and Calcein AM, a probe for cell viability. All samples were imaged using confocal microscopy and ImageJ was used to measure fluorescent area of stain captured in each sample. Data collected was analyzed by one-way ANOVA. In addition to this, a tissue culture model consisting of 4 mm-diameter osteochondral explants from bovine stifle joints was collected and incubated in saline, glucose, or mannitol for 24 hours and placed into culture media for recovery for 0 or 24 hours (n = 3 per treatment group). ATP and DNA levels were quantified using Sigma FLAA ATP Bioluminescent assay (Sigma-Aldrich) and PicoGreen dsDNA Fluorescence assay kits (Thermo Fisher Scientific). A microplate reader was used to measure fluorescent intensity of stain captured in each sample. Resulting ATP levels were normalized to DNA content within each sample, and data was analyzed by two-way ANOVA with post-hoc Tukey test.

Results: Bovine chondrocytes cultured in agarose hydrogels with normal saline showed a significant increase in DHE signal compared to the other groups ($p = 0.048$). After 24-hour recovery, DHE ratio in normal saline was reduced approximately 40%. The addition of glucose and mannitol did not appear to affect ATP levels in the 0-hour recovery group; however, after 24-hour recovery explants incubated in mannitol demonstrated significantly recovered ATP levels compared to explants incubated in saline ($p = 0.0005$) or glucose ($p = 0.0111$).

Conclusion: Although further tests are needed in order to fully evaluate the effects of normal saline on cartilage health, our current results indicate that saline induces oxidative stress and metabolic impairment on articular chondrocytes during joint irrigation. These findings suggest that the addition of osmotic agents to irrigation solutions may be beneficial to improve articular cartilage health during arthroscopy.

Elucidating the Host-Pathogen Interactions between C. trachomatis and IFN-Induced Transmembrane Protein 3 (IFITM3)

Steven B. Huang, B.S.; Brianna Steiert, B.A.; Mary Weber, PhD

Background:

The obligate intracellular pathogen, *Chlamydia trachomatis,* depends entirely on a eukaryotic host cell for its survival and thus has developed several mechanisms to subvert host compartments for growth and immune evasion. One subset of type III-secreted protein effectors vital to the life cycle of *C. trachomatis* are the inclusion membrane proteins (Incs). Incs function to establish a replicative niche, evade host-immunity detection, and maintain chlamydial inclusion integrity. There are 59 predicted Incs for *C. trachomatis.* Although some Incs have been functionally characterized, the role of most Incs in the life cycle of *C. trachomatis* remains unknown. To combat intracellular infections, host interferons (IFN) and interferon-stimulated genes (ISG) are stimulated in-response to TLR and STING activation by *C. trachomatis*. One set of ISGs are the Interferon-induced transmembrane proteins (IFITMs). IFITMs have well-described antiviral actions, but whether it plays a role in limiting intracellular bacterial infection is still unclear.

Hypothesis/Aims:

Previous affinity-purification mass spectrometry (AP-MS) data suggests an interaction between IFITM3 and chlamydial inclusion membrane protein C (IncC). In an *IncC::bla* interruption mutant, chlamydial inclusions exhibit a premature lysis phenotype at 24hrs. We hypothesize that IFITM3 is involved in the lysis of inclusions, and that IncC acts as a protective factor with specificity against IFITM3 targeting. Additionally, a considerable amount of structural homology is shared between inclusion membrane proteins. We aim to explore the specificity of IFITM3 targeting to IncC as well as other chlamydial inclusion membrane proteins.

Methods:

Growth curves - At a MOI of 5, WT HeLa or IFITM3-KO HeLa cells were infected with either WT *C. trachomatis* L2 or *IncC::bla C. trachomatis*. Cells were incubated for 24hrs at 37°C and 5% CO_2. *C. trachomatis* was detected via immunofluorescence.

LDH release assay - At a MOI of 3, WT HeLa or IFITM3-KO HeLa cells were infected with either WT *C. trachomatis* L2 or *IncC::bla C. trachomatis*. Cells were incubated for 18hrs at 37°C and 5% CO_2. LDH absorbance was read on a Tecan Infinite Pro m200 plate reader.

Co-immunoprecipitations assay – WT *C. trachomatis* L2 strains were transformed with an overexpression pBomb plasmid. FLAG-tagged Inc constructs were induced by tetracycline induction. WT HeLa cells were infected to an MOI of 5, and incubated for 24 hrs. Following incubation cells were lysed, and the lysate was applied to pre-chilled anti-FLAG magnetic beads.

Results and Conclusions:

Our current work demonstrates a growth improvement, and reduced host-toxicity of an *incC::bla* interruption mutant when IFITM3 is absent in a host. Additionally, chlamydial inclusions were also observed to be more regular in size and distribution when IFITM3 is absent. Co-immunoprecipitation assays revealed an IFITM3 enrichment in-response to IncC. This observation was also seen with the following chlamydial inclusion membrane proteins: CT229, CT222, and CT223. Overall, our results demonstrate the diverse roles of chlamydial inclusion membrane protein and highlights the immune evasion mechanisms at play during a chlamydial infection.

Flatfoot Deformity Correction Using Longitudinal Arch Support Ankle-Foot Orthosis: A Weight-Bearing CT Prospective Case-Control Study

Student: Caleb Iehl
Mentor: Dr. Cesar de Cesar Netto, MD, PhD

Background:

Flatfoot deformity is a prevalent and potentially debilitating orthopedic foot and ankle problem. It comprises a multifocal three-dimensional (3D) deformity of the foot marked by progressive hindfoot valgus, medial longitudinal arch collapse, and forefoot abduction. Conservative treatment includes the use of corrective insoles and orthotics aiming to support the collapse of the medial longitudinal arch, decrease dynamic hyper-pronation during gait, and correct and stabilize hindfoot valgus deformity. Different options of insoles and orthotics are available. The longitudinal arch support ankle-foot orthosis (AFO) has been commonly used with reported success in controlling pain symptoms in flatfoot deformity patients. However, no study has assessed the ability of these braces in correcting the 3D components of the deformity.

Purpose/Hypothesis

The aim of this prospective case-control study was to assess the ability of longitudinal arch support AFOs to influence traditional 3D flatfoot alignment measurements in a flatfoot patient cohort and in healthy controls. Our hypothesis states that a significant amount of foot alignment change/correction would be observed in both groups, with a more pronounced correction in flatfoot patients.

Methods

In this prospective IRB-approved case-control study, we consecutively enrolled symptomatic flatfoot deformity patients and asymptomatic healthy volunteer controls. Patients were excluded if under 18 years old, pregnant, or if they had prior foot and ankle surgery. The control group was constructed to match the experimental group for mean age, sex, and BMI. Included patients were scanned using a Weightbearing Computed Tomography (WBCT) (Curvebeam, HiRise) in a bipedal standing position, with and without an inflatable longitudinal arch support AFO (Donjoy, Aircast Posterior Tibial Tendon Dysfunction Orthotic Brace). Various conventional flatfoot measurements were performed in all acquired images. Utilized measurements were chosen based on prior published literature, aiming to assess the overall 3D deformity (Foot and Ankle Offset -FAO) as well as the two-dimensional deformity components: hindfoot moment arm (HMA) for hindfoot valgus; talonavicular coverage angle (TCA) for forefoot abduction; forefoot arch angle (FAA), talus-first metatarsal angle (Meary's Angle), and medial cuneiform-to-floor distance for medial arch collapse; subtalar joint middle facet subluxation for peritalar subluxation. Normality of the data was assessed by the Shapiro-Wilk test. Comparisons within and between the groups was performed using paired T-tests or paired-Wilcoxon tests, depending on normality. P-values of less than 0.05 were considered significant.

Results

We included a total of 12 symptomatic flatfoot patients (7 females/5 males; 17 feet) and nine controls (4 females/5 males; 17 feet). The average age and BMI were respectively 49.4 years (range, 24-70) and 32.5 (standard deviation – SD, 7.4) for flatfoot patients and 45.8 years (range, 23-75) and 29.2 (SD 9.0) for controls. When comparing patients within their groups (flatfoot or controls), bracing showed significant deformity correction in both flatfeet and control groups only for medial longitudinal arch collapse measurements. Average improvement/correction of significant measures with a 95% Confidence Interval (95% CI) was, respectively: medial cuneiform-to-floor distance, 7.9 mm ($p<0.0001$; 95% CI, 4.87 to 11.08mm) for flatfeet and 4.13mm ($p<0.041$; 95% CI, 0.17 to 8.09mm) for controls; Forefoot Arch Angle (FAA), 5.77^o ($p=0.002$; 95% CI, 2.22 to 9.33^o) for flatfeet and 3.85^o ($p=0.036$; 95% CI, 0.26 to 7.45^o) for controls; talus-first metatarsal angle, -5.85^o ($p=0.011$; 95% CI, -10.25 to -1.45^o) for flatfeet. The talus-first metatarsal measurement in controls did not show significant changes ($p=0.74$). No improvements/changes were noted for 3D deformity as measured by the FAO, nor the other 2D components of the deformity including hindfoot valgus (HMA), forefoot abduction (TCA), or peritalar subluxation (middle facet subluxation), for both flatfoot and control patients. When comparing the average deformity improvement/change with brace correction between groups (flatfeet and controls), the improvement was more pronounced in flatfeet patients than in controls for only medial cuneiform-to-floor distance 3.84mm ($p=0.0025$; 95% CI, 1.45 to 6.23mm) and talus-first metatarsal angle 6.41^o ($p=0.0036$; 95% CI, 2.25 to 10.57^o) (Figure 2/3).

Conclusion

In this prospective case-control study, we found that the longitudinal arch support AFOs significantly improved measurements of medial longitudinal arch collapse for both flatfeet and control patients with a more pronounced and significant correction in flatfeet patients compared to controls. However, the use of the orthotic device did not improve the overall 3D deformity, nor the deformity components of hindfoot valgus, forefoot abduction, and pertitalar subluxation. This isolated correction of medial arch collapse, limited to a single component of the deformity, should be considered when utilizing longitudinal arch support AFOs in the treatment of flatfoot deformity patients.

Figure 1

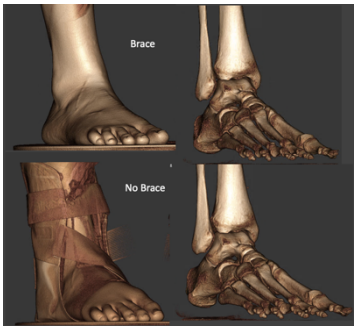


Figure 2

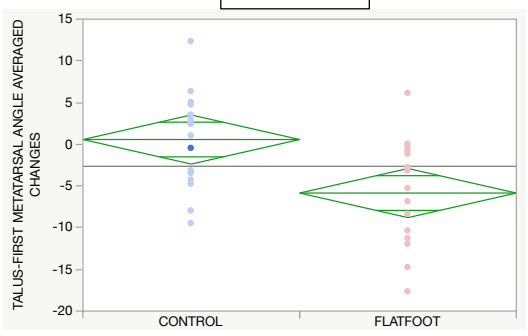
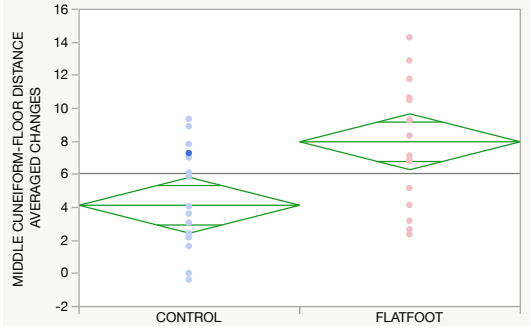


Figure 3



Evaluating the Disease-Modifying Effects of Naltrexone on the Development of Post-Traumatic Epilepsy using a Novel, Automated EEG Analysis Algorithm

Kyle Jackson, Shaunik Sharma, Saul Rodriguez, Grant Tiarks, Angela Wong, Dave Keffala-Gerhard, Alexander G. Bassuk

Background: Traumatic brain injuries (TBIs) affect more than 3 million Americans each year resulting in nearly 300,000 hospitalizations and 50,000 fatalities. TBIs trigger mechanisms that cause neuroinflammation, glial cell activation, neuronal network remodeling, and post-translational synaptic protein modification that can cause deficits in cognitive function. Sustained disruption of normal homeostasis can ultimately result in dementia, anxiety, and post-traumatic epilepsy (PTE), with a probability of developing PTE in more than 50% of severe TBI cases. First-line pharmacological agents such as anti-epileptic drugs (AEDs) are commonly prescribed following TBIs, however, their efficacy is still disputed. Additionally, no treatment currently exists that can prevent epileptogenesis or reverse the neurodegenerative changes observed in PTE. Using high throughput transcriptome profiling, we identified Naltrexone as a potential candidate for preventing or slowing the progression of epileptogenesis. Recent work evaluated the effect of Naltrexone in a pentylenetetrazole (PTZ)-induced mouse model of epilepsy and found that mice pre-treated with Naltrexone were resistant to PTZ-induced seizures, suggesting that Naltrexone may play a role in the development of PTE.

Methods: Four-week-old C57BL/6J mice were subject to diffuse brain injury using free-fall weight drop. One day post injury (dpi), electroencephalogram (EEG) electrodes were implanted with telemetry devices for EEG monitoring. Three dpi, mice were administered a sub-convulsive dose of PTZ (30 mg/kg i.p.) followed by Naltrexone (NTX) or vehicle treatment 2-hours following PTZ administration. Mice were then given two doses of Naltrexone or vehicle for 3 days, followed by a single dose for four days. All mice were video EEG (vEEG) monitored continuously for 7 days and intermittently thereafter for 3 months. After euthanasia, serum was collected for cytokine analysis, and brain tissues were harvested for immunohistochemistry (IHC) and Western blot (WB) studies. A novel, automated algorithm was developed in MATLAB to quantify the number of spikes and epileptiform discharges in the EEG data, which were used to assess the efficacy of Naltrexone at preventing or reducing the severity of PTE.

Results: Analysis of the 3-month vEEG data revealed that 38% of the untreated animals with TBI developed PTE, whereas none of the Naltrexone-treated mice became epileptic. Epileptiform discharges were significantly reduced in the Naltrexone-treated mice compared to the vehicle group. IHC studies showed increased gliosis in the cortex and hippocampus of mice that suffered brain injury compared to the controls. Neurodegeneration (FJB+NeuN positive cells) was also greater in these mice, and NTX treatment significantly reduced neurodegeneration when compared to the untreated mice. Additional western blot analyses revealed increased protein levels of activated mu-opioid receptors, nitroxidative stress markers (3-NT and iNOS), and oxidative stress markers ($gp91^{phox}$ and 4-HNE) in the brains of injured mice. These biomarkers were significantly reduced in mice treated with Naltrexone following injury. Serum cytokine analysis using the Quantibody 45-multiplex assay revealed a significant reduction in multiple proinflammatory cytokines and an increase in anti-inflammatory cytokines (IL-4 and IL-10) in the serum of Naltrexone-treated mice.

Conclusions: Naltrexone treatment post-TBI suppresses neuroinflammation, neurodegeneration, epileptiform discharges, and spontaneous recurrent seizures, thus preventing epileptogenesis. These findings suggest that Naltrexone may be used to prevent the development of or progression of PTE. Additionally, the use of our automated algorithm for EEG quantification was shown to be effective for determining the presence of PTE and spontaneous recurrent seizures via EEG epileptiform discharges and spiking activity. Thus, this algorithm can serve as a reliable method for rapidly analyzing large amounts of EEG data in future studies.

Convolutional Neural Network Analysis of Retinal Microcirculation Imaging

Student: Matthew Jones, M1
Mentor: Dr. John Cromwell, M.D., Division of Gastrointestinal Surgery

Background: Literature provides evidence that alterations in microcirculation underpin biological aging. Non-invasive analysis of retinal microcirculation imaging of surgical patients offers a unique opportunity to assess age-related risk of adverse events following surgery. The images must be properly captured and not contain artifacts for valid scientific analysis to occur. Convolutional neural networks (CNNs) can be utilized as classifiers to differentiate between medical images not suitable for analysis and those that are suitable. Historically, CNNs have performed well in predictive modeling and classification of medical imaging, and they are well-documented with respect to functionality in programming languages.

Purpose: The purpose of this project was to develop a validated CNN capable of assessing suitability of retinal microcirculation images for further analysis. This CNN will then be deployed as an API designed for use with retinal images in the electronic health record (EHR) to enable faster assessment and documentation of image quality.

Hypothesis: A CNN constructed for assessing quality of retinal microcirculation images will demonstrate its potential for clinical incorporation into the enterprise EHR as an API by producing high classification accuracy.

Method: Retinal images obtained from surgical patients were classified as either suitable or not suitable in quality for further analysis according to manual assessment by a clinician. R programs were constructed that successfully developed a CNN for training and testing on different subsets of the data. The CNN's hyperparameters were tuned using grid search, specifically targeting convolution filters, number of layers, learning rate of the algorithm, pool size, and kernel size. 864 total models were tuned using 75 percent of the total data in 2 folds of cross-validation. Overfitting and elapsed execution time were minimized by restricting number of epochs to 60. Mean training and validation accuracies across all cross-validation folds were obtained from each tuned model. The final model was selected with a view toward optimizing accuracy while minimizing overfitting, with a mean training accuracy of 0.92, a mean validation accuracy of 0.82, 2 convolution layers in the model, and a total of 21,145,001 parameters in the model. A CNN with the selected hyperparameters was freshly trained on the 75 percent of total data previously used in the tuning process, saved for reproducibility, and tested for predictive and classification ability on the remaining 25 percent of retinal images that had been held out-of-sample.

Results: The optimized CNN was tested on 34 retinal images and results were summarized in a confusion matrix. 32 predictions were correct, with 21 true positives and 11 true negatives. 2 predictions were incorrect, with 1 false positive and 1 false negative. An ROC curve was developed, with a corresponding AUC score of 0.985. Accuracy was calculated to be 0.941, with a 95% confidence interval of (0.803, 0.993). Cohen's kappa statistic was calculated to be 0.871.

Conclusion: CNNs are useful for supervised learning problems, especially image classification. The accuracy, AUC, and Cohen's kappa statistic show that a CNN was developed with high predictive power of retinal image quality. The image classification portion of the study could be improved by comparing these documented results with results from another binary classifier, such as a logistic regression model or pre-trained neural network, as well as by collecting more retinal images for use in training the CNN.

Title: Psychosocial Issues for Post-treatment Head and Neck Cancer Survivors: A Narrative Review

Authors: Vijayvardhan Kamalumpundi[1], BS; Seyedehtanaz Saeidzadeh[2], PhD, RN

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Background: Currently, a Head and Neck cancer (HNC) diagnosis is associated with a three-time higher rate of suicide compared to the general population in the US. The number of survivors of head and neck cancer (HNC) are increasing given the innovations in cancer treatment and research. Despite these innovations in cancer treatment however, patients frequently suffer from physical effects of HNC-related treatment such as: shoulder dysfunction, xerostomia, dysphagia, neck/throat lymphedema and more, leading to greater levels of anxiety, distress, and depression. To understand what psychosocial issues contribute to the HNC survivor experience and to help support this patient population in their recovery, a review is urgently needed.

Purpose: The aim of this narrative review is to describe rates and severity of psychosocial issues in HNC survivors, identify the demographic and clinical predictors of psychosocial issues in this population, describe the impact of psychosocial issues on HNC survivors, and to summarize therapies/interventions impacting psychosocial outcomes among HNC survivors.

Methods: We searched databases including PubMed, Scopus, PsycINFO, Cochrane, and CINAHL from 1990 until 2021. We included studies that had: an adult population (≥18 years) and HNC survivors during or after completion of curative intent treatment. All study designs except systematic reviews were included. Study quality was assessed using the Mixed Methods Appraisal Tool. Exclusion criteria were studies that had a mixed population of metastatic disease/cancer survivors or if studies did not explicitly define the population to be receiving curative intent HNC treatment.

Results: 13 of the 2440 screened studies met the inclusion criteria. Most of the included studies were cross-sectional studies (n=7), but prospective studies (n=3), randomized controlled trials (n=2), and qualitative study designs (n=1) were also found. Most participants among the studies were male (Range: 58-78%) and identified as white. Nine studies focused on all HNC types, though some studies focused on specific HNCs such as nasopharyngeal cancer (n=2), oral cancer (n=1), and laryngeal cancer (n=1). In addition, the studied psychosocial issues included: anxiety, depression, distress, coping and adjustment, fear of cancer recurrence, sexual satisfaction, and body image. Quality assessment by the MMAT showed that all quantitative studies (n=10) were of high quality in the domains of sampling strategy, measurement, and statistical appropriateness, and only six studies were rated as “can’t tell/no" for study quality in representativeness of sample, and risk of non-response bias. The included qualitative study was of high quality on all domains, and the two RCTs were lacking in the domains of: complete outcome data, blinding, and/or participant adherence.

Conclusions: This review demonstrates that only a handful of studies are currently available that address psychosocial issues in HNC survivors. Many demographic and clinical characteristics were found to be related with psychosocial issues in HNC survivors such as age, gender, tumor characteristics, comorbidities, working status, and laryngeal stoma among many others. Patients reported a negative impact of treatment on quality of life, body image, sexual satisfaction, and functional status. Future research should be dedicated to studying the long-term change in psychosocial issues for HNC survivors.

Assessing Neuropsychiatric Outcomes after Pediatric Cerebellar Tumor Resection

Kinnari Karia, M2, Aaron Boes, MD, PhD

Background: Approximately 25% of pediatric patients experience transient complications with language, emotional lability, executive function, and motor control after cerebellar tumor resection. These symptoms have been termed posterior fossa syndrome (PFS), cerebellar cognitive affective syndrome, or cerebellar mutism syndrome. Patients who develop PFS are at risk for long term neurocognitive impairments, with consistent emphasis on deficits in executive function and motor skills. In 2019, Albazron et al.[1] reported that damage to the cerebellar outflow tract was implicated in patients with PFS and additionally, highlighted the mediodorsal nucleus of the thalamus, right temporal stem, and right red nucleus as being functionally connected to lesion locations of patients with PFS. The neuropsychiatric outcomes in pediatric patients with PFS and the relationship to the anatomy of the surgical resection site is relatively unexplored.

Aim and Hypothesis: This analysis examined neuropsychiatric assessment data of pediatric patients after cerebellar tumor resection to determine if there was a link with cerebellar outflow pathway damage and posterior fossa syndrome (PFS). We hypothesized that 1) patients with PFS would demonstrate poorer performance on neuropsychiatric tests compared to patients without PFS and 2) neuropsychiatric impairment would be associated with higher cerebellar outflow pathway damage.

Methods: Participants included 116 pediatric patients who had undergone cerebellar tumor resection between 1985-2014 at Massachusetts General Hospital. 34 neuropsychiatric tests were included but the particular tests administered varied between participants. Neuropsychiatric test performance was statistically compared between the PFS and non-PFS group with and without score outliers (defined as ± 3 standard deviations from the mean). There was no significant difference in mean age at diagnosis or mean age at date of neuropsychiatric testing between patients with PFS ($n = 30$) and without PFS ($n = 86$), but lesion volume was larger in patients with PFS ($p = 0.047$). Lesion load across the cerebellar outflow pathway was higher in the PFS group, as previously quantified by Albazron et al.[1]

Results: Statistical analysis revealed that patients with PFS had poorer performance on various tests including WISC-IV Full Scale IQ ($p = 0.047$), WISC-IV Perceptual Reasoning Index ($p = 0.002$), Purdue Pegboard Test ($p < 0.001$), BRIEF Behavioral Regulation Index ($p = 0.021$), and BRIEF Global Executive Composite ($p = 0.033$) compared to patients without PFS. After correcting for lesion volume, age at diagnosis, and age at date of testing, weak correlations were found between lower test scores and higher lesion load across cerebellar outflow pathways, superior cerebellar peduncles, and/or deep cerebellar nuclei. For example, lower scores on Scales of Independent Behavior – Broad Independence were slightly correlated with higher lesion load in the right superior cerebellar peduncle ($r = -0.263$, $p = 0.007$). Additionally, lower scores on WISC-IV Perceptual Reasoning Index and Purdue Pegboard Test were correlated with connectivity between a patient's lesion location and the three regions previously identified being functionally connected to the lesions of patients with PFS: thalamic mediodorsal nucleus, right temporal stem, and right red nucleus. Fisher's Exact Test comparing PFS development and impairment (1.5 standard deviations or more below the mean) on Purdue Pegboard Non-dominant ($p < 0.001$) and Purdue Pegboard Both Hands ($p < 0.001$) was significant. Patients with scores below the impairment threshold in these tests, amongst others, also had significantly larger lesion loads ($p < 0.05$) across the cerebellar outflow pathway and its components.

Conclusion: Patients with PFS tended to show more impairment on neuropsychiatric testing, with assessments involving motor skills as the strongest differentiator of patients with and without PFS. In all patients, damage to cerebellar outflow pathways were correlated with poorer test performance in various domains. The current analysis reinforces prior description of neurocognitive impairment in patients with PFS while extending the results reported by Albazron et al.[1] relating cerebellar outflow pathway damage to PFS development. Future work clarifying PFS pathogenesis and prognosis can contribute to better surgical approaches and clinical follow-up in addition to a more robust understanding of the neuropsychiatric role of the cerebellum.

Reference:

1. Albazron FM, Bruss J, Jones RM, Yock TI, Pulsifer MB, Cohen AL, et al. Pediatric postoperative cerebellar cognitive affective syndrome follows outflow pathway lesions. Neurology. 2019;93(16):e1561-e71.

Student: Tanner Kempton
Mentor: Lane Strathearn

Title: Stress, depression and anxiety in mothers of toddlers with autism spectrum disorder

Abstract:

Background:
Autism spectrum disorder (ASD) is recognized as one of the most common intellectual and developmental disabilities. Currently, it is estimated that almost 3% of US children are diagnosed with ASD. Those diagnosed with ASD often struggle with life-long social, physical, and mental health difficulties. Recent advancement in research and treatment have largely focused on the individual diagnosed with ASD. However, there are potential effects on the caregiver, including parental stress and mental health challenges, related to raising a child with ASD, which are not always appreciated or understood.

Studies suggest that raising a child with ASD is associated with higher levels of stress, depression, and anxiety, especially among mothers of children with ASD possibly due to their more traditional role as primary caretaker. Better understanding how measures of maternal mental health are associated with their child's developmental disability could help management of the disorder in both an individual and family centered manner.

Aims:
The aim of this study is to evaluate maternal levels of depression, anxiety, and stress among mothers of children with autism spectrum disorder (ASD), children with other developmental delays (DD), or typically developing children (TD).

Methods:
Participants are part of the larger research study examining the influence of social environment and epigenetic changes on the development of autism spectrum disorder. Mothers of children between the ages of 14 and 36 months were recruited. Mothers completed several questionnaires evaluating different aspects of current and long-term mental health, including the Maryland Trait Depression Scale (MTSD), State-Trait Anxiety Inventory (STAI**)**, Perceived Stress Scale (PSS), and Chronic Stress Survey (CSS) as well as a demographic questionnaire.

Results:
Measures of maternal depression, anxiety and stress were elevated among mothers of children with developmental delays (DD) when compared with mothers of children with autism (ASD) or typically developing children (TD). Measures of maternal mental health were not significantly different between mothers of children with autism (ASD) and typically developing children (TD).

Conclusions:
In contrast to these findings, several previously published studies have shown a positive association between maternal depression, anxiety, or stress in mothers of children with ASD compared with TD children. This could possibly be explained by recruitment methods of DD group in this study, which could have skewed the study population to include more severe developmental delays. If observed difference is due to an actual difference between the groups, this could suggest the presence of addition factors such as family composition or social support affecting the mental state of the mother.

A comparison of corneal endothelial cell loss in narrow-lumen DMEK tissue injectors

Matthew Kigin

Primary Supervisor: Christopher Sales, MD, MPH

Purpose:

To determine if there is a difference in corneal endothelial cell damage when loading Descemet membrane endothelial keratoplasty (DMEK) tissue in graft injectors varying in lumen size and technique.

Methods:

This study evaluated 10 donor corneal mate pairs with similar initial endothelial damage that met surgical-grade criteria. Each cornea was stripped and prepared following an eye bank standard protocol for a typical DMEK surgery. In each of the first 5 mate pairs, one member was loaded into a Straiko Modified Jones Tube, while the other into a LEITR Modified Jones Tube. Of the second 5 mate pairs, one pair member was loaded into the front of a LEITR Modified Jones Tube, while the other into the rear of the same injector. Endothelial cell loss (ECL) was then evaluated and compared after the expelling of each graft through their respective injector and compared to the graft's respective mate.

Results:

There was no clinical significance ($\Delta \geq 10\%$) when comparing the ECL of grafts through the Straiko Modified Jones Tube with grafts through the LEITR Modified Jones Tube ($\Delta = 6.842\% \pm 5.61$). Similarly, there was no clinical significance ($\Delta \geq 10\%$) comparing the ECL of grafts loaded into the front of a LEITR injector with those loaded into the rear ($\Delta = 7.876\% \pm 5.38$). Qualitatively, no consistent pattern of cell damage was notated when comparing the ECL of both injectors and techniques.

Conclusions:

The endothelial cell loss was not clinically significant when comparing both injector type and loading location. Based on these observations, decisions for injector type and loading location may be based on the surgeon and eye bank technician's discretion.

Aspirin Reduces Triglycerides in Both Preeclamptic and Non-Preeclamptic Pregnancies

Tarynne E. Kinghorn BS, Donna A. Santillan PhD, Debra S. Brandt PhD RN, Ashlyn S. Mulcahey BS, Emily S. Leibold BS, Monica C. Myers BS, Wendy S. Hamilton BS, Mark Santillan MD PhD

Objective

Preeclampsia, a multisystem disorder of pregnancy characterized by hypertension and proteinuria, is associated with elevated triglyceride levels above the expected physiologic increase in pregnancy. Low-dose aspirin (81mg) is commonly used in pregnancy to prevent the development of preeclampsia, although its mechanism of effect is not fully understood. The objective of the study is to determine if aspirin is effective in lowering the elevated triglyceride levels associated with preeclampsia.

Study Design

In this retrospective case control study, subjects were selected from the University of Iowa Maternal Fetal Tissue Bank (IRB#200910784) based on aspirin use and preeclampsia in pregnancy. Banked plasma samples from the third trimester of pregnancy were analyzed via triglyceride colorimetric assay. Statistical analyses were performed with aspirin use and preeclampsia as dependent variables. Alpha was set at 0.05.

Results

The plasma samples for aspirin cases without preeclampsia (n=36), aspirin cases with preeclampsia (n=13), control cases without preeclampsia (n=51) and control cases with preeclampsia (n=15) were comparable in gestational age of the pregnancy (219.3 ± 33.3 vs. 219.8±32.0 vs. 219.4±31.1 221.4±30.9 days, p=0.996). In the third trimester, patients without preeclampsia who took aspirin had significantly lower triglycerides compared to those who did not take aspirin (112.4 ± 39.5 vs. 134.9 ± 50.8 mg/dL, p=0.039). A significant decrease in triglycerides was also demonstrated in patients with preeclampsia who took aspirin compared to those who did not (129.7 ± 46.1 vs. 171.975±78.5 mg/dL, p=0.004).

Conclusion

These data suggest that aspirin use does not completely prevent the expected triglyceride rise in pregnancy, but it is effective at lowering 3rd trimester triglyceride levels in pregnancy for women with and without preeclampsia. As elevated triglycerides are associated with preeclampsia, these data represent possible further elucidation of aspirin's role in preeclampsia prevention.

Murine chorioamnionitis causes a dampened innate immune response that persists into infancy

Jessica Knobbe, Shikha Malik, Jennifer Bermick
University of Iowa

Introduction: Chorioamnionitis is inflammation and/or infection of the chorion, amnion, and placenta, and complicates up to 70% of preterm births. This early-life inflammatory exposure causes an initial fetal inflammatory response followed by a secondary hypo-responsive phenotype in neonatal monocytes. Chorioamnionitis increases the risk of many immune-mediated morbidities during the neonatal period, including both early- and late-onset sepsis, necrotizing enterocolitis and bronchopulmonary dysplasia. Chorioamnionitis is also associated with long-term immune-mediated morbidities, including wheezing and asthma.

Study Purpose: To understand the persistence of chorioamnionitis-induced immune hypo-responsiveness. We hypothesized that chorioamnionitis-exposed neonatal and infant mice would display dampened innate immune responses compared to controls.

Methods: Genetically homogenous C57Bl/6 mice were bred, and dams were injected intraperitoneally (IP) with 100μg/kg of lipopolysaccharide (LPS) or phosphate-buffered solution (PBS) on embryonic days 17-18. Pups were born naturally and euthanized at postnatal days 4-6 (neonate) or postnatal days 14-16 (infant). Splenic CD11b+ cells were isolated and used for cell culture. Cells were either unstimulated or stimulated with 100ng/mL LPS, 100μg/mL lipoteichoic acid (LTA), or 25μg/mL polyinosinic-polycytidylic acid (poly(I:C)) for 24 hours. Cell supernatants were analyzed using the Bio-Rad Bio-plex 200 system to quantify IL-1β, IL-6, IL-10, IL-12, KC, MCP-1, MIP-1α, and TNF-α.

Results: LPS-stimulated CD11b+ cells from chorioamnionitis-exposed infants displayed significantly lower concentrations of IL-6 ($p=.0465$) and MIP-1α ($p=0.008$) compared to control infants. LPS-stimulated CD11b+ cells from control mice displayed a significant increase in IL-6 ($p=0.0251$) and IL-1β ($p=0.0013$) from the neonatal to infancy period. This increase was not observed in LPS-stimulated CD11b+ cells from chorioamnionitis-exposed mice, whose levels of IL-6 ($p=0.6771$) and IL-1β ($p=0.0930$) at infancy were similar to that of the neonates.

Conclusions: Murine chorioamnionitis alters the developing neonatal immune system, resulting in a dampened innate immune response that persists into infancy. These persistent immune changes may be responsible for some of the immune-mediated morbidities seen in chorioamnionitis-exposed offspring, but additional studies are needed to understand this further.

Title: Flow cytometric analysis of peripheral regulatory T cell abundance in ferret tracheal graft transplants
Student name: Kelsey Kolasa
Mentor: Kalpaj R. Parekh, MBBS (Division of Cardiothoracic Surgery, Department of Surgery) and Thomas J. Lynch, PhD (Department of Surgery)

Background: A significant challenge limiting the success of tracheal transplants is the widespread use of non-specific immunosuppressive therapies to prevent graft rejection.[1] Malignancy is a common indication for tracheal transplant and current non-specific immunosuppressive therapies can be especially detrimental to this subset of patients.[1] Enhancing the activity of regulatory T cells (Tregs) while allowing for the development of targeted immunosuppressive therapies is a potential solution to this challenge that could be utilized in the context of other forms of solid organ transplant as well.[2] We have developed a translational ferret model to study tracheal transplants. Development of methods to identify ferret peripheral Tregs and the study of the physiologic baseline of Treg abundance is critical to the further investigation of Treg therapies utilizing this ferret model and other ferret models of transplant rejection.
Purpose: The primary aim of this project was to develop flow cytometric methods capable of identifying ferret peripheral Tregs and to use these methods to investigate the physiologic baseline of Treg abundances within the context of a ferret tracheal transplant model. It was hypothesized that peripheral Treg abundance decreases in ferrets receiving immunosuppression.
Methods: A flow cytometry panel was designed using the markers CD4, CD25, and Foxp3 to identify Tregs.[2] This panel additionally incorporated CD8a and CD79a. Confirmation of the ability to detect Tregs was established through the differentiation and expansion of Tregs from CD4+ ferret T cells and the completion of flow cytometric analysis. Treg expansion was accomplished with Immunocult™ Treg Differentiation Supplement, Immunocult™ Human CD3/CD28 T cell activator, and human recombinant IL-2 purchased from StemCell™ Technologies. Flow cytometric analysis was completed on peripheral blood mononuclear cell (PBMC) samples collected from ferrets receiving auto-tracheal or allo-tracheal transplants. Tracheal allografts were decellularized and reseeded with ferret small airway epithelial cells prior to transplant. Auto-tracheal transplant recipient peripheral blood samples were collected from ferrets receiving full or no immunosuppression prior to surgery and at approximately one week. Allo-tracheal transplant recipient peripheral blood samples were collected from immunosuppressed ferrets both prior to surgery and at 33 days. PBMCs were isolated from peripheral blood samples and cryostored prior to the completion of direct and intracellular staining for flow cytometry. Flow cytometric analysis was used to determine the percent of Tregs present relative to the total lymphocyte count due to variable total cell counts in initial samples. Paired t-tests and Welch's t-test were used to assess for significance.
Results: Flow cytometric analysis of CD4+ T cells expanded in the presence of Immunocult™ Treg Differentiation Supplement (StemCell™ Technologies) demonstrated reliable identification of peripheral Tregs, with 83% of CD4+ lymphocytes additionally detected as CD25+Foxp3+. Auto-tracheal transplant PBMCs demonstrated no significant difference in percent Tregs regardless of time point or immunosuppression status. At day 0, average percent Tregs for autotransplant samples with and without immunosuppression were 0.50% ± 0.32% and 2.73% ± 8.79%, respectively (95% CI). At day 7, average percent Tregs for autotransplant samples with and without immunosuppression were 1.87% ± 5.92% and 0.20% ± 0.39%, respectively. There was additionally no significant difference in allograft samples from ferrets receiving immunosuppression, with 0.76% ± 2.20% Tregs at day 0 and 0.13% ± 0.14% Tregs at day 33. Paired and Welch's t-tests failed to reach significance for each condition and timepoint previously described.
Discussion/Conclusion: Though results did not demonstrate a significant difference in percent Tregs, percent Tregs were observed to trend upwards over the course of a week in autotransplant ferrets receiving full immunosuppression and downwards in ferrets without immunosuppression. Percent Tregs trended downwards in allograft samples collected one month after surgery. Failure to demonstrate significance could be in part attributed to low sample size (n=3 for each condition) and variability of ferret conditions resulting from the use of archival PBMC samples. Repetition of this analysis with greater sample size and more time points would allow for the improved elucidation of ferret Treg population dynamics following transplant. Importantly, this project successfully developed flow cytometric methods capable of identifying ferret peripheral Tregs. The ability to identify and potentially isolate ferret Tregs will allow for future investigations into Treg therapies utilizing a ferret model.
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Morphometric analysis of Arhgap29-deficient murine excisional wounds

Student: Alexis Kollasch
Collaborator: Lindsey Rhea
Mentor: Martine Dunnwald, PharmD, PhD

Introduction: In humans as well as murine models, the healing of a cutaneous wound follows a predictable yet overlapping process of inflammation, epithelialization, angiogenesis, and dermal repair. Epithelialization is the process by which keratinocytes, the major cell type present in the epidermis, migrate toward and repair a wounded area of skin. Interferon Regulatory Factor 6 (IRF6) is a transcription factor required for *in vivo* wound healing in mice, where it mediates the proliferation and differentiation of keratinocytes during epithelialization. Mutations in the human *IRF6* gene cause the orofacial clefting disorder Van der Woude syndrome, and patients with this disease are at a higher risk for wound healing complications following their surgical cleft palate repair compared to individuals with a cleft and no *IRF6* mutations, indicating that IRF6 plays a key role in wound healing in human patients. IRF6 has been suggested to work in conjunction with RhoA, a protein which regulates the cytoskeleton and cell division, to regulate keratinocyte migration and proliferation. Particularly, the work of the Dunnwald lab has demonstrated that *IRF6*-deficient keratinocytes exhibit increased levels of active RhoA and decreased levels of Arhgap29, a positive regulator of RhoA. Recent preliminary work showed that Arhgap29 is also required for keratinocyte migration. However, nothing is currently known about a potential role for Arhgap29 in wound healing *in vivo*.

Purpose: The aims of this study are twofold: 1) to determine whether Arhgap29 is required for excisional wound healing, and 2) to evaluate the phenotypic characteristics of excisional wounds. We hypothesize that Arhgap29 in basal keratinocytes of the epidermis is required for proper wound healing.

Methods: To characterize the potential role of Arhgap29 in wound healing, the Dunnwald lab initiated *in vivo* studies using an excisional wound healing model in combination with unique *Arhgap29* alleles: one *Arhgap29* null allele (AN) and one *Arhgap29* floxed allele (FA) combined with a Cre-recombinase driven by the keratin 14 promoter allowing the deletion of Arhgap29 in basal keratinocytes only. Carefully chosen murine crosses allowed the study of four genotypes: A29 WT (two wild-type copies of *Arhgap29*); A29 Het (one wild-type allele of *Arhgap29* and one null allele of *Arhgap29*); A29 cKO (knockout of both copies of *Arhgap29* only in K14-positive cells); and cKO;Het (one null *Arhgap29* allele and K14-conditional knockout of one *Arhgap29* allele). Excisional wounds were performed on these animals and epidermal samples were excised at day 4 (corresponding to the peak of inflammation), day 7 (time point at which wounds under the current protocol are re-epithelialized), and day 11 (corresponding to the maturation of the granulation tissue) following injury. For my project, morphometric analysis (wound volume, epidermal volume, percentage of epithelialization) of day 11 wounds was performed. Paraffin-embedded wounds were serially sectioned, stained with hematoxylin and eosin, and visualized using a brightfield microscope with digital acquisition capabilities. Wounds were analyzed with Image J.

Results: While previous analysis of day 7 wounds revealed no difference in wound healing parameters among the four A29 genotypes, preliminary data from day 11 wounds suggests that A29 Het and cKO;Het animals exhibited smaller wounds (epidermal and wound surface area as well as epidermal and wound volume) compared to the wildtype and A29 cKO animals. All day 11 wounds were fully epithelialized.

Discussion: We were not surprised to find that the wounds from all A29 genotypes were fully epithelialized by day 11, which is a late time point in wound healing. By day 11, keratinocytes would have ample time to migrate, even if Arhgap29 had an effect on migration. Wound volume is highly influenced by the presence of collagen and the dynamic of myofibroblasts in the granulation tissue. Previous reports indicate that increased RhoA favored Collagen I deposition. Because reduction of Arhgap29 would lead to increased RhoA, it would be interesting to determine collagen deposition and the presence of myofibroblasts in these samples as a future direction of research. While we have analyzed the morphology of excisional wounds in Arhgap29-deficient mice at days 7 and 11 of wound healing, further study of the morphology of day 4 wounds is also necessary to gain a more complete understanding of how Arhgap29 deficiency affects all stages of wound healing.

Appropriateness of Type of Blood Culture Orders used to Diagnose CLABSI at UIHC

Student: Elias Kovoor

Mentor: Dr. Jorge Salinas

Contributors: Elias Kovoor, Dr. Jorge Salinas, Dr. Dan Diekema, Dr. Lori Scheeler, Dr. Taka Kobayashi

Background: Central Line Associated Blood Stream Infections (CLABSI) is a major public health problem. According to the CDC, CLABSI is defined as infection due to pathogen from a blood culture in a patient who had a central line at the time of infection or within 48 hours before development of infection. The infection cannot be related to any other infection the patient might have and must not have been present or incubating when the patient was admitted to the facility. CLABSI occurs in almost 80,000 patients per year in ICUs and the cost for treating patients with CLABSI ranges from $34,000 to $56,000 annually. In order to diagnose CLABSI, blood cultures from the catheter as well as peripheral line need to be obtained before initiating antibiotic treatment. We analyzed the trends of blood culture ordering at The University of Iowa Hospitals and Clinics in CLABSI suspected patients.

Methods: The University of Iowa Hospitals and Clinics is an academic institution with 811 hospital beds. We analyzed 4000 blood cultures taken from 1600 patient encounters between the time period Jan 1st 2020 to Dec 31st 2020. We initially began with a data set of 27000 blood cultures obtained from EPIC. We used the software SAS to restrict the data to cultures that met the inclusion criteria. To be included, patients had to be above the age of 18, cultures had to be taken within the first 24 hours of the first blood culture taken for each hospital admission, the patient had to have an active central line at the time of specimen collection. We then looked at the number of peripheral or central line blood cultures each patient had within the first 24 hours of collection in each admission. We defined 'appropriate' as having at least 1 central line and at least 1 peripheral blood culture. At least 2 peripheral could considered acceptable in certain septic cases. We defined 'inappropriate' as having only 2 central line or only 1 peripheral or only 1 central line culture as more would be necessary to properly diagnose CLABSI. According to IDSA criteria, 1 central line and 1 peripheral culture is necessary and according to CDC, 1 central line and 2 peripheral cultures are necessary to diagnose CLABSI.

Results: According to the IDSA guidelines, 25.03% of the orders met the requirements, and according to CDC guidelines, only 9.84% met the requirements. 67.34% of the orders were deemed 'acceptable' as some sepsis cases warrant the use of 2 peripheral cultures. Overall, 7.63% of orders were placed in the 'inappropriate' category as only 2 central line or 1 peripheral or 1 central line culture was ordered. This information was stratified by location, and of the various departments, SNICU, CVICU and Ward were the major units performing poorly with 13.21%, 12.34%, and 8.67% inappropriate order sets placed respectively out of 212, 154, and 150 separate patient encounters respectively in each unit.

Conclusion: Analysis of blood culture data allowed us to identify units at our institute that were underperforming in terms of ordering the necessary blood cultures to diagnose CLABSI. Improving the percent of blood cultures that meet the guidelines to diagnose CLABSI will help improve proper diagnosis of CLABSI which can reduce overprescribing antibiotics for prophylactic treatment.

The impact of strabismus on quality of life in adults

Madeline G. Kroeger, BA; Alina V. Dumitrescu, MD

Introduction

Strabismus is a condition where the eyes are not properly aligned and is estimated to affect 4% of adults. It can be caused by sensory imbalances, cranial nerve palsies, or conditions that affect extraocular muscle function or structure (thyroid eye disease, myasthenia, etc). It impacts patients' ability to make eye contact and creates a recognizable physical disability, and in many cases, causes visual impairment due to diplopia and decreased depth perception. Vision-related quality of life (VRQOL) questionnaires are one way to study the impact of strabismus on patients' daily lives. Since vision accounts for around 80% of humans' overall senses, measuring the impact of strabismus is essential to understand and recognize the physical and emotional challenges of those it affects. These challenges include both difficulties with daily tasks as well as with social relationships. Strabismus surgery can reduce these challenges by improving appearance and binocularity.

Purpose

To understand and evaluate the physical and emotional impact on quality of life in adults with strabismus.

Methods

The National Eye Institute's Visual Function Questionnaire-25 (NEI VFQ-25) was administered prospectively to adult patients with strabismus evaluated and treated at the Pediatric Ophthalmology and Adult Strabismus Clinic at the University of Iowa Hospitals and Clinics. The questionnaires were scored according to the NEI VFQ-25 Manual into 10 different subscales. The 10 subscales are difficulties with near and distance activities, limitations in social functioning, role limitations, dependency on others, mental symptoms, driving difficulties, limitations with peripheral and color vision, and ocular pain. The data from the questionnaires was used to evaluate the impact of strabismus on quality of life. The changes before and after strabismus surgery were also evaluated.

Results

28 adult patients with strabismus were enrolled in this study. 6 patients underwent surgery during the study period and were evaluated before and after their operation. All patients showed decreased scores in all subscales compared to a reference population without strabismus from Franke et al.[1] The lowest scoring questionnaire subscale, on average, was mental health. There was no significant correlation in questionnaire scores with age, sex, visual acuity, presence of diplopia, strabismus type, strabismus size, or duration of strabismus. Patients with long-standing strabismus (developed in childhood) had a better quality of life than those who acquired it in adulthood. For patients who underwent strabismus surgery (N=6), there was a significant improvement in questionnaire score post-operatively in the following subscales: near activities ($p=0.041$), social functioning ($p=0.045$), mental health ($p=0.0036$), and role difficulties ($p=0.012$). All other subscales either remained the same or increased slightly in average scores before and after surgery without reaching statistical significance. No patient showed a decrease in their pre-operative scores in any subscale.

Conclusions

Strabismus impacts patients in various ways, like hindering their ability to do daily tasks such as driving and walking and impacts their mental health and well-being. In this study, we showed the impact of strabismus on visual functioning and quality of life, as well as the positive impact of correcting strabismus surgically. Therefore, strabismus surgery should not be considered cosmetic, as it functions to restore normal appearance, binocularity, and improves multiple aspects of patient lives.

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[1] Franke GH (1999) Handbuch zum National Eye Institute Visual Function Questionnaire (NEI-VFQ) - ein psychodiagnostisches Verfahren zur Erfassung der Lebensqualität bei Sehbeeinträch- tigten. Eigendruck, Essen

A Survey Exploring Contributing Risk Factors for Pediatric Lawn Mower Injuries

Treyton Krupp, Priyanka Vakkalanka PhD, Charles Jennissen M.D

Introduction

Annually, over 9400 children are injured by lawn mowers with 5% resulting in amputations, making it the 3rd leading cause of pediatric amputations. Prior research has shown that children <5 years of age is the group most frequently and severely injured by riding lawn mowers, sometimes as passengers but more frequently as bystanders. Despite increased mower safety specifications and requirements, injury incidence rates have remained constant over the past 40 years. An American Academy of Pediatrics' policy statement concluded, "additional research regarding the circumstances and contributing factors of lawn mower-related injuries is needed, especially injuries involving mower instability or situations in which a person has been run over or backed over." We hypothesize that children who have riding lawn mower injuries as a bystander are more likely to have been given prior lawn mower rides, thus making young children more likely to approach them during their operation. Our study's aim was to investigate the circumstances surrounding pediatric riding lawn mower injuries to identify potential contributing risk factors and behaviors that lead to these events.

Methods

Followers and members of both a public and a private lawn mower injury support and prevention Facebook page with children who had suffered serious lawnmower-related injuries were invited to complete an electronic survey on Qualtrics, a cloud-based platform for creating and distributing web-based surveys. Multiple choice and open text questions addressed the circumstances, injuries, and behaviors before and at the time of the incident, including a history of prior recreational rides on lawn mowers or other vehicles. Data was cleaned including removal of duplicate cases and those involving push mowers. Frequencies and chi-squared analysis was completed with IBM SPSS Statistic Build 1.0.0.1327.

Results

A total of 152 surveys were used in the final analysis with ~70% completed by a parent of the injured child and ~20% by adult survivors of a childhood incident. About 70% of respondents were from the South or Midwest census regions. The majority of injured children were Caucasian (94%), male (62%) and ≤5 years of age at the time of the incident (82%). Bystanders were 69% of those injured, 24% were riders on the lawn mower, and mower operators and others were both ~4% each. Overall, bystanders were younger than other injured children with 88% vs. 69% being ≤5 years of age, respectively ($p=0.012$). The highest proportion of incidents occurred in May and June (~40%) and approximately half occurred between 1-5pm. The lawn mower operator was male in ~75% of the incidents with a father/step-father being the operator in half of the total. Overall, 60% of injuries occurred while traveling backwards, and 30% while moving forward. Three-quarters (76%) of bystander incidents occurred while moving in reverse as compared to 17% of non-bystander incidents ($p<.0001$). Overall, 90% had an amputation or permanent disability. Nearly all (95%) of injured bystanders had an amputation and/or permanent disability versus 78% of non-bystanders ($p<0.05$). Only 5% of bystander injuries occurred to the upper extremity as compared to 40% of non-bystanders ($p<0.01$). Over three-quarters of bystanders (77%) had received a ride on some type of work or recreational vehicle prior to their injury. One-half of bystander victims had received at least one ride on a lawn mower prior to their incident.

Discussion

This study examined the factors that may contribute to pediatric lawn mower injuries and the circumstances involved. One-half of bystander victims had been given rides on a riding lawn mower prior to their injury which is quite concerning and may have played a part in the occurrence of these incidents. However, this proportion is less than we expected. Some limitations to the study are that the survey may not reflect all pediatric lawn mower injuries as the survey population were followers and members of a Facebook interest page. Our results may help inform future lawn mower safety and injury prevention efforts.

Factors Influencing Complete Retinal Vascularization (Retinal Maturity) in Premature Infants who Meet the Screening Criteria for Retinopathy of Prematurity

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Mentor: Alina Dumitrescu, MD- Department of Ophthalmology and Visual Sciences
Other Collaborators: Scott Larson, MD, Margaret Strampe, MD- Department of Ophthalmology and Visual Sciences

Introduction: Premature infants (born before 30 weeks of gestation or less than 1500g) are at risk of developing Retinopathy of Prematurity (ROP). ROP is a disease that affects retinal blood vessel development and is a leading cause of childhood blindness both in the United States and worldwide. All infants at risk undergo frequent ocular examinations until they reach complete retinal vascularization (also called retinal maturity), which means retinal vasculature has reached the retinal periphery within a 1.5 disc diameter distance of the ora serata. While these exams are not harmful, they are stressful for both infants and parents. For infants born at term, retinal maturity is expected to be achieved at 40 +/-2 weeks of gestation.

The incidence of ROP has been increasing in the United States as more and younger premature infants survive. Additionally, anecdotal reports in the University of Iowa NICU and Ophthalmology Department suggest that the duration of persistent avascular peripheral retina (or the time to reach retinal maturation) has been increasing as well.

To date, numerous studies have identified factors that influence the incidence for development and progression of ROP. However, minimal research has reported the length of time needed to reach full retinal maturity in premature infants, with or without ROP, and the factors influencing this process.

Purpose: To determine the timing of reaching retinal maturity and the factors that influence this process in premature infants meeting the screening criteria for ROP.

Methods: A retrospective chart review of all patients examined for ROP at UIHC between December 13th, 2007 and December 27th, 2017 was conducted. Data extracted from patient charts included: demographics, gestational age and weight at birth, ROP details, age and weight at which full retinal maturity was reached, surgical procedures, ventilation >96 hours, antibiotic treatment ≥14 days, positive blood cultures, ≥5 RBC transfusions, and central line placement. Incomplete charts were excluded.

Results: 1600 charts were reviewed. Of these, 1077 charts were complete and able to be included in the analysis. The average age for retinal maturity was 44.63 weeks post conception. 69% of patients never developed ROP greater than stage 0, while 31% developed stage I to III ROP. 4% required laser treatment. The mean gestational age at maturity of the patients with stage 0 ROP was significantly lower than those with stage I to III ROP (43.3 versus 48.1 weeks, $p=7.3x10^{-22}$). Additionally, gestational age at maturity of patients with stage I ROP was significantly lower than those with stage II (45.9 versus 49.6 weeks, $p=2.9x10^{-7}$) as well as those infants who required laser treatment (45.9 versus 48.2 weeks, p=0.01). Infants with stage II ROP had the longest course to retinal maturity at 49.6 weeks.

The mean gestational age at birth for infants in the stage 0 group was significantly higher than those in stage I to III ROP group (29.1 versus 25.8 weeks, $p=6.3x10^{-77}$). No significant difference was noted in birth weight between the two groups. Worst stage of ROP was weakly positively correlated with gestational age at maturity ($r^2=0.31$), while gestational age at worst ROP exam was moderately positively correlated ($r^2= 0.69$).

Conclusions: In this retrospective study, we evaluated the time it takes to reach retinal maturity in premature infants who meet the screening criteria for ROP. The results of this study suggest that children who have ROP greater than stage 0 will reach retinal maturity at a later gestational age than those who don't. These results also suggest that those who develop the disease more severe than stage I, or requiring treatment, will reach retinal maturity the latest. These conclusions can help inform both providers and parents of the expected time to reach retinal maturity in premature infants.

Examining Long-Term Outcomes of High Tibial Osteotomies & Distal Femoral Osteotomies

Student: Jace Lapierre, M2
Mentors: Robert Westermann, MD & Kyle Duchman, MD

Background

Osteoarthritis (OA) affects over 32.5 million adults in the United States. Osteoarthritis occurs when the articular cartilage within the joint degenerates, usually progressing slowly over time.

Osteoarthritis of the medial knee compartment can be particularly difficult to treat, especially if patients may not be a suitable candidate for knee replacement based on a variety of factors. One non-arthroplasty option in patients with medial knee arthritis and varus alignment is the high tibial osteotomy (HTO). High tibial osteotomy is a surgical procedure designed to shift the load away from the degenerative medial knee articular cartilage in order to reduce the progression and symptoms associated with osteoarthritis. While several different methods exist for performing high tibial osteotomy, the medial wedge opening technique for correction of varus malformation is most consistently utilized. While less common, isolated lateral compartment osteoarthritis can cause pain and limited function in active individuals. Like the unloading effects of the high tibial osteotomy on the medial compartment cartilage, a distal femoral osteotomy (DFO) aims to shift the load away from the lateral knee compartment in cases of valgus deformity. Previous research has shown good long-term outcomes when considering survivorship following unloading osteotomies about the knee, with survival rates typically defined as the percentage of osteotomies not converted to knee arthroplasty over a given time.

Specific Aims of Study

1. To evaluate the long-term success of high tibial osteotomies, as well as distal femoral osteotomies, by measuring the rates of conversion to total knee arthroplasty.
2. To assess if the quality of correction is associated with outcomes.
3. Determine the number of subsequent surgeries performed following osteotomy and prior to (if performed) knee arthroplasty.

Methods

Potential subjects were identified via retrospective electronic medical review of patients who previously underwent a high tibial osteotomy or distal femoral osteotomy procedure at UIHC prior to July 1, 2011. The electronic medical record was then reviewed for listed contact information including email address, home address, and telephone numbers. Patients were contacted and asked to fill out the Knee Injury and Osteoarthritis Outcome Score for Joint Replacement (KOOS Jr.) survey, as well as a second survey asking them to list any additional procedures performed on that knee outside of UIHC, including total knee arthroplasty. For those patients who completed the surveys, the electronic medical record was then reviewed for any additional procedures performed at UIHC, including total knee arthroplasty. Categorical variables were assessed using chi squared tests, while continuous variables were assessed with Student's t-test with significance set to $p<0.05$.

Results

The initial case list generated a possible 164 candidates for recruitment. Of those, 11 were excluded due to the subject being deceased, undergoing an amputation, or the case being a secondary osteotomy procedure. Of the remaining 153 subjects, 43 responded to the surveys with a mean follow-up time of 11.524 years from surgical date to survey completion. 34 respondents had undergone a HTO vs. 9 a DFO. 24 of the respondents were female and 19 were male. The average interval KOOS Jr. score of these subjects was 71.896. 24 of the 43 subjects (55.814%) underwent an additional procedure, with the average being 1.083 additional procedures. 14 of the 43 subjects (32.558%) underwent a TKA, with a survivorship at 10-years of 67.442%. Survivorship for HTO specifically was 67.647% (11 out 34 underwent TKA), and for DFO specifically was 66.667% (3 out of 9 underwent TKA). In these 14 subjects, the average time from HTO/DFO to TKA was 7.781 years.

Discussion

The average interval KOOS Jr. score of the 43 participants was 71.896, which indicates above average subjective functioning of the subjects' knees (The interval score ranges from 0 to 100 where 0 represents total knee disability and 100 represents perfect knee health). The combined survivorship rate was 67.442%, HTO specific was 67.647% and DFO specific was 66.67%. A systematic review published in 2020 by Ollivier et. al, examined the long-term survival rates for HTO with the 10-year survival rates ranged from 64-97.6%, consistent with our 10-year survivorship being 67.647%, albeit at the lower end of the range. A systematic review published in 2012 by Saithna et. al, examined the long-term survival rates for DFO with the 10-year survival rates ranged from 64-82%, again consistent with our 10-year survivorship of 66.667%. The main limitation of the study was the poor follow-up, facilitated by the long-term follow-up nature of the study.

Seizure susceptibility, post-ictal breathing, and death in a mouse model of amyloidopathy.

Molly JE Larson, Ben L Kreitlow, and Gordon F Buchanan

Background

Epilepsy and Alzheimer's Disease (AD) are complex, multifactorial conditions that impact millions of people worldwide. AD is associated with increased seizure risk and thought to be due to amyloid-beta deposition. Epilepsy is associated with an increased risk of dementia and has been suggested to be an early indicator of AD (Romoli, et al., 2021). It is thought that amyloid-beta and synaptic hyperexcitability found in epilepsy create a pathological feedback loop that worsens both conditions (Romoli, et al., 2021). AD alone creates sleep disturbances and dysregulated breathing, which, when compounded with epilepsy, may increase the risk of sudden, unexpected death in epilepsy (SUDEP). In this study, we used APP/PS1 mice which express humanized genes for amyloid precursor protein and presenilin 1. These mice display progressive amyloidopathy and experience spontaneous seizures.

Hypothesis

We hypothesized that APP/PS1 mice will be more susceptible to amygdala kindled seizures, have worse post-seizure breathing outcomes, and increased mortality compared to wild-type (WT) littermates.

Method

APP/PS1 WT littermates (n=6) were instrumented with a bipolar amygdala depth electrode and an electroencephalography (EEG) and electromyography (EMG) headcap. After recovery, we determined the minimum current to induce an epileptiform discharge in the amygdala. Amygdala kindling was performed by using this minimum current to induce two seizures per day until fully kindled. Fully kindled animals display consistent generalized tonic-clonic seizure (GTCS) when exposed to the minimum threshold current. GTCS were induced while animals were either awake or in non-REM sleep with parallel video, EEG, EMG, and plethysmography recording. Unfortunately, transgenic APP/PS1 mice could not be subjected to wake and non-REM trials due to their high mortality, but were still instrumented for chronic EEG and EMG recording.

Results

There was a significant difference in the mortality between transgenic and WT mice (WT n=14, APP/PS1 n=15, $p<0.0001$). We expected most mice to survive up until 12-16 weeks based on previous publications. Instead, many transgenic mice began dying suddenly around 8 weeks. We did not see any difference between the after-discharge threshold of the two groups. There was a non-significant trend in the number of stimulations it took for the mice to be fully kindled, with the APP/PS1 requiring fewer stimulations (WT n=6, APP/PS1 n=4, $p=0.0515$).

Discussion

Work is still ongoing on this project. Several APP/PS1 mice are still being chronically recorded. We plan in the future to implement earlier instrumentation and video recording, ahead of the sudden deaths, to better characterize the seizure and death phenotype timeline. We also plan to characterize the breathing of APP/PS1 animals over time and analyze the sleep architecture of both transgenic and WT littermates.

Return to Sport and Testing following Hip Arthroscopy For FAI in High School and Collegiate Athletes

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Mentor:
Robert W. Westermann, MD

Abstract

Background: Femoroacetabular impingement (FAI) is a known cause of hip pain and dysfunction in young, active patients and can be successfully managed with hip preservation surgery. For athletes with FAI, however, there is inconsistent data regarding the ability to return to competitive sport after surgery and how performance level is impacted.

Purpose: To evaluate patient factors contributing to return to sport after hip preservation surgery.

Study Design: Retrospective cohort

Methods: We retrospectively reviewed patients aged 14 to 44 who underwent hip preservation surgery between December 2018 and May 2021 and who participated in a competitive or recreational sport pre-operatively. All patients underwent formal return-to-sport (RTS) t esting between 4 and 6 months after surgery. Patient-reported outcomes (PROs) w ere obtained at initial RTS testing using the International Knee (Hip) D ocumentation Committee (IKDC) questionnaire, Hip Outcome Score – Sports Specific Subscale (HOS-SSS), a nd Hip Return to Sport After Injury (Hip-RSI) s cale. Regression analysis was performed to evaluate the relationship between RTS tests, PRO's, BMI, pre- and post-operative alpha angles, and degree of correction. Degree of correction was the difference between pre- and post-operative alpha angles measured on Dunn view hip x-rays.

Results: We identified 40 patients, 47 operative hips (34 females, 85%). T hree patients (4 hips) were excluded for incomplete testing data. Mean age was 17.73 ± 2.7 years. All patients underwent hip arthroscopy for FAI including one case of single-stage bilateral hip arthroscopy. The most common primary sports were dance (7), s oftball (6), and basketball (5). M ean alpha angles were 67.15 ± 10.9° pre-operatively and 41.37 ± 4.5° post-operatively. Average time from surgery to first RTS testing was 26.79 ± 6.5 weeks (median 25.1 weeks). Mean HOS-SSS score at initial testing was 85.98 ± 11. Posteromedial (PM) and posterolateral (PL) re ach on Y-balance test were significantly associated with HOS-SSS score at initial testing (PM: $r=0.54$, $p<0.001$; PL: 0.53, $p<0.01$). Com posite Y-balance score was also significantly associated with HOS-SSS score ($r=0.6$, $p<0.01$). A ll other comparisons between PROs and RTS tests were not significantly associated. Similarly, there were no significant associations between time to initial RTS testing and BMI, pre-operative alpha angle, or degree of correction.

Conclusion: Higher Y-balance scores at initial RTS testing are associated with improved PROs and perceived readiness to return to sport. This test can be easily incorporated into an assessment for safe return after FAI surgery; further prospective studies are warranted.

Peripheral Trigeminal Nerve Blocks for Chronic Orbital Pain: Clinical Features and Outcomes

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Background: Chronic orbital pain in the absence of orbital inflammation or other active disease process is debilitating for patients and is often difficult to treat. While peripheral nerve blocks have been used to treat diverse clinical conditions, therapeutic responses to peripheral trigeminal nerve blocks in patients who have chronic orbital pain of undetermined etiology or despite resolution of the underlying etiology of pain deserve special attention. It is currently unknown to what extent neural blockade of peripheral trigeminal afferents can modulate orbital pain, regardless of its underlying neuropathic process. A thorough characterization of the relationship between pain subgroups and treatment outcomes may provide insights into chronic orbital pain and approaches to restore quality of life in affected patients.

Purpose: To characterize chronic orbital pain in patients who benefitted from peripheral trigeminal nerve blocks and to explore the relationship between pain etiologies and phenotypes, injection attributes, and positive response to treatment.

Methods*:* In this IRB-approved single-center retrospective descriptive study, patients who underwent peripheral trigeminal nerve blocks for chronic orbital pain from November 2016 to May 2021 were selected. Data reviewed included inciting factors, neuropathic symptoms of orbital pain, injection composition (anesthetic alone versus anesthetic + dexamethasone), and corneal epitheliopathy grades. Primary outcomes assessed were response to injection, duration of injection effectiveness, and overall treatment efficacy. Associations between subgroups of chronic orbital pain, injection attributes, and treatment outcomes were examined.

Results*:* Nineteen patients who underwent a total of 94 peripheral trigeminal nerve blocks for chronic orbital pain were included. During a mean follow-up period of 2.4 years after initial injection (range 7 days – 4.6 years), 16 (84.2%) patients achieved either partial or complete improvement. Ocular versus non-ocular origin of orbital pain or the presence of neuropathic sensory characteristics was not associated with a treatment outcome. Injections containing dexamethasone had a lower positive efficacy (relative risk 0.88, 95% CI 0.81 – 0.97) and no statistically significant association with prolonged effect. Twenty-nine (50.9%) of the 57 injections for which effect duration was recorded produced a response lasting greater than 6 weeks.

Conclusion: Modulation of trigeminal afferent nerve activity with peripheral trigeminal nerve blocks containing anesthetic with or without dexamethasone may be a promising treatment strategy for chronic orbital pain of diverse etiologies and phenotypes.

Hospitalization in persons with dementia receiving care coordination

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Background: Dementia care management interventions improve outcomes for persons with dementia (PWD). However, most interventions have not reduced hospitalization, a common and costly outcome in dementia. The aim of this study was to identify primary reasons for hospitalization, as reported by family caregivers, for PWD in two care coordination studies.
Methods: This pooled analysis included 646 PWD who participated in a randomized controlled trial or CMS Health Care Innovation Award project evaluating a dementia care coordination intervention (MIND at Home). These two projects occurred simultaneously in Maryland between 2015 and 2019 and used nearly identical assessment methods. Serious adverse events (SAE), including hospitalization and events leading to it, were recorded in detail by trained research staff during the intervention using caregiver report at the time of the event or planned data collection intervals. In this study, one person (YL) coded the reason for first hospitalization for each PWD hospitalized based on SAE forms. 49 unique reasons were consolidated into 15 categories based on prior literature, clinical reasoning, and emerging data. A second rater coded randomly selected 10% of the events for reliability (HA).
Results: Among 646 PWD participating in the MIND at Home studies, 282 (44%) had at least one recorded hospitalization over an 18-month period. The most common reasons for first hospitalization were falls (19.5% of hospitalizations), infections (19.1%), and neuropsychiatric symptoms (worsening behavioral symptoms and delirium) (10.3%). Other common reasons for hospitalization were GI (9.9%), dehydration/syncope (7.1%), and cardiovascular (5.7%). Causes that occurred less than 5% of the time included surgery, pulmonary, deep vein thrombosis/pulmonary embolism, pain, acute functional decline, and renal. Interrater reliability was strong (kappa statistic 0.89 95% CI [0.78, 1.00]).
Conclusions: Potentially preventable causes (falls, infections, and neuropsychiatric symptoms) were the three most commonly reported reasons for a hospital admission among this sample of community-residing PWD. Evidence-based interventions and care management approaches that target these specific areas and prevent or proactively manage these common complications of dementia may reduce costly hospital admissions.

Early pregnancy urine copeptin as an early pregnancy predictor of preeclampsia

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Background: Preeclampsia (PreE) is a hypertensive disorder affecting 5-7% of pregnancies worldwide. Early risk assessment for PreE in rural areas may assist providers in appropriate triage of care. Previously published data demonstrate that human maternal plasma copeptin, as a marker of arginine vasopressin (AVP) secretion, is elevated throughout gestation in pregnancies affected by PreE and is robustly predictive of the development of preeclampsia as early as the 6th week of gestation.

Objective: Our study aimed to determine if elevated maternal urine copeptin concentration in samples collected before 20 weeks gestation is associated with the later development of PreE.

Methods: In this nested case-control study, we measured maternal urine copeptin obtained between 10-20 weeks gestation using banked samples from the Iowa Maternal Fetal Tissue Bank (IRB#200910784) and the Iowa statewide AHA-sponsored PREDICTV Study (IRB#201503835). Clinical data was harmonized from both studies for a total of 49 PreE samples and 277 controls. Copeptin was quantified using a commercially available competitive colorimetric enzyme-linked immunoabsorbent assay (Phoenix Pharmaceuticals). Continuous variables were tested using T-test or Mann-Whitney U as appropriate. Categorical variables were tested using Chi square analysis. Logistic regression was performed to investigate the association of PreE and urine copeptin levels while controlling for confounding. Receiver operating characteristic (ROC) curves were constructed for regression diagnostics. Alpha was set at 0.05.

Results: Mean maternal urine copeptin less than 20 weeks gestation was significantly lower in women who developed PreE in comparison to non-preeclamptic controls (0.210 vs. 0.313 ng/mL, p=0.03). There was a significantly higher proportion of diabetics in the preeclamptic group (35% vs. 20%, p=0.04). Differences in race (p=0.687) and age (p=0.174) were not observed between cases and controls. After controlling for diabetes and chronic hypertension, urine copeptin < 20 weeks gestation remained significanty associated with the development of PreE (OR=0.06, 95% CI 0.007-0.6, p=0.018). Urine copeptin at less than 20 weeks is moderately predictive of the development of preE (ROC AUC=0.61, p=0.02, sensitivity 45% and specificity 80% at 0.2345 ng/mL cutoff).

Conclusion: Contrary to our original prediction, *low* urine copeptin concentration in the first 20 weeks of pregnancy is moderately predictive of the development of PreE. Copeptin is known to counteract the actions of AVP and plasma AVP is significantly elevated early in pregnancies affected by PreE. These low urine copeptin levels may represent a novel physiologic compensatory mechanism for the early pregnancy immunovascular action of AVP in PreE by allowing more bioavailable copeptin to stay in circulation. Current investigation is ongoing to determine the clinical application of a point-of-care, urine copeptin-based tool for the early prediction of preE. Novel mechanistic investigations will examine the counter-regulatory role of copeptin in circulation.

Characterizing the Effects of Diet Composition on Feeding Behavior and Energy Expenditure in Mice

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Background: One of the most paramount national public health crises in America is the persistent rise in the incidence and prevalence of obesity. Obesity, as defined by the WHO, is abnormal or excessive fat accumulation that presents a risk to one's health. Addressing the growing rate of obesity is vital as it can lead to worse overall mental and physical health while being directly associated with several major causes of death including cardiovascular disease, cancer, diabetes, and stroke. Currently in the United States, greater than 60% of adults are considered overweight or obese costing nearly $150 billion in healthcare spending. The cause of obesity is multifactorial including genetic, environmental, and behavioral components. Furthermore, the autonomic nervous system, specifically the sympathetic nervous system (SNS), plays a significant role in energy balance and body weight- increasing sympathetic activation leads to decreased food intake and increased energy expenditure. An unbalanced diet composition that is high in fat and sucrose is implicated as a leading behavioral factor increasing the risk of obesity in America. The Western diet is a common name for this diet. Earlier work has shown that high-fat diets can drive increasing portion size, increased appetite, and increased adiposity directly leading to obesity. In previous studies, Western diet fed mice ate larger quantities at faster rates while also eating more frequently when compared to standard diet fed mice.

Purpose: We sought to characterize how the composition of the diet can alter feeding behavior and energy expenditure, ultimately driven by changes in sympathetic activation. To investigate how high-fat and high-sucrose in the diet impacts feeding behavior and overall energy expenditure, we observed several metabolic changes in three diet groups of ad libitum fed mice: high-fat, high-carbohydrate (sucrose), and normal chow.

Methods: A total of 21 mice were divided into three ad libitum fed diet groups: high-fat, high-carbohydrate (sucrose), and normal chow. Each group was fed their respective diet for 7 weeks. Additionally, 21 mice were divided into the three diet groups and fed a restricted, isocaloric diet for 7 weeks as a comparative control. Changes in weight and percent body fat were recorded. At week 5, glucose tolerance and insulin tolerance tests were performed on all mice. At week 6, metabolic data, including 24-hour heat production and respiratory exchange ratio, were collected on each group using the CLAMS metabolic cage system. All mice were sacrificed at the conclusion of week 7 and several organs were collected for molecular analysis.

Results: We show that mice on an ad libitum high fat and high carbohydrate diet consume more kcal per day when compared to normal chow. Both a high fat and high carbohydrate diet significantly increased body weight and percent body fat when compared to normal chow over 7 weeks of feeding. A high fat diet significantly impairs glucose tolerance. Mice on a high fat diet had a lower 24-hour average heat production per body mass when compared to normal chow whereas high carbohydrate diet fed mice had an increased average 24-hour heat with increasing body mass. Preliminary molecular analyses show decreased sympathetic tone in mesenteric fat for mice on a high fat diet.

Discussion: The study indicates that high fat in the diet may decrease sympathetic activation and therefore lead to uncontrolled feeding with decreased energy expenditure and lipolysis. White adipose tissue is implicated as the location of the decreased SNS activity. Future work will continue to explore differential changes in SNS tone in additional organs including the visceral and subcutaneous white adipose tissue and the hypothalamus. We will also continue to analyze changes in endocannabinoid system activity in these organs.

Quantifying the Reverse Total Shoulder Arthroplasty Clinical Exam

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Collaborators: Maria Bozoghlian, MD, Joshua E. Johnson, PhD, Brendan M. Patterson, MD, MPH

Background: Reverse Shoulder Arthroplasty (RSA) is associated with a higher mid-term (6-month to 1-year) complication rate as compared to anatomic shoulder arthroplasty. Post-operative complications include instability, scapular notching, and functional limitations. Based on the expanding range of clinical indications for RSA from osteoarthritis to rotator cuff arthropathy, patients undergoing RSA often present with a range of soft tissue integrities. Prior modeling work has also identified that degree of soft-tissue stiffness and parameters such as implant placement can impact simulated post-RSA biomechanics. However, it is currently unclear what measures are the greatest contributors to patients' post-RSA function and which metrics should be prioritized for further detailed modeling and clinical investigations of patients' post-operative functional limitations that might impair their ability to conduct activities of daily living.

Purpose: The primary study objective was to assess the relationship of pre-operative rotator cuff quality (degree of fatty infiltration and atrophy, muscle area) with post-RSA quantitative functional outcome measures (active range of motion and strength), and subjective patient assessment of these measures.

Methods: A quantitative shoulder clinical assessment was performed on a single surgeon cohort of patients (n=13) at their six-month or one-year post-RSA clinic visit. Subjects underwent a strength and range-of-motion (ROM) multiplanar assessment. Subjects' soft tissue quality for the rotator cuff musculature (subscapularis, infraspinatus/teres minor, supraspinatus) was quantitatively assessed via calculation of muscle cross sectional area (CSA) by outlining muscle bellies on pre-operative CT scans. Percentage of muscle occupation and relative fat/muscle occupation ratios were calculated using standardized Hounsfield unit cutoffs for identification of tissue types. Qualitative imaging assessment was also conducted to grade degree of rotator cuff atrophy and degree of rotator cuff fatty infiltration using established Warner and Goutallier classification systems respectively. A chart review was also conducted for all patients to extract demographic information, surgical details (procedure indication, intraoperative confirmation of rotator cuff severity, implant type and size, stem and liner details, presence of augmentation and glenosphere lateralization offset) and medical history relative to conditions that might impair wound healing. Pre and post-operative patient reported outcome measures (PROs) were extracted for validated scales including the American Shoulder and Elbow Surgeons (ASES), Promis Pain Interference and Global Health-12 scores with composite mental health, physical health, general health and social activities T scores. Analyses included Pearson and Spearman correlations to investigate relationships between functional, imaging, and self-reported measures. Mann Whitney U analysis was used to assess differences in functional outcomes and PROS on the basis of surgical or demographic parameters.

Results: Pre-operative soft tissue measures are not closely associated with 6-month and 1-year post-RSA strength and ROM or PROs. Among the weak associations, the strongest observed relationships concerned the supraspinatus and fat/muscle occupation ratio measures. Greater supraspinatus CSA is weakly associated with greater ER strength ($r=0.607$). Greater supraspinatus fat % and fat/muscle occupation is weakly associated with greater ABD ROM ($r=0.579$). Greater supraspinatus fat/muscle occupation is also weakly associated with greater flexion ROM ($r=0.588$). Subscapularis and infraspinatus/teres minor soft tissue measures were not well associated with measured and reported functional outcome scores. Eleven of thirteen subjects underwent subscapularis repair. No strong relationship was observed between implant parameters including implant size alone or liner thickness, and measured functional limitations. Post-operative PRO measures are not well correlated with post-operative functional measures or pre-operative soft tissue condition. Greater improvements in PROs were not strongly associated with greater post-RSA function ($r=0.398$). Lower initial pre-operative PRO scores were also not associated with significantly greater change in PROs.

Conclusions: Subjects' post-RSA shoulder function was not limited by pain (pain reported for 1/169 trials). However, decreased function did not appear strongly associated with surgical implant parameters such as size and liner thickness. Lack of direct implant related impairment of post-RSA function suggests potential alternative mechanical or multivariate influence on post-RSA function. We were successfully able to implement a quantitative shoulder functional assessment protocol for strength (ABD, ER, IR) and range-of-motion (Flex, Ext, ABD, ADD, IR, ER, behind the back reach) into our high-volume outpatient orthopedic clinic (mean time: 10 mins). However, pre-operative rotator cuff tissue quality displayed a weak to no association with post-RSA quantitative functional outcome measures, including active ROM and strength, and subjective patient assessment of these measures. The observed lack of consistent, strong correlation of both post-operative PROs and change in pre to post-operative PROs to objectively measured post-RSA physical function raises the importance of further reexamination of collected self-reported measures for internal consistency. The lack of strong relationships in this small population is likely related to the heterogenous nature of the patient population with a range of soft tissue integrities and surgical details, which strengthens the need for future patient-specific RSA investigation. However, mild relationships identified in this study might help to guide starting parameters of interest for future modeling work including supraspinatus and fat/muscle occupation ratio, while negating the immediate need for labor-intensive complete cuff soft tissue modeling. The lack of observation of a negative impact of fat related measures on muscle strength was unexpected. It is possible that an inability to distinguish fibrotic tissue from health muscle on CT examination, may have confounded measured fat/muscle occupation ratios. This is especially important since degree of fatty infiltration and fibrosis may influence muscle distensibility and stiffness which can affect ROM. Future studies may benefit from further investigation distinguishing the degree of fibrosis from fatty or normal muscle quality and its influence on ROM and midterm post-RSA function to help improve understanding of key factors governing biomechanical function in post-RSA patients.

Exomic Analysis of a Pedigree with Primary Open-Angle Glaucoma

Shana Liu, Benjamin Roos, Dr. John Fingert

Background:
Glaucoma is a progressive optic neuropathy characterized by retinal ganglion cell degeneration and optic nerve damage. The most common form of glaucoma is primary open-angle glaucoma (POAG), approximately 5% of which is inherited as an autosomal dominant, single-gene disease. Mutations in myocilin, optineurin and TANK binding kinase 1 (*TBK1*) have been identified as direct causes of POAG. We have identified a three-member pedigree with POAG (GGA-1165) that tested negative for the known glaucoma-causing mutations.

Aims:
The primary aims of our study were to identify novel disease-causing mutations using a whole-exome sequencing approach (WES).

Methods:
We obtained whole-exome sequencing from members of pedigree GGA-1165 using SureSelect exon capture (Agilent) and the Novagene 6000 DNA sequencer (Illumina). The exome data were analyzed using a customized pipeline to filter sequences for adequate quality and coverage. Next, variants were selected from exome data that were 1) present in population databases at a frequency of <0.1% and 2) present in the exomes of all family members with glaucoma. We conducted a tiered analysis of these variants. First, variants in 127 known glaucoma risk factor genes were analyzed. Next, exome-wide analyses were conducted. Variants were evaluated for potential pathogenicity using mutation analysis algorithms (PolyPhen, SIFT, and Blosum62). Top candidate variants were confirmed by Sanger DNA sequencing. We attempted to confirm the pathogenicity of mutations in candidate genes by testing a second, independent cohort of patients and controls using a combination of mutation detection methods (high resolution melt analysis, TaqMan SNP assays, and Sanger DNA sequencing).

Results:
Exome sequencing produced good coverage with an average read depth of 56.51X. A total of 1553 DNA variants were detected overall. After filtering for frequency and co-inheritance with glaucoma, we identified 95 variants that are consistent with causing glaucoma in this family. One of these 95 variants, Arg387His, was detected in the transmembrane receptor gene *ANTXR1*, which is one of the 127 known glaucoma risk factor genes. The *ANTXR1* mutation is very rare, with a 0.0001 allele frequency in European Non-Finnish populations, and is moderately expressed in the optic nerve, optic nerve head, and the trabecular meshwork. The *ANTXR1* SNP is designated as “probably-damaging” by PolyPhen and “deleterious” by SIFT. We are testing an additional cohort of 186 unrelated POAG patients for *ANTXR1* mutations and the results of this work are pending.

Discussion:
We analyzed a three-member familial pedigree for a novel, disease-causing mutation with whole exome sequencing. Detected variants were assessed for their likely pathogenicity using several mutation evaluation algorithms as well as features of the candidate gene that would support its function in glaucoma pathogenesis (expression in ocular tissues, gene function, etc.). Our initial findings suggest that mutations in the *ANTXR1* gene may be involved in glaucoma pathogenesis. One limitation of this study is the small sample size and statistical power. Future research to extend and confirm these findings with studies of additional glaucoma patients and controls are underway.

Title: The Anterolateral Ligament of the Knee: An Updated Systematic Review of Anatomy, Biomechanics, and Clinical Outcomes

Connor P. Littlefield, B.A., John W. Belk, B.A., Darby A. Houck, B.A., Matthew J. Kraeutler, M.D., Robert F. LaPrade, M.D., Ph.D., Jorge Chahla, M.D., Ph.D., Eric C. McCarty, M.D.

Purpose

To perform an updated systematic review of the anatomy, biomechanics, and function of the anterolateral ligament (ALL) and the clinical outcomes of anterolateral ligament reconstruction (ALLR) when performed in conjunction with anterior cruciate ligament reconstruction (ACLR).

Methods

A systematic search of the literature was performed by searching PubMed, the Cochrane Library, and Embase with the search phrase anterolateral ligament for articles published from February 2017 to May 2020. Inclusion criteria included studies that evaluated the anatomy, function, or biomechanics of the ALL; surgical technique articles on ALLR; clinical articles reporting outcomes of ALLR; studies published in English; and full-text articles. Exclusion criteria included studies published before February 2017. A subjective synthesis was performed, where ranges were reported, and individual study data were presented in forest plots.

Results

Overall, 40 articles were included in this systematic review, with 11 articles describing ALL anatomy, 14 articles analyzing ALL function and biomechanics, 7 articles discussing the surgical technique of combined ACLR and ALLR (ACLR/ALLR), and 8 articles describing the clinical outcomes of ACLR/ALLR. The addition of ALLR in combination with ACLR (ACLR+) results in lower graft failure rates for ACLR/ALLR (0.0%-15.7%) when compared to isolated ACLR (I-ACLR) patients (7.4%-21.7%). Three of five studies using the Subjective IKDC score, two of five studies using the Lysholm score, and one of two studies using the Tegner score reported significantly better scores at latest follow-up among ACLR+ patients compared to I-ACLR ($p < 0.05$).

Conclusion

The ALL acts as a secondary stabilizer to the ACL and helps resist internal knee rotation and anterior tibial translation. Based on current literature, combined ACLR with ALLR may result in lower graft failure rates and improved patient-reported outcomes when compared to I-ACLR in patients with specific indications, though several studies have demonstrated equivalent outcomes between these two cohorts.

Title: Modeling the Effects of Two Eye Diseases on Choroidal Endothelial Cells *in vitro*
Presenter: Lola Lozano
Research Mentor: Robert Mullins, PhD
Collaborator: Budd Tucker, PhD and Tucker Lab

Background
Multiple eye diseases affect the endothelial cells of the choroid, the vascular network that supplies the outer third of the retina.

One such disease is Age-Related Macular Degeneration (AMD), the early stage of which is characterized by formation of lipid-like deposits known as drusen. Previous work[1] revealed cores at the center of drusen, composed of O-linked glycoproteins, and that abnormal endothelial cells in advanced AMD have altered cell surface glycans. Recent work (unpublished) from the Mullins lab found that *GALNT15*, which encodes an enzyme involved in O-linked glycosylation, is upregulated in choriocapillaris endothelial cells of patients with early AMD.

Another eye disease that affects endothelial cells is Von Hippel-Lindau (VHL) disease caused by mutations in the *VHL* gene. Loss of function of the VHL protein leads to upregulation of the Hypoxia Response Pathway in cells which increases glycolysis, cell migration and proliferation, as well as angiogenesis. VHL disease is an inherited cancer syndrome that causes various tumors to form in different organs. Hemangioblastomas are tumors made up of blood vessels and are commonly found in the central nervous system and retinas of patients with VHL disease. Retinal hemangioblastomas can cause vision loss by causing hemorrhage as well as retinal fibrosis, exudation, and even detachment[2].

Purpose
In order to identify the glycosylation targets of GALNT15 protein and to better understand the role it might play in drusen biogenesis in early AMD, we sought to optimize a protocol to knock-down *GALNT15*.

Similarly, we optimized a knock-down protocol for *VHL*. Since VHL disease is caused by dysfunction of the protein, we performed cell function assays after *VHL* knock-down in order to determine the pathological effects the disease might have on choroidal endothelial cells *in vitro*. We hypothesized that the *VHL* knock-down cells would exhibit both increased cell migration and tube formation due to upregulation of the Hypoxia Response Pathway.

Methods
We conducted all experiments in an immortalized cell line of choroidal endothelial cells (iCECs) previously generated in the lab[3]. Expression of the two genes of interest and their respective protein products in iCECs was first confirmed via RT-qPCR, ICC, and Western blot. Optimization of knock-down for each gene was performed by transfecting cells with siRNA molecules encapsulated in liposomes for 24, 48, 72, and 96 hours and determining level of knock-down via RT-qPCR. After protocol optimization, *VHL* knock-down was repeated for 24- and 48-hour transfections. In addition to confirming *VHL* knock-down via RT-qPCR, endothelial cell migration and ability to form tube-like structures when plated in a synthetic extracellular matrix were assessed in 48-hours post-transfection cells. All experiments included untreated cells and scrambled siRNA negative control cells and all cell conditions were run in duplicate.

Results
Relative to scrambled siRNA negative control treated cells (Mean Gene Expression: 1.00, Standard Deviation: 0.03), cells treated with *GALNT15* siRNA showed greatest gene knock-down at 96-hours post-transfection (Mean: 0.39, SD: 0.04).

Relative to scrambled siRNA negative control treated cells (Mean: 1.00, SD: 0.09) cells treated with *VHL* siRNA showed greatest gene knock-down at 24-hours post-transfection (Mean: 0.52, SD: 0.15). However, when siRNA knock-down was repeated for 24-hours (Mean: 0.43, SD: 0.06) and 48-hours (Mean: 0.29, SD: 0.04) post-transfection, the latter time showed greatest knock-down. Assays to assess changes in endothelial cell function *in vitro* were performed on the 48-hours post-transfection cells. Results were opposite to what we hypothesized; *VHL* knock-down cells showed decreased cell migration and tube formation.

Conclusion
After optimizing a protocol for *GALNT15* knock-down, future assays can now be performed to identify glycosylation targets of the GALNT15 protein (e.g., Western blots probed with lectins for O-linked glycoproteins).

Repeating *VHL* knock-down experiments under varying oxygen tensions might induce expression of the expected disease phenotype including increased cell migration and tube formation. Additionally, further work in the lab with induced pluripotent stem cells from patients with VHL disease will permit not only investigation into disease pathology but insight into genetic modifiers unique to individual patients that might predict the severity of their disease phenotype and serve as potential targets for therapy.

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Self-Reported Visual Functioning in Adults with Albinism

Angela Mahoney; Arlene Drack, Noel Estrada-Hernandez

Background: Albinism is a group of disorders characterized by hypopigmentation and central vision impairment sometimes as severe as legal blindness. The visual deficits are caused by maldevelopment of ocular structures and misrouting of optic nerve fibers to the visual cortex.[1] At a recent lecture to patients with a subtype of albinism, Hermansky-Pudlak Syndrome, adult audience members reported early onset of glaucoma and cataracts. The literature was reviewed to investigate if earlier onset of cataracts or glaucoma was part of the albinism disease process. The review revealed a gap in the literature as most ophthalmologic studies focus on children[2,3,4].

Purpose: To determine if adults with albinism develop age related ocular conditions at the same rate and timing as the general aging population, and to merge the distinct findings of the medical aspects of albinism such as poor vision and hypopigmented appearance, and the psychosocial outcomes by combining the two areas of analysis into one study. We hypothesize that adults with albinism have an earlier onset of age-related ocular conditions than adults without albinism and that living with the reduced vision and atypical appearance affect many aspects of daily living and self-perception throughout the lifespan.

Methods: University of Iowa Institutional Review Board (IRB) approved online Qualtrics survey (IRB 202005083).
Inclusion: Any person with albinism aged 18 years or older was eligible to participate.
Recruitment: Letter invitations for the survey were mailed to patients with albinism identified through a search of the patient database from the Department of Ophthalmology, University of Iowa Hospital and Clinics (UIHC). Survey invitations were also handed out to eligible patients in the ophthalmology clinic. Finally, survey invitations were posted to the Drack Research website, Vision of Children Foundation website, and the websites and social media for the Hermansky-Pudlak Syndrome Network Inc. and the National Organization for Albinism and Hypopigmentation.
Survey Questionnaire: A Qualtrics survey was designed with 120 questions pertaining to demographics, ocular and general health, visual function, and psychosocial data. The demographic data included age, gender, race/ethnicity, highest educational degree, and employment status. The ocular health data included visual acuity, eyeglass prescription, type of albinism, and presence as well as treatment of eye conditions such as cataracts, glaucoma, macular degeneration, nystagmus, and strabismus. Visual function data included mobility questions and the Visual Functioning Questionnaire. The general health data included presence of bleeding problems, lung or breathing problems, cancer, ADHD, and arthritis. Psychosocial data was collected through 5 questionnaires including the Adaptation to Disability Scale-Revised, Brief Resilience Scale, and Rosenberg Self-Esteem Scale. The 5 psychosocial questionnaires were located at the end of the survey, and the sequence of the 5 questionnaires was random for each participant.
Statistics: Descriptive statistics were used to summarize the data set. Binomial tests were used to compare the prevalence of ocular and general health problems to the prevalence of these conditions in the general public. Mann-Whitney nonparametric tests were used to compare psychosocial questionnaires scores between groups, for example between those who drive versus those who do not drive.

Results: 117 surveys were completed as of July 27, 2021. Average age of participants was 43.1 years (range 18 to 86 years). Types of albinism included oculocutaneous albinism (n=51), ocular albinism (n=18), and Hermansky-Pudlak Syndrome (n=44). Visual acuity ranged from better than or equal to 20/40 to worse than or equal to 20/400. Median visual acuity was between 20/125 and 20/200. Vision remained stable in 54% of participants and worsened in 29%. Average age of those who reported worsening vision was 48 years (range 22 to 81 years). Median age for participants with cataract surgery was 61.5 years compared to 67.7 years of age at first cataract surgery for the general population. Cataracts were more prevalent in our survey population in the 40-49 years ($p=0.0265$) and 50-54 years ($p=0.0040$) age ranges compared to these age ranges in the general public. Cataracts were also more prevalent in men with albinism than in men in the general population ($p=0.0032$). 67% of participants had a Bachelor's degree or higher, and 67% of participants below retirement age were employed. 33% of the survey population reported driving, however up to 68% of participants would be eligible to obtain a driver's license based on visual acuity requirements in the state of Iowa. Average scores of the psychosocial questionnaires were 3.5 for the Brief Resilience Scale, 23.6 for the Rosenberg Self-Esteem Scale, and 13.8 for the Fear of Negative Appearance Evaluation Scale. These scores indicate normal resilience, good self-esteem, and moderate fear of how others may perceive themselves based on their appearance. None of the scores correlated with whether respondents have a driver's license.

Conclusion: People with albinism are at a greater risk for developing cataracts. Our data suggests that albinism may not be a stable visual condition, and the vision of some people with albinism may begin to deteriorate earlier than expected for the normal aging population. The education, employment, resilience, and self-esteem data suggest that the participants in our survey are well-adjusted to their disability. The finding of good self-esteem is a particularly important because previous research has documented that individuals with albinism have low self-esteem stemming from both their physical appearance and visual disabilities[5]. Lastly, there appears to be a lack of awareness in the albinism community on the vision requirements for gaining a driver's license. Eligible albinism patients may be missing out on the opportunity to drive, which can be remedied by educational outreach.

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Sympathetic Nervous System Effects on End Organ Blood Flow and Vascular Resistance in the Eye

Smrithi Mani, BA, Randy Kardon, MD, PhD, Julie Nellis, RN, BSN, Tom Tedeschi BS

Introduction: In diseases such as glaucoma, ischemic optic neuropathy, diabetic retinopathy, and macular degeneration, there is evidence that drops in blood pressure during sleep negatively impacts end organ blood flow and causes vision loss. There are also bursts of sympathetic nervous system activity during sleep, that can be precipitated by hypotension, sleep apnea and restless leg syndrome. The effect of these bursts on end organ blood flow to vital organs and the eye has yet to be studied. While it is not possible to measure blood flow to the eye during sleep when the bursts occur, we can stimulate the sympathetic nerves in the awake state using cold water immersion and study blood flow to the eye.

Purpose: The purpose of our experiment was to characterize changes in blood flow and vascular resistance in the different vascular beds of the eye due to sympathetic nerve activation. In addition, our experiment also examined if the change in blood flow and resistance in the eye correlated to peripheral arterial tone of the finger which can be monitored during sleep non-invasively with a wearable device.

Methods: 10 control subjects over the age of 50 with no pre-existing eye condition were recruited for the study. Each subject was asked to submerge one foot in ice water for two minutes. The intraocular pressure (IOP) was measured in all subjects before immersion. In each subject the following measures were taken at 4 time points (baseline, during immersion, immediately after to two minutes post immersion, and ten minutes post immersion): blood flow in the three vascular beds of both eyes (optic nerve, retina, and choroid), heart rate, blood pressure, and peripheral arterial tone. Blood flow in the three vascular beds was measured non-invasively using the Laser Speckle Flowgraphy instrument (Softcare LTD). Heart rate and mean arterial blood pressure (MAP) were measured using a traditional ambulatory cuff. Peripheral arterial tone of the finger was measured non-invasively using a WatchPAT device (ITAMAR). Using IOP and MAP, the ocular perfusion pressure (OPP) was calculated for each subject at all four time points. The OPP was divided by blood flow to calculate vascular resistance in each vascular bed for all four time points. Repeated measures Analysis of Variance (AVOVA) was used to assess significant changes in recorded measures between baseline, ice water immersion, and post ice water immersion time points.

Results: In response to ice water immersion, there was a significant increase in vascular resistance in the vascular bed of the optic nerve head (median change=20% ; p=0.03), retina (median change=29% ; p=0.02), and choroid (median change=24% ; p=0.003). In addition, there was a significant reduction in finger pulse amplitude with ice water immersion (median reduction=38% ; p=0.03), which is considered a measure of finger arteriolar constriction. Measures were significant for both right and left eyes and right and left fingers.

Conclusion: Ice water immersion produced significant vasoconstriction in normal subjects as evidenced by increased vascular resistance in the ocular vascular beds in the optic nerve head, retina and choroid, (measured by Laser Speckle Flowgraphy) and in the finger (measured by WatchPAT). Sympathetic nerve activation may represent a significant risk factor associated with end-organ ischemia, especially during sleep, which can result in vision loss and dysfunction in other vital organs such as the brain and heart.

SEQUENTIAL INTRAVESICAL GEMCITABINE AND DOCETAXEL FOR BCG-NAÏVE HIGH-RISK NON-MUSCLE INVASIVE BLADDER CANCER

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Introduction (113/150):

Bacillus Calmette-Guerin (BCG) is currently recommended as adjuvant therapy following complete transurethral resection of bladder tumor (TURBT) for high-risk non-muscle invasive bladder cancer (NMIBC). Unfortunately, continued BCG production shortages have precluded the use of BCG in many urologic practices. Efficacy of sequential intravesical gemcitabine and docetaxel (Gem/Doce) for BCG-failure was established in 2015, and has subsequently been reproduced across multiple institutions. In response to the continuing BCG shortage, Gem/Doce has also been utilized in the BCG-naïve setting, although robust data supporting this practice is lacking. Our institution has transitioned to utilization of first-line Gem/Doce and thus, herein, we report outcomes of a large cohort of patients with high-risk BCG-naïve NMIBC treated with Gem/Doce.

Methods (123/150):

We retrospectively identified all patients with BCG-naïve high-risk NMIBC who were treated with Gem/Doce between May 2013 and April 2021. We included patients with intent to receive 6 weekly intravesical instillations of sequential 1 gram gemcitabine and 37.5mg docetaxel after complete TURBT. Monthly maintenance for 2 years was initiated whenever possible if disease free at first follow-up. The primary outcome was recurrence-free survival (RFS) and efficacy was evaluated in an intention-to-treat manner. Recurrence was defined as pathologically proven tumor relapse in the bladder or prostatic urethra. Progression was defined as T-stage increase from Ta or CIS to T1, or development of muscle invasive or metastatic disease. Survival was assessed using the Kaplan-Meier method and log rank test, calculated from start of Gem/Doce induction.

Results (147/150):

The final cohort included 107 patients and median follow-up for survival was 15 months. The cohort had high-risk characteristics including 44% of patients harboring CIS, 51% with T1 disease, and 7% with micropapillary variant histology (Table 1). There were 19 (18%) patients with recurrence during follow-up. RFS was 89%, 85%, and 82% and high grade-RFS was 91%, 87%, and 84% at 6, 12, and 24 months, respectively (Figure 1). RFS was similar for patients with or without CIS (p=0.42). Over the duration of follow-up there were no progression events. One patient underwent cystectomy due to end-stage lower urinary tract symptoms, with final pathology pTisN0. No patients died of bladder cancer. Overall survival was 84% at 24 months. The most commonly reported side effects were urinary frequency/urgency (36%), hematuria (11%), and dysuria (8%). Induction was stopped in 3 patients due to hematuria and 1 patient due to frequency/nocturia.

Conclusions (74/150):

We found that use of Gem/Doce in a large cohort of patients with high-risk, BCG-naïve NMIBC resulted in 84% 2-year high-grade RFS, which is comparable to efficacy demonstrated in modern BCG cohorts. There were no progression events during the duration of this study and there was an excellent tolerability profile. In the setting of BCG shortage, these results support an alternative first-line treatment for newly diagnosed high-risk NMIBC, for which prospective evaluation is underway.

Title

The Acquired Long QT-Prolonging Drugs Haloperidol and Terfenadine Cause Defects in HERG Trafficking

Authors

Abagail McKernan, BS; Haider Mehdi, PhD; Alexander Greiner, BA; Jin-Young Yoon, PhD; Diana Colgan, PhD; Jason Dierdorff, BS; Barry London, MD PhD

Background

Mutations in $K_v11.1$ (HERG) cause inherited long QT syndrome (LQTS) type 2 by disrupting channel function or membrane trafficking. Acquired LQTS is caused by drug binding to HERG and directly blocking the channel pore, reducing I_{Kr} and prolonging QTc in persons with decreased repolarization reserve. Alternatively, these drugs could bind to HERG and interfere with trafficking, reducing the number of HERG channels at the membrane.

Objective

We sought to understand the effects of known acquired LQTS-causing drugs from various classes (terfenadine, haloperidol, ondansetron, fluconazole, azithromycin) on HERG trafficking.

Methods

HEK293 cells stably expressing HERG (HERG-HEK293) were cultured in varying concentrations of selected drugs for 24 hours. Differences in trafficking were identified by immunoblot using the terminally-glycosylated HERG at 155 kD and the immature core-glycosylated HERG at 135 kD. Both the mutant HERG-G601S and HERG-HEK293 cells treated for 24 hours with arsenic trioxide (As_2O_3) served as trafficking-deficient controls.

Results

HERG-HEK293 cells treated with haloperidol ($\geq$50 μM) demonstrated a decrease in the size of the terminally glycosylated band, appearing at 140-145 kD in comparison to the fully glycosylated 155 kD (Fig. 1A). HERG-HEK293 cells treated with terfenadine ($\geq$15 μM) demonstrated a deficiency in terminal glycosylation (Fig. 1B). Ondansetron, fluconazole, and azithromycin treatments at 1, 10, and 100 μM demonstrated no effect on the fully glycosylated band.

Conclusions

These data suggest terfenadine and haloperidol interfere with HERG trafficking, resulting in less mature HERG at the membrane. Together, these data provide insight into a non-pore blocking mechanism that may underlie some cases of acquired LQTS.

Title: The Role of Pharmacological Ascorbate in Selective Peroxide-Induced Glioblastoma Cell Killing

University of Iowa Carver College of Medicine
Department of Free Radical and Radiation Biology
Student: Zain Mehdi, M2
Mentor: Bryan G. Allen MD, PhD

Introduction:

One of the most detrimental, yet widespread, diseases humans face is cancer. While cancers range in their virulence, an especially aggressive and debilitating cancer is glioblastoma (GBM). Comprising of over 50% of all central nervous system tumors and resulting in more than 15,000 deaths in the U.S. each year, median GBM overall survival (OS) is 15 months despite current treatments of maximum safe surgical resection, radiation therapy (RT), and chemotherapy with temozolomide (TMZ). With poor survival and encumbering side effects, novel treatment options are being considered for GBM. Specifically, high dose vitamin C (pharmacological ascorbate or P-$AscH^-$ has shown selective cytotoxicity towards cancer cells with minimal toxic effect on normal cells when given intravenously (IV). The Allen lab is exploring the mechanism of action of P-$AscH^-$ and conducting clinical trials to further understand this potential adjuvant treatment option for GBM as well as other cancer types. Based on current literature and data collection, we hypothesized that P-$AscH^-$ selectively radiosensitizes GBM cancer cells via an H_2O_2-mediated mechanism that is also dependent on physiological differences in redox chemistry between neoplastic and normal tissues.

We conducted pre-clinical research assessing clonogenic cell survival as well as DNA damage induced by P-$AscH^-$ in both GBM cells and normal human astrocytes (NHA), while evaluating the roles of H_2O_2 and redox active metals in the hypothesized mechanism of action. Catalase induction/treatment was utilized as an evaluation of the role of H_2O_2 for cytotoxicity, while metal chelators were used to evaluate the role of labile iron. The results demonstrated that P-$AscH^-$ cytotoxicity is H_2O_2-mediated and dependent on redox active iron, which also was increased in GBM cells compared to NHA cells. DNA damage analysis via H2AX flow cytometry exemplified the radiosensitizing role P-$AscH^-$ has when combined with radiation therapy. Orthotopic xenograft models of P-$AscH^-$ treatment in combination with standard-of-care therapy (temozolomide and radiation therapy) showed a synergistic effect that reduced tumor growth and improved survival.

Future experiments will further evaluate the mechanism of P-$AscH^-$ cytotoxicity in cancer, but this data supports the presented mechanistic hypothesis and supports the role of P-$AscH^-$ as a radiosensitizer. This research is an innovative route to improving treatment of GBM because of the non-toxic nature of P-$AscH^-$ that may also alleviate side effects from chemoradiation therapy in not only GBM but other difficult-to-treat cancers.

ABSTRACT-Prediction Models for Severe Manifestations and Mortality due to COVID-19: A Rapid Systematic Review

Student: Jamie Miller

Mentor: Sangil Lee

Background

Throughout 2020, the coronavirus disease 2019 (COVID-19) has become a threat to public health on national and global level. There has been an immediate need for research to understand the clinical signs and symptoms of COVID-19 that can help predict deterioration including mechanical ventilation, organ support, and death. Studies thus far have addressed the epidemiology of the disease, common presentations, and susceptibility to acquisition and transmission of the virus; however, an accurate prognostic model for severe manifestations of COVID-19 is still needed because of the limited healthcare resources available.

Objective

This systematic review aims to evaluate published reports of prediction models for severe illnesses caused COVID-19.

Methods

Searches were developed by the primary author and a medical librarian using an iterative process of gathering and evaluating terms. Comprehensive strategies, including both index and keyword methods, were devised for PubMed and EMBASE. The data of confirmed COVID-19 patients from randomized control studies, cohort studies, and case-control studies published between January 2020 and May 2021were retrieved. Studies were independently assessed for risk of bias and applicability using the Prediction Model Risk Of Bias Assessment Tool (PROBAST). We collected study type, setting, sample size, type of validation, and outcome including intubation, ventilation, any other type of organ support, or death. The combination of the prediction model, scoring system, performance of predictive models, and geographic locations were summarized.

Results

A primary review found 445 articles relevant based on title and abstract. After further review, 366 were excluded based on the defined inclusion and exclusion criteria. Seventy-nine articles were included in the qualitative analysis. Inter observer agreement on inclusion 0.84 (95%CI 0.78 - 0.89).When the PROBAST tool was applied, 70 of the 79 articles were identified to have high or unclear risk of bias, or high or unclear concern for applicability. Nine studies reported prediction models that were rated as low risk of bias and low concerns for applicability.

Conclusion

Several prognostic models are reported in the literature, but many of them had concerning risks of biases and applicability. For most of the studies, caution is needed before use, as many of them will require external validation before dissemination. However, nine articles were found to have low risk of bias and low concern for applicability, so these can be useful tools to prognosticate the COVID-10 patients.

A comparison of GIS-based measures on spatial accessibility to obstetricians and associations with adequate prenatal care utilization in Pennsylvania birth records from 2011-2015

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Abstract

Objective: To evaluate spatial accessibility to obstetricians using three separate measures and its association with the adequacy of prenatal care utilization

Methods: We used live births ≥20 weeks gestation (676,795 pregnancies) in Pennsylvania birth records (2011-2015). We measured spatial accessibility using three methods: distance to the nearest obstetrician, obstetrician count within a 15km radius, and the obstetrician-to-mom ratio within a 15km radius. We used Kotelchuck's Adequacy of Prenatal Care Utilization for dichotomous adequacy classification. We used restricted cubic splines to model nonlinear relationships. Multivariate models were used to calculate adjusted odds and odds ratios with 95% confidence intervals.

Results: Spatial accessibility measures had low to moderate correlations (0.24-0.57). Nonlinear associations varied for each spatial accessibility measure and the adjusted predicted odds of adequate prenatal care utilization. Patterns of predicted odds were left-skewed with distance, right-skewed with obstetrician count, and j-shaped for obstetrician-to-mom count. An obstetrician-to-mom count of 113 per 1,000 moms was associated with the highest odds of adequate prenatal care of 0.99 (0.99, 0.99). The maximum obstetrician count of 484 in a 15-km radius was associated with the lowest odds of adequate prenatal care utilization (0.60 (0.60, 0.61)).

Conclusions: Associations between spatial accessibility to obstetricians and prenatal care adequacy changed based on the measure used. Adequate prenatal care utilization was highest in areas with larger obstetrician numbers per moms. Increasing obstetrician count alone did not significantly improve prenatal care utilization. Shorter driving distances significantly increased prenatal care adequacy odds but a decrease in odds at the shortest distances signifies a complex relationship.

Screening for Carcinoid Heart Disease: Future Perspectives

Bryan Mouser; Olivia Atari; James Howe, MD; Thomas O'Dorisio, MD; Kalpaj Parekh, MD; Mohammad Bashir, MD

Background and Purpose

In 2017, definitive guidelines were published for surveillance of Carcinoid Heart Disease (CHD). CHD develops in over half of patients with neuroendocrine tumors (NETs) due to vasoactive substances released into the bloodstream, frequently resulting in right-sided valvular disease. Patients with CHD often require treatment from cardiac surgery to replace diseased heart valves, and those with undiagnosed and untreated CHD can develop heart failure. The purpose of this retrospective study is to evaluate screening trends for CHD in NET patients, referral patterns to cardiology and cardiac surgery, and how guidelines might impact future practice patterns.

Methods

Charts of 300 randomly selected NET patients referred to our center from 1998 to 2018 were reviewed for the presence of CHD screening criteria outlined by expert guidelines: (1) Midgut tumor with presence of liver metastasis, (2) Serotonin level greater than 5 times the upper level of normal (>1000 ng/mL), (3) NT-ProBNP level > 260 ng/ml, or (4) clinical features suggestive of CHD (edema, chest pain, shortness of breath, ascites). Charts were also reviewed to evaluate if patients received echocardiograms, referrals to cardiology or cardiac surgery, and medical or surgical treatments.

Results

After review, 86% of patients (258/300) met one or more criteria for CHD screening described by guidelines. 108 patients received an echocardiogram, 103 of which met one or more criteria for cardiac screening. Only 41.9% of patients (103/258) suggested for CHD evaluation by guidelines received an echocardiogram. Patients that met a greater number of CHD screening criteria received echocardiograms more frequently (Table 1). A total of 35 patients were referred to cardiology or cardiothoracic surgery; 25 patients were referred to cardiology only (all met one or more criteria, average 2.76 criteria), 9 patients were referred to both cardiology and cardiothoracic surgery (all met two or more criteria, average 3.0 criteria), and 1 patient was referred to only cardiothoracic surgery. One documented abnormal echocardiogram was found in 52.9% of patients referred to cardiology (18/34). Surgical treatment was performed in 70% of those referred to cardiothoracic surgery (7/10).

Conclusion

CHD has been significantly under-screened in neuroendocrine patients over the past decades. While development of standard guidelines is a step in the right direction, larger multi-institutional studies with dedicated screening according to guidelines and long-term follow-up will help assess the true risk-benefit ratio of screening for CHD.

Title: Characterizing nipple skin injuries in postpartum women
Presenter: Ananya Munjal MS
Mentor: Jennifer Powers MD
Collaborators: Stephanie Radke MD MPH, Chaorong Wu PhD

Background
Postpartum hormonal deviations can lead to changes in nipple skin that can be painful and irritating. Oftentimes these skin conditions remain undiagnosed and under-treated and can cause women to abandon breastfeeding due to pain or irritation. Atopic dermatitis is especially prevalent and is the cause of about half of all breast and nipple dermatitis that occurs during breastfeeding. Prior research has characterized some of the changes to nipple skin and classification of nipple trauma in response to breastfeeding, but no study has looked at the specific dermatological conditions in postpartum women with skin of color and a variety of skin types and tracked these changes over an extended period. There is also little photographic or survey-based evidence of which specific nipple skin injuries are prevalent in this population of women.

Purpose/Hypothesis
This study aimed to characterize the specific nipple skin injuries in postpartum women and had several hypotheses. We hypothesized that incidences of postpartum nipple skin disease are underreported in clinic-based studies and that there has been an underreporting of the specific entities of dermatitis, infection, and wounds. We wanted to identify both short and long-term themes in nipple skin injury in postpartum women and establish a resource database characterizing these injuries across varied skin types. We hypothesized that women are under-utilizing healthcare resources and healthcare providers to treat their lactation skin injuries, and that there is an especially low utilization of dermatologic expertise to treat. We also wanted to evaluate factors contributing to nipple skin injury and suggest accessible therapeutic treatments that are available to women in this population.

Methods
An anonymous 24 question survey was distributed virtually through a variety of different Facebook groups for new and expecting mothers. This survey included multiple choice questions and free response prompts. Photos of current nipple injuries secondary to lactation were also gathered from these women. All surveys and photos were collected securely through RedCap. This data was then analyzed to objectively categorize nipple injuries using criteria from clinical guidelines established by the American Academy of Dermatology.

Results
A total of 391 postpartum women were included in this study. Our analyses thus far have shown that the incidence of nipple skin injury was significantly greater in women over 35 (39.85%) as compared to women 34 and under (23.81%, P=0.0038). Additionally, nipple skin injuries are common in women breastfeeding in the first six months (28.97%), decrease from six to twelve months (21.33%), and then drastically increase in mothers breastfeeding over one year (38.66%, P=0.0342). Qualitative data demonstrated that the biggest skin-related concerns of breastfeeding women were pain (55%), appearance (34%), and breastfeeding ability (16%). Additional analysis is pending.

Conclusions
Our results demonstrate significant age-related impact of breastfeeding on nipple skin of older mothers. They also show how long nipple skin injuries can persist, with almost two out of every five mothers who breastfeed for longer than one year experiencing nipple skin injury. These results also depict the concerns of currently lactating mothers, shedding light on the discomfort that breastfeeding can cause. This information can be utilized clinically to better predict which women are likely to experience nipple skin injury, educate these women, and perhaps treat them prophylactically to allow longer duration of breastfeeding.

Title: COVID-19 Related Delays in Treatment of Melanoma
Presenter: Ananya Munjal MS
Mentor: Jennifer Powers MD
Collaborators: Vincent Liu MD, Raghav Tripathi MD, Madalyn Walsh MD, Pavane Gorrepati

Background
The COVID-19 pandemic caused many adverse medical effects, the most detrimental being delays in time to diagnosis and treatment of life-threatening health conditions. Due to stay-at-home orders and fear of contracting COVID-19, fewer people visited the hospital in 2020 than in years prior, inevitably resulting in fewer diagnoses of emergent medical conditions such as is melanoma. Expedited diagnosis, staging, and treatment of melanoma results in the best prognosis for patients with melanoma, and patients treated after three months of diagnosis have a higher risk of mortality as compared to patients treated after one month of diagnosis. Despite predicted delays in melanoma treatment due to postponed appointments and surgeries during this pandemic, no quantitative research has yet been published on the social and medical implications of COVID-19 on diagnosis or treatment of melanoma.

Purpose/Hypothesis
The main purpose of this study was to determine how the results of the COVID-19 pandemic affected time to treatment of melanoma at the University of Iowa Hospitals and Clinics and establish if these delays in treatment affected patient outcomes, health, and life expectancy for these patients. Our hypothesis was that the COVID-19 shutdown resulted in an increased number of later stage melanoma diagnoses.

Methods
Data for this study was collected retrospectively from pathology specimens collected at the University of Iowa Hospitals and Clinics from 1/1/2019 to 12/31/2020 that had a positive diagnosis of melanoma. No exclusion criteria were applied. Seventeen patient records were randomly reviewed for each month in this period for a total of 408 records. Patient medical records and dermatology clinic notes were utilized to collect additional deidentified demographic and clinical information. Documented telephone encounters were utilized to determine whether biopsies or excisions were delayed or rescheduled due to COVID-19.

Results
Preliminary results for this study show a potential increase in the staging of melanoma in the year 2020 vs. the 2019 in our sample population, as determined by increased average Breslow thickness and margin status on pathological samples. Despite this increase in initial staging, there was no significant increase in time to treatment between 2019 and 2020 once a positive melanoma diagnosis was established. Additionally, there was no significant documentation of COVID-19 related delays in treatment. Further statistical evaluation and analysis of significance is pending.

Conclusions
Our results demonstrate a potential higher average staging in melanoma pathology specimens taken from patients in 2020 as compared to 2019, pending further analysis. This finding is suggestive of the COVID-19 pandemic resulting in a higher proportion of later stage tumors due in part to patients delaying hospital visits for fear of contracting the virus. Despite this higher staging, it is encouraging to note that time to treatment was not increased between 2019 and 2020, suggesting that oncological care at UIHC was not hindered once a positive melanoma diagnosis was established. As delays in care is known to worsen outcomes, this information can inform dermatologists' clinical practices in the future and be used to guide public health planning for future medical emergencies.

Impact of Patient Outcome Feedback Reports on Emergency Department Physicians' Re-Access of Critically Ill Children's Electronic Health Records

Priynt Patel, BS, Erik Westlund, PhD, Cody R. Tigges, DO, Sarah L. Miller, MD, Raquel E. Gomez, BA, Alison R. Pauley, MSN, Patrick TenEyck, PhD, Priyadarshini R. Pennathur, PhD, Dean F. Sittig, PhD, Hardeep Singh, MD, MPH, Christina L. Cifra, MD, MS

Background: Emergency department (ED) physicians can improve the care they provide to acutely ill children by learning from past performance. Physicians commonly obtain patient outcome information by re-accessing their electronic health records (EHRs) after their ED visit; however, our prior work showed that ED physicians' selective re-access of critically ill children's EHRs after PICU transfer results in missed learning opportunities from information such as changes in diagnosis or transfers to a higher level of care. We have since developed an electronic semi-automated process to deliver patient outcome feedback to ED clinicians for all patients that they transfer to the PICU. Our objective is to determine the impact of receiving feedback reports on ED physicians' re-access of patients' EHRs after PICU transfer.

Methods: We performed a retrospective cohort study of 180 patients admitted to a single PICU from the same institution's ED. We compared patient/clinician/encounter characteristics and physician's EHR re-access characteristics between patients for whom physicians received (n=80) vs. did not receive (n=100) individual feedback reports. Using EHR access logs, we determined the frequency and characteristics of EHR re-access by ED physicians up to 30 days from the patient's ED visit. We only included EHR access episodes which occurred after physicians signed their ED note, signaling that documentation for the ED visit was complete.

Results: There were significant differences between patients for whom ED physicians did not receive vs. received feedback reports, with the former cohort being younger (median age [IQR] 4.2 [1-13.4] vs. 9.8 [2.3-16.4] years, *p*-0.001), more severely ill (pediatric risk of mortality-III score [IQR] 2.5 [0-6.5] vs. 0 [0-4], *p*=0.030), and treated by more pediatric-trained physicians (62% vs. 42.5%, *p*=0.011). Compared with ED physicians who did not receive feedback reports, significantly more physicians who did receive them re-accessed EHRs (87.5% vs. 37%, *p*<0.001) with more frequent re-access episodes (median [IQR] 0 [0-1] vs. 1 [1-2] episode, *p*<0.001), and access farther out in time (median time between ED visit and last EHR re-access episode [IQR] 1.8 [0.8-4.7] vs. 5.6 [4.1-8.1] days, *p*<0.001). Among patients whose ED physicians received feedback, the most frequently re-accessed EHR section was clinician notes (mean [SD] of 2.3 [5.6] re-access episodes per patient.

Conclusion: Receipt of feedback reports increased ED physicians' re-access of patients' EHRs after PICU transfer, which may allow them to obtain additional patient outcome information that can be used to improve their practice. More research is needed to further investigate the effects of standardized feedback to clinicians on the emergency care and outcomes of critically ill children.

Table. Characteristics of emergency department physicians' electronic health record re-access after patients were transferred to the Pediatric Intensive Care Unit before and after receiving patient outcome feedback reports

Characteristics of EHR Re-access*	Patients for whom clinicians did NOT receive feedback reports (n=100)	Patients for whom clinicians received feedback reports (n=80)	*p* value**
EHR was re-accessed at least once after ED visit, n (%)	37 (37)	70 (87.5)	<0.001
Number of times patient's record was re-accessed, median (IQR)	0 (0-1)	1 (1-2)	<0.001
Physicians re-accessed patient's EHRs:			
By searching for the patient (patient lookup), n (%)	20 (20)	9 (11)	0.153
As prompted by an In Basket message, n (%)	25 (25)	68 (85)	<0.001
EHR sections accessed most frequently, mean access episodes per patient (SD)			
Clinical notes	3.5 (9.4)	2.3 (5.6)	0.395
Miscellaneous reports summarizing patient data***	0.4 (1.8)	1.0 (2.4)	0.001

EHR - electronic health record, ED - emergency department, IQR - inter-quartile range, SD - standard deviation

*Only EHR access episodes which occurred after the clinician signed their ED note were included. Note-signing signaled that documentation responsibilities were complete, thus EHR re-access afterward would more likely reflects clinicians' intent to follow-up on patient outcomes.

**Statistical comparisons were performed using the Wilcoxon rank-sum test for continuous variables and the Fisher's exact test for categorical variables.

***Includes sections such as demographic data and clinical summaries (allergies, medications, lines and catheters, etc.)

Volumetric Analysis of Unruptured Intracranial Aneurysms Using Magnetic Resonance Angiography

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Introduction: Unruptured intracranial aneurysms (UIA) are present in 2-5% of the global adult population and can potentially lead to fatal aneurysmal subarachnoid hemorrhage. Multiple previous studies have shown size to be a predictor of UIA instability and rupture. Volume measurements may allow for the detection of changes in UIA shape and morphology that may be undetectable by conventional clinical size measurements. 3D rotational angiography (3DRA) is the gold standard for UIA imaging because it provides higher spatial resolution than noninvasive modalities such as magnetic resonance angiography (MRA) and computed tomography angiography (CTA). However, 3DRA is unsuitable for long-term UIA surveillance because it exposes patients to radiation and involves risk of procedural complications. Instead, long-term UIA surveillance typically involves serial imaging with CTA or MRA.

Purpose: The purpose of this study is to establish a tolerance for volume measurements based on MRA and evaluate the use of volumetric analysis for detecting longitudinal changes in UIA morphology through serial imaging.

Method: Following institutional review board approval, patients with untreated UIAs underwent serial 3T MRI imaging between April 2018 and June 2021. Contrast enhanced-MRA (CE-MRA) images were used for volume measurements. The Vascular Modeling Toolkit (VMTK) was used to perform semi-automatic 3D reconstruction of baseline and follow-up CE-MRAs for 18 UIAs. Parent vessels were segmented first using the colliding fronts algorithm and then the UIA sac was segmented using the fast-marching algorithm. Follow-up 3D reconstructions were registered to the baseline 3D reconstructions using the iterative closest points algorithms. Saccular UIAs were isolated from the parent vessel by making perpendicular cuts to the parent vessel near the UIA neck. Fusiform UIAs were isolated from the parent vessel by making perpendicular cuts at all vessel bifurcations. To establish a tolerance for volume measurements based on CE-MRA separate 3D reconstructions were created from the CE-MRA and 3DRA imaging of ten saccular UIAs (> 3 mm in largest diameter). The calculated tolerance was defined as the average percent error of the volume measurements between the modalities. Two 3D printed UIA phantoms from Biomodex were imaged using 3DRA and time-of-flight magnetic resonance angiography (TOF). During TOF imaging, the phantoms were affixed in agar and blood flood was mimicked using a peristaltic pump. 3D reconstructions were created for each phantom from both 3DRA and TOF using VMTK as described above with the modification that registration was not attempted.

Results: The average percent volume difference between the 3DRA and CE-MRA 3D reconstructions was 7.3% (IQR: 4.5-8.1%). However, only six of these ten UIAs were well registered; the subset of these six UIAs had a smaller average percent volume difference of 5.9% (IQR: 3.9-7.7%). In one of these aneurysms, the 3DRA 3D reconstruction showed a bleb or daughter sac that was not present in the CE-MRA 3D reconstruction. For the 3D printed UIA phantoms, the TOF 3D reconstruction volumes were 12.3 and 20.2% smaller for phantoms 1 and 2 respectively. 7 of the 18 UIAs had volume increases greater than our calculated tolerance. For all 18 UIAs, registration of the follow-up 3D reconstruction to the baseline 3D reconstruction was suboptimal.

Conclusion: The calculated tolerance for CE-MRA based UIA volume measurements was 8%, which was similar to interobserver and intraobserver variabilities previously reported for size metrics used clinically to evaluate UIAs. Without optimal registration between follow-up and baseline 3D reconstructions, one cannot reliably determine from the data whether increases in volume reflected changes in UIA morphology. Furthermore, even UIAs that showed little change in volume cannot be reliably classified as stable without optimal registration. Registering the 3D reconstructions themselves was suboptimal, however in the future registering the underlying images may provide more useful data. For one of the aneurysms, CE-MRA did not detect a bleb detected by 3DRA. This is problematic, because blebs are an example of irregular UIA shape, which is a risk factor for UIA rupture. The greater difference in volume during the phantom imaging compared to those from patient data may reflect the fact that TOF has lower spatial resolution than CE-MRA.

Title: What is the fate of total joint arthroplasty patients who are asked to quit smoking before surgery?

Authors: Katelyn Paulsen, BFA[1], Alyssa Conrad, MS[2], Natalie Glass, PhD[2], Nicolas Bedard, MD[2]

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Introduction: Smoking is an established risk factor for complications following primary total joint arthroplasty (TJA). As such, many recommend smoking cessation prior to elective TJA. However, little is known regarding the fate of patients who are asked to quit smoking before receiving a surgical date. The purpose of this study was to evaluate the success of smoking cessation in this patient population and determine the impact of smoking cessation on perioperative outcomes following TJA.

Methods: A retrospective review identified all patients with a documented history of smoking who presented for evaluation to a single institution's TJA clinic between 2010-2020. At this institution, it is common practice to require smoking cessation confirmed by urine testing prior to scheduling an elective, primary TJA. Subjects were included in the study if they were asked to quit smoking prior to proceeding with TJA and had up-to-date contact information. The study cohort then completed a survey, either electronically or over the phone, to inquire about their smoking history, how and if they were able to quit, if they sought surgery elsewhere without having to stop smoking and whether they had complications following TJA. Multivariate analyses were performed to evaluate the relationship between demographic variables, smoking cessation, and postoperative complication rates.

Results: 209 patients received the survey, and 102 subjects completed the survey for a 49% response rate. Overall, 64 patients (63%) quit smoking before proceeding with surgery. An additional 15 patients subsequently underwent TJA without smoking cessation before surgery. The average time to reach smoking cessation prior to TJA was 45 days (range: 01-365 days) and 58% of patients quit without medication or nicotine replacement therapy (NRT). Of the patients who stopped smoking in preparation for TJA, 50% remained smoke-free at 6 months following surgery. Patient demographics (age, sex, body mass index, years smoking, total pack-years, and hip vs knee) were statistically similar between the patients who stopped and did not stop smoking, as well as those who did and did not return to smoking after TJA. NRT was more likely to be utilized by patients who had smoked for more years ($p=0.008$) or had a higher pack-year history ($p=0.01$). The overall complication rate was significantly higher for patients who did not stop smoking prior to TJA (7 of 15, 47%) compared to those who did stop smoking before surgery (8 of 64, 13%; $p = 0.006$).

Conclusions: Smoking is known to increase the risk of postoperative complications following TJA. This study demonstrates that most patients (63%) will stop smoking, if required, prior to TJA. This requirement appears to be an effective intervention given a significantly lower complication rate amongst patients who quit smoking before surgery. Furthermore, 50% of patients remained abstinent from smoking 6 months following TJA, which is dramatically higher than many published rates of smoking cessation and has major public health implications. In conclusion, TJA appears to be an effective motivator for smoking cessation, which directly correlates with improved surgical outcomes.

Improving Procedural Pain in Burn Patients: A Quality Improvement Project - Phase II

Student: Albert Pedroza
Mentors: Lucy Wibbenmeyer, MD; Colette Galet, Ph.D., ELS – Department of Surgery

Background

Clinical management of pain associated with burn injuries continues to be a challenge. Notably, burn pain can be classified into background pain, procedural pain, and breakthrough pain. This quality improvement project focused on reducing procedural pain, which is intense pain present during wound care procedures. The initial phase (phase I) of our quality improvement project (QI) demonstrated a need to improve our patients' and nurses' satisfaction with pain control management. In this phase (Phase II), we educated the nursing staff on how to 1) optimize the timing of opioid administration (Oral and IV) and 2) increase the frequency of midazolam administration before wound care. We also assessed the safety and feasibility of ketamine administration for pain control during wound cleaning procedures. We hypothesized that education would help us improve our patients' and nurses' satisfaction with pain control during wound cleaning procedures. We also hypothesized that the use of ketamine would be safe, feasible, and would ease the pain of our patients.

Methods

Patients undergoing wound cleaning procedures were surveyed either prior to their first skin grafting or during their first takedown after surgery. Pregnant patients, incarcerated patients, and patients unable to understand/answer survey questions were all excluded. A single patient could be surveyed for up to three hydrotherapy encounters. Between Phase I and Phase II of this QI, nurses were educated on pain control during wound cleaning procedures. This included education on the administration of midazolam and opioid administration (oral and IV) and timing prior to the procedures. In addition, a convenience sample of patients were chosen to undergo ketamine administration. Ketamine was administered per protocol starting at 0.3 or 0.4 mg/kg with intermittent boluses of 0.25 mg/kg as needed. Demographics, comorbidities, injury related data, and admission data were collected. Opioid administration amount and timing, midazolam, and ketamine administration dose and time were collected for those who received them. Adverse effects categorized as emergent hallucinations or hypertension (SBP>180) that required treatment were recorded. Patient pain scores (1-10) were collected before and after the wound cleaning procedure while patient and nurse satisfaction scores (1-10) were collected by surveying nurses and patients after the wound cleaning procedure. Nurses were also asked to rate how easy it was to perform the procedure. Paired t-tests and one-way ANOVA were performed to assess significant differences between pre and post procedure patient pain scores and satisfaction ratings across encounters, respectively using SPSS 25.0. $P < 0.05$ was considered significant. Patients were monitored per Sedation Policy Guidelines by the nursing staff and the attending physician.

Results

Thirty patients and 50 encounters were surveyed during Phase I of this QI. During Phase II, 9 patients and 19 encounters were analyzed; these included 10 events where ketamine was administered. Comparing Phase I and Phase II data showed that education of the nursing staff resulted in a significant improvement in opioid administration, with 52.6% of the patients receiving both oral and IV opioids prior to the procedure compared to none before ($p < 0.001$). However, we did not improve on administering opioids (oral and/or IV within the window of efficacy compared to Phase I (42.1% vs. 43.8%). Midazolam was more frequently administered prior to the procedure (78.9% vs. 10%; $p < 0.001$). There was also a significant improvement in both patient and nurse satisfaction scores regarding pain control (8.7 ± 2.4 vs. 7.7 ± 2.1; $p = 0.011$ and 8.2 ± 2.1 vs. 7.3 ± 1.9; $p = 0.021$, respectively). The ease of dressing change scores did not change significantly (9.2 ± 1.3 vs. 8.4 ± 2.2; $p= 0.211$). Our data also showed that the use of ketamine is both safe and efficacious. None of the patients experienced adverse effects. Notably, the use of ketamine improved nurse satisfaction scores with patient pain control (9.2 ± 0.8 vs. 7.1 ± 2.6; $p = 0.035$). On average, the use of ketamine improved patient pain control satisfaction without reaching significance (9.4 ± 1.1 vs. 7.9 ± 3.2; $p = 0.315$). Finally, there was no difference in change in pre-post procedure pain scores compared to standard of care (opioids and midazolam) (2.3 ± 3.9 vs. 1.6 ± 2.6, $p = 0.549$).

Conclusion

Overall, Phase II demonstrated that nurse education regarding medication administration proved to be efficacious, but further education is needed to improve the administration of opioids within the window of efficacy. The current study also demonstrated that ketamine is both safe and efficacious, but more encounters are needed to observe changes over a larger sample size.

Impact of Obesity on Posterior Cervical Fusion for Cervical Myelopathy Eli A Perez BS[1], Royce W. Woodroffe MD[2], Brian Park MD[2] , Colin Gold MD[2], Logan C. Helland MD[2,3], Scott C Seaman MD[2], Patrick W. Hitchon MD[2]

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ABSTRACT

Study Design: Retrospective Cohort Study

Objective: The aim of this study was to investigate the effect of body mass index (BMI) on the reoperation rate and cervical sagittal alignment of patients who underwent posterior cervical decompression and fusion for cervical spondylotic myelopathy (CSM).

Summary of Background Data: Cervical sagittal balance has been correlated with postoperative clinical outcomes. Previous studies have shown worse postoperative sagittal alignment and higher reoperation rates in patients with high BMI undergoing anterior decompression and fusion. Similar evidence for the impact of obesity in postoperative sagittal alignment for patients with (CSM) undergoing posterior cervical decompression and fusion (PCF) is lacking.

Methods: A retrospective analysis of 198 patients with cervical myelopathy undergoing PCF was performed. Demographics, need for reoperation, and perioperative radiographic parameters were collected. Cervical lordosis (CL), C2-7 sagittal vertical axis (SVA), and T1 slope (T1S) was measured on standing lateral radiographs. Comparative analysis of the patient cohort was performed by stratifying the sample population into three BMI categories (<25, 25-30, ≥30).

Result:
Of the 198 patients that met inclusion criteria, 53 had BMI normal (<25), 65 were overweight (25-30), and 80 were obese (≥30). Mean SVA increased postoperatively in all groups, 4 mm in the normal group, 13 mm in the overweight group, and 13 mm in the obese group (p=0.003). There was no significant difference in the postoperative change of cervical lordosis or T1 slope between the groups. Multivariate analysis demonstrated fusions involving the cervicothoracic junction and those involving 5 or more levels significantly affected alignment parameters. There were 27 complications requiring reoperation (14%) with no significant differences among the groups stratified by BMI (p=0.386).

Conclusions
Overweight patients (BMI >25) with CSM undergoing PCF had a greater increase in SVA than normal weight patients. While preoperative CL increased with increasing BMI, this trend was not significant and there was not found to be a significant difference between the change in CL between the BMI cohorts. Reoperation rates were also not found to be associated with BMI. Overall, BMI is an important factor to consider when attempting to optimize sagittal alignment in patients undergoing PCF.

Intra-Arterial Encephalography from Acutely Implanted Aneurysm Embolization Device in Awake Humans

Student: Anthony Piscopo
Mentor: David Hasan

Background

Endovascular electroencephalography (evEEG) utilizes the cerebrovascular system as a minimally-invasive conduit to record electrical activity from adjacent neural structures, mitigating the poor spatial resolution and risks of invasive, open craniotomy associated with extracranial EEG and electrocorticography, respectively. The safety, feasibility, and efficacy of using the Woven Endobridge (WEB) intracranial aneurysm embolization device for evEEG has yet to be investigated in humans.

Methods

Fifteen patients undergoing awake endovascular treatment of unruptured cerebral aneurysms using the WEB device were included. The WEB Device, composed of nitinol with platinum core, served as a single-electrode intravascular contact by connecting its distal deployment wire to an EEG receiver. After deployment into the aneurysm dome and before detachment, subjects were presented with a monetary, value-based decision-making task for 10 minutes while endovascular recordings were captured and referenced with scalp electrodes.

Results

All patients underwent successful embolization and evEEG recording with no perioperative complications. Event-related potentials (ERP) were detected on scalp EEG in 6/15 (40%) patients. Of these 6 patients, low-gamma (30-70Hz) response on WEB channels were captured in 4/6 (75%) cases. In these 4 patients, the WEB device was deployed in the middle cerebral artery, anterior communicating artery x2, and the basilar tip. Recording of EKG artifact in the WEB channels was present in the remaining 11 cases.

Conclusions

Placement of an implantable WEB device within the cerebral aneurysms of awake subjects is capable of capturing task-specific brain electrical activities. Future studies are warranted to establish efficacy and offer further support for evEEG as a potential tool to monitor neurological activity while mitigating the risks of open craniotomy and general anesthesia.

The use of EKGs to screen Athletes for myocarditis following COVID-19 infection

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Background: Myocardial inflammation can occur in some patients with SARS-CoV-2. Given that myocarditis is a major cause of sudden cardiac death (SCD) in athletes, effective screening strategies are necessary. Most athletes with myocarditis who suffered SCD were asymptomatic before death; therefore, a symptoms-based screening approach can be inadequate. Conversely, performing a cardiac MRI (CMR) on every athlete would be impractical. Electrocardiograms (EKGs) are an inexpensive, widely available screening tool that may help identify myocarditis.

Methods: Participating University of Iowa athletes who tested positive for COVID-19 by a polymerase chain reaction test received a comprehensive cardiac screening including a history, physical, EKG echocardiogram, and a CMR. Athletes' EKGs were classified as normal, abnormal, or borderline using the refined criteria described by Sheikh et al. The association between EKG classification and other variables such as demographic factors, CMR classification and illness characteristics was examined. Medians or frequencies were calculated, and a Mann-Whitney-U test, Chi-Squared test, or Fisher's exact test was performed to determine statistical significance.

Results: Of the 219 athletes included in this study, 23 had EKG abnormalities. The most common findings were T wave inversion (9), ST depression (3), ectopic atrial rhythm (3) and complete RBBB (3). There was no statistically significant association between the prevalence of EKG abnormalities and sex, age, race, sport played, symptomatic COVID-19 infection, or the presence of chest pain/dyspnea (see chart). Those with abnormal EKGs experienced symptoms for a significantly longer duration (median duration 7 days vs 4 days, p=0.0318). The association between CMR abnormalities and EKG abnormalities trended toward significance (p=0.0830).

Conclusions: EKGs are an affordable diagnostic modality that may help identify athletes who require further evaluation. Additionally, the data suggests that an extended duration of symptoms is a risk factor for developing EKG abnormalities. A larger study is necessary to confirm the association noted above.

Table1: Cross sectional look at EKG in correlation with other variables.

Variables	**EKG Normal or Single Borderline Finding**	**EKG Abnormal (% of total)**	**Total or Range**	**P value**
Males	122	11 (8%)	133	0.1740
Females	70	12 (15%)	82	
Median Age	19	19	Range 17-24	0.6355
White	150	17 (11%)	167	>0.9999
All other Races[1]	41	5 (10%)	46	
Football	55	8 (13%)	63	0.7890
Track	26	3 (10%)	29	
All other sports[2]	115	12 (16%)	127	
Patient experienced at least one COVID-19 symptom	114	13 (10%)	127	>0.9999
Patient did not experience any COVID-19 symptoms	82	10 (11%)	92	
Patient experienced chest pain or dyspnea	14	2 (13%)	16	0.6781
Patient did not experience chest pain or dyspnea	182	21 (10%)	203	
Median Symptom duration	4	7	Range 0-23	0.0318
CMR Abnormal	6	3 (33%)	9	0.0830
CMR Normal	107	13 (11%)	120	

1: Includes African American or Black, American Indian or Alaska Native, Asian, Other, and Unknown
2: Includes rowing (20), swimming (15), gymnastics (10), basketball (10), golf (9), wrestling (8), baseball (8), volleyball (6), cheerleading (5), tennis (4), field hockey (4), dancing (3), softball (2), soccer (2), diving (2), cross-country (2), and other (17)

Agricultural Workers in Meatpacking Plants Presenting to an Emergency Department with Suspected COVID-19 Infection are Disproportionately Black and Hispanic

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Objective

Facilities that process and package meat for consumer sale and consumption (meatpacking plants) were early sites of coronavirus disease 2019 (COVID-19) outbreaks. The aim of this study was to characterize the association between meatpacking plant exposure and clinical outcomes among emergency department (ED) patients with COVID-19 symptoms.

Methods

This was a retrospective cohort study of patients presenting to a single ED, from March 1 to May 31, 2020, who had: 1) symptoms consistent with COVID-19 and 2) a COVID-19 test performed. The primary outcome was COVID-19 positivity, and secondary outcomes included hospital admission from the ED, ventilator use, intensive care unit (ICU) admission, hospital length of stay (LOS; <48 or ≥48 h), and mortality.

Results

Patients from meatpacking plants were more likely to be Black or Hispanic than the ED patients without this occupational exposure. Patients with a meatpacking plant exposure were more likely to test positive for COVID-19 (adjusted relative risk [aRR] = 2.37, 95% confidence interval [CI] = 1.59 to 3.53) but had similar rates of hospital admission (aRR = 0.94, 95% CI = 0.82 to 1.07) and hospital LOS (aRR = 0.76, 95% CI = 0.45 to 1.23). There was no significant difference in ventilator use among patients with meatpacking and nonmeatpacking plant exposure (8.2% vs. 11.1%, p = 0.531), ICU admissions (4.1% vs. 12.0%, p = 0.094), and mortality (2.0% vs. 4.1%, p = 0.473).

Conclusions

Workers in meatpacking plants in Iowa had a higher rate of testing positive for COVID-19 but were not more likely to be hospitalized for their illness. These patients were disproportionately Black and Hispanic.

Title: The effect of the PICO negative-pressure dressing on cesarean section infection rates in obese women

Student: Elijah Reische
Mentors: Colleen Stockdale, MD and Abbey Hardy-Fairbanks, MD
Other collaborators: Alexandra Sharp

Background

Obesity is increasingly common among pregnant women in the United States. Obese women are more likely than non-obese women to give birth by cesarean section, and obese women who undergo cesarean section are at increased risk for post-surgical complications, including surgical site infections.

One method that may be used to prevent post-cesarean infections is negative-pressure wound therapy (NPWT), in which a device is placed on the wound that applies negative pressure, drawing fluid out of the wound and accelerating the healing process. NPWT has been used in many settings to promote healing after surgery, but little is known about its utility in preventing post-cesarean infections, particularly among obese women. One option for NPWT is the PICO device, which uses a small pump attached by tubing to an absorbent dressing to draw fluid out of the wound. It has been shown to reduce surgical site infections across many types of surgeries.

Purpose: To determine whether the PICO NPWT device is superior to a standard dressing in preventing post-cesarean surgical site infections in obese and diabetic women.

Methods: The electronic medical record was reviewed for patients who underwent cesarean delivery at UIHC between 1/1/2018 and 1/1/2021, received a PICO device as a wound dressing, and had a body mass index > $30 kg/m^2$ or a diagnosis of diabetes mellitus. Data abstracted from patient records included demographic information, co-morbidities, pre- and post-partum complications, and antibiotics given before cesarean. Outcomes from women in the PICO group were compared to previously collected data from women who underwent cesarean section in the same time frame and received standard dressings.

Results: 8.52% of women in the PICO group had a surgical site infection within 30 days of surgery, compared with 5.51% of women in the control group ($p=0.036$). Of women who had a surgical site infection, women in the PICO group were significantly more likely than women in the control group to have a deep incisional infection ($p=0.024$). There was no significant difference between incidence rates of seroma, hematoma, or wound dehiscence between the PICO and control groups. Overall, 14.43% of women in the PICO group had any wound complication, compared with 9.27% of women in the control group ($p=0.0102$). Women in the PICO group had different indications for cesarean than women in the control group ($p=0.036$), with higher rates of cesareans for arrest of descent ($p=0.034$) and failed induction ($p=0.014$). They were also more likely to have cesareans that were unplanned ($p<0.001$) or emergent ($p=0.009$). Women in the PICO group were also more likely to have had prolonged rupture of membranes during labor ($p=0.004$).

Discussion: Women who received PICO dressings after cesarean sections were significantly more likely than women who received standard dressings to develop surgical site infections within 30 days. In general, women who received PICO dressings were also significantly more likely than women who received standard dressings to have any wound complication within 30 days following surgery. These results suggest that the PICO negative-pressure device is inferior to a standard dressing in terms of preventing wound complications, including infection, among obese and diabetic women following cesarean section. As the PICO device is also more expensive than a standard dressing, our findings indicate that the standard dressing may be the superior choice for this patient population.

Impact of High Spinal Anesthesia Technique on Fast-track Strategy in Pediatric Cardiac Surgery: a Retrospective Study

Alex Rier, Rakesh Sondekoppam Vijayashankar MD, Sudhakar Subramani MD, Satoshi Hanada MD

Background

Previously investigated in adults, high spinal anesthesia (HSA) in addition to general anesthesia (GA) has shown to increase the frequency of fast-track extubation (less than 6 hours) and extubation in the operating room (OR) when compared to only GA in cardiac surgery patients.[1] Neuraxial blocks such as caudal, epidural, and spinal anesthesia have been used in pediatric cardiac surgery patients to limit the stress response caused by surgery and lessen the negative effect associated with opioid-induced respiratory suppression, which may lead to prolonged ventilation.[2-4] The benefits and complications of fast-tracking have been outlined in pediatric cardiac surgery patients.[5] However, minimal literature exists focusing on fast-track extubation with HSA and GA compared to only GA in pediatric cardiac surgery patients.

Purpose

Evaluate the impact of HSA in addition to GA on fast-track extubation in pediatric cardiac surgery patients. Primary outcome: extubation in the operating room (OR). Secondary outcomes: extubation time after the procedure, length of stay (LOS) in the intensive care unit (ICU), and LOS in the hospital.

Methods

Patients aged 1 day–18 years who had open cardiac surgeries at UIHC from 2010-2020 were included. Patients who were not a candidate for fast-track extubation, such as patients who underwent left ventricular assist device implantation, Norwood procedure, heart transplantation, and atrial switch procedure, were excluded. Data was retrieved and confirmed from the electronic medical record (EMS). The cases were divided into two groups: cases with HSA in combination with GA (HSA group) and cases with GA without any additional neuraxial blocks (GA group). Greater than 500 pediatric cardiac surgery patients were screened. Preliminary results show that approximately 300 of the 500 screened cases will meet the inclusion criteria and be analyzed. Comparisons were made between the HSA group and GA group. The primary outcome is extubation in the OR. Secondary outcomes include extubation time after the procedure, LOS in the ICU, and LOS in the hospital. Statistical analysis was done using the generalized linear mixed modeling (GLMM) framework for the dichotomous outcomes. ASA physical status, type of surgery, and length of surgery was controlled for while assessing the primary and secondary outcome differences between the two groups.

Results

Greater than 500 pediatric cardiac surgery cases were reviewed and a projected 300 cases will be included. Statistical analysis is still in progress, with preliminary results showing that extubation in the operating room was more frequent in the HSA group. We are still pending results on the secondary outcomes and controls.

Discussion

Fast-tracking in pediatric cardiac surgery patients is important to minimize morbidity due to prolonged ventilation. The less opioids needed intraoperatively also leads to better outcomes in these patients. Specific procedures, such as the Fontan procedure, immensely benefit from patients spontaneously breathing immediately after surgery for adequate circulation[6], which may be more prevalent due to neuraxial blocks. Future studies comparing the neuraxial blocks and extubation time could delineate which block is best. As more literature on the HSA technique is published, its benefits could be standard procedural care for select cardiac surgery patients.

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Iowa and Advanced Bionics Study: Optimization of Fitting for Incomplete Electrode Insertions

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Introduction
Cochlear implants (CIs) partially restore hearing for adults and children with bilateral moderate-to- severe, severe-to-profound sensorineural hearing loss [1]. CIs separate incoming sound into different frequency bands or filters. Then, the output of that is sent to a fixed number of electrodes. The electrodes are situated in the inner ear from base to apex of the cochlea. Low frequency sounds are coded by a low frequency channel that then directs that sound to an electrode positioned closer to the apex. The same organization applies to high frequency sounds to the base of a cochlea. These channels are limited by the number of electrodes implanted which are about 8-20 electrodes [2]. Hearing preservation CI were then developed for patients that were not benefiting from hearing aids' amplification alone but still had some functional acoustic hearing. These hearing preservation CIs offer the possibility of preserving the residual low-frequency hearing while receiving the benefits of a CI (Electroacoustic stimulation, EAS). These newer electrodes have been designed thinner to facilitate round window insertion, shorter and more flexible to minimize trauma to intra-cochlear tissues. To avoid trauma to intra-cochlear tissues due to the CI electrodes and preserve residual low frequency hearing, surgeons often insert an electrode array only part way into the cochlear (partial insertion) [3]. There has a been a variability in electric performance and acoustic benefit in the Advanced Bionics Naida CI Q90 Sound Processor.

Purpose of the Study
The study fits and assesses the performance of Electric Acoustic Stimulation (EAS) and Electric only participants with incomplete insertions. The acoustic component of EAS and Electric only participants plus a separate hearing aid are compared. To assess the electrical component, the optimal use of intra-cochlear electrodes in both types of participants are evaluated.

Methods
5 EAS Subjects: Custom Slimtip earmold are ordered from Phonak for EAS subjects using non-custom earpieces. Phonak Target 6.1 assesses hearing instrument fitting with Phonak Naida Link RIC hearing aid and Power xReceiver (xP) and Acoustic ear hooks donated by AB. Soundwave 3.2 evaluates cochlear implant fitting. EFI measurements are obtained through the AIM tablet. Test conditions were CA+CE, OA+CE (acoustic cutoff 2 steps above recommended cutoff value), OA+OE1 (disable 1 additional basal electrode), OA+OE2 (M level of the most basal active electrode to 0 CU). Speech perception was evaluated using CNC words twice and AzBio sentences in noise once per test condition at 60 dBA speech presentation level. Aided sound field thresholds were analyzed at 250, 500, 1000, 2000, 4000 and 6000 Hz. Subjective ratings were acquired at the end. The condition with the highest CNC score was used for 2-3 weeks. Outcome measures for CA+CE and OA+OEx was assessed after along with a chronic questionnaire. 3 Electric only Subjects: Test conditions were CE, OE1 (disable 1 additional basal electrode), OE2 (M level of most basal electrode to O CU). For subject GG, OE2 was 1 additional basal electrode disabled and OE3 (2 additional basal electrode).

Results
The OEx that Patient "GR" used for chronic use was OE1, Patient "JO" was OE1 and Patient "GG" was OE2.

Conclusion
Fitting recommendations for electric are to direct speech power to contacts deeper in the cochlea, disable extra-cochlear electrodes and additional 1 basal electrode and verify comfort level of remaining active electrodes with tone stimuli. Fitting recommendations for acoustic are to update audiogram, maximize acoustic bandwidth, ensure appropriate acoustic coupling by fitting a SlimTip, assign electric cutoff per Soundwave recommendation and acoustic cutoff at least 520 Hz and 2 steps above electric cutoff. Study is on-going to collect additional subject data and further guidance on fitting optimization.

The role of type I interferon signaling in mice following a model of traumatic brain injury

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Introduction: Traumatic brain injury (TBI) causes about 30% of all injury-related deaths in the United States. With no current treatment options, those that survive experience permanent loss of executive functions, sensory deficits, and an overall decrease in their quality of life. After recovery from the initial TBI, ongoing inflammation, excitotoxicity, and oxidative stress causes secondary neural tissue injury. Growing evidence suggests that type I interferon (IFN) signaling is a key contributor to inflammatory cell activation following TBI. We have recently demonstrated significant upregulation of interferon stimulated genes (ISGs) in microglia and astrocytes following experimental TBI. Type I IFN activation following TBI has been associated with increased neurodegeneration and synaptic loss, but the exact mechanisms by which this occurs are unclear. Our objective was to examine the impact of type I IFN signaling on astrocyte and microglial immune cell activation and its impact on TBI pathophysiology.

Hypothesis: We hypothesize that TBI results in type I IFN pathway activation due to the release of IFNs, nucleic acids, or myelin from injured neurons. We also hypothesize a link between type I IFNs and C3 production as a cause of secondary injury and chronic neurobehavioral impairments after TBI.

Method: Anesthetized 8–16-week-old adult old wild-type C57BL/6J male mice were exposed to the TBI model, lateral fluid percussion injury (FPI). FPI induces both focal and diffuse axonal injury by delivering a fluid pressure pulse directly to exposed dura following craniectomy. Sham control mice underwent craniectomy without exposure to FPI. Following injury, FPI (n=5) and sham (n=5) brains were collected and regionally dissected. A regional time course evaluation of IFN stimulated gene expression was conducted via quantitative polymerase chain reaction (qPCR). After observing increased levels of ISGs and complement pathway gene expression 1-, 3- and 7-days post injury, we compared protein levels of potential triggers for type I IFN signaling. As morphological changes for inflammatory mediators indicate activation, we utilized neural immunolabelling to evaluate immune cell activation and contribution to continued inflammation and cognitive deficits after TBI. At 3-days post-injury, FPI and sham brains were collected and processed for immunohistochemical detection of complement component 3 (C3). Cell source was assessed through evaluation for co-localization with, neuronal, and astrocytic markers by using C3 + DAPI, NeuN and GFAP immunohistochemistry staining, respectively.

Results: FPI astrocytes displayed significantly increased ISG (*Ifi27, Oasl2, Irf9, Ifit1*) and complement pathway gene (*C4b, C1ql*) expression 7-days post-injury compared to sham. In the hippocampus, ISGs and C3 gene expression were additionally upregulated at 1-, 3- and 7-days post-injury. At 3-days post-FPI, we observed severity-dependent morphological changes in astrocytes and neurons with a trend in regional-dependent C3 upregulation in response to FPI compared to sham. Elevated C3 expression predominately co-localized with dying neurons in the cortex and activated astrocytes in the hippocampus after injury.

Discussion: Experimental TBI results in increased glial ISG expression and neural inflammation that includes elevated astrocyte activation and is associated with neuronal cell death. These glial cells are activated by various inflammatory cytokines, including the type I IFNs, and perpetuate inflammatory cytokine signaling through C3 that may lead to the chronic cognitive deficits observed in TBI models. Future experiments will focus on demonstrating a causal link between IFN protein release, downstream C3-mediated glial activation and ISG expression following FPI. By characterizing this inflammatory pathway, subsequent development of pharmacological inhibitors of its mediators may improve long term neurological outcomes and quality of life in TBI patients.

Physician transfer of Clinician Communication Skills to workplace settings: Insights from communication skills coaches

Emily Ruba, Kipton Pedersen, Theresa Brennan, Marcy Rosenbaum

INTRODUCTION

In the last decade, communication skills training programs for practicing health care providers has increased. The central component of most of these programs is an experiential workshop which includes evidence-based communication skills content and opportunities for practice and feedback through role play with peers and/or simulated patients. While participants have reported some increase in use of skills learned in workshops in self-assessment measures, transfer and sustainment of communication skills into daily clinical practice has been noted to be challenging. Post-workshop coaching has been identified as one approach to help providers transfer workshop communication skills learning into their workplace interactions with patients and families. The current study uses coaching observations and feedback to identify if and how providers were able to incorporate communication skills into their clinical interactions after participating in a communication skills workshop.

METHODS

Healthcare providers, (including physicians, advanced nurse practitioners and physician assistants) in a large U.S. teaching hospital completed a five-hour experiential workshop on evidence-based approaches to relationship-centered communication skills. Approximately 30 and 60 days after participating in the workshop, each provider was observed interacting with patients in their respective clinical settings by Patient Experience Coaches. Coaches provided immediate verbal feedback on the communication skills providers were using effectively and those that were lacking or could benefit from improvement. In addition, each provider was given written feedback on their communication skills after each observation. The workshop curriculum was utilized as a framework for this feedback in order to help build provider skills beyond the workshop. To avoid overwhelming the provider, coaches focused feedback on highlighting skills that were used particularly effectively and a limited number of skills that could be incorporated more effectively.

All written feedback reports were entered into an Nvivo database to allow for systematic searching and coding. Analysis of these written feedback reports for physician participants is being used to identify the extent to which providers were able to transfer skills from the workshop into their specific clinical setting.

RESULTS

Written feedback reports for 150 participating physicians from a broad spectrum of clinical departments and settings are in the process of being analyzed. Preliminary analysis results across all 30 and 60 day observations reveal communication skills from the workshop that providers used less or more frequently in interactions with patients/families following the workshop. Providers in this cohort were most frequently noted as effectively establishing rapport, using open ended questions, plain language and summary. The skills which were most frequently identified as either missing or needing increased or more effective use included agenda setting by eliciting the whole patient list of concerns and priorities, responding to emotions with empathy and teach back. Further analysis will compare of 30 and 60 day feedback reports for each physician to examine the potential impact of coaching feedback on reinforcement during 30 day observations on the efficacy of applying these skills in each providers' specific clinical setting at 60 days post-workshop.

Preliminary Discussion:

Findings from this study may help increase understanding of if and how health care providers are able to apply communication skills recommended in the literature and taught in workshops within their specific practice settings. While demonstrating effective use of many skills, the skills that providers seemed to struggle to transfer into practice the most, specifically agenda setting and teach back, may be perceived by providers as more novel and less applicable to specific clinical contexts or disciplines.

A Peripheral Compressive Neuropathy Model to Visualize Pathology at the Neuromuscular Junction

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Background:

Peripheral compressive neuropathies (PCNs) are a frequent cause of disability. The most common PCN is carpal tunnel syndrome (CTS)[1], which results from median nerve compression in the carpal tunnel by the surrounding structures, leading to wasting of the muscle groups distal to the compression. Decompression surgery is frequently a successful treatment option, but the indication for surgical release is less clear in diabetic patients due to difficulty distinguishing PCN from generalized diabetic peripheral neuropathy. To guide the treatment of diabetic PCN, we must further understand the pathophysiology of the disease.

It is well known that nerve transection results in degeneration of the pre-synaptic terminals and upregulation of post-synaptic nicotinic acetylcholine receptors (NAChR). However, the effects of PCNs on the NMJ still remain unclear. Synaptophysin is a presynaptic vesicle protein and NAChR is a motor endplate protein, both of which can be targeted to visualize the NMJ. The purpose of this study is to define if pathological changes occur distal to the site of compression at the neuromuscular junction (NMJ).

Hypothesis:

Compression of the sciatic nerve in female Sprague Dawley rats will result in decreased synaptophysin expression and increased NAChR expression. Decompression of the sciatic nerve will result in the opposite effects of compression, until the expression patterns return to baseline.

Methods:

Two groups of seven 63-week-old female Sprague Dawley rats were established, a compression group, and a decompression group. In the compression group, animals were sacrificed at 1, 2, 4, 6, 8, 10, and 12 weeks after sciatic nerve compression. In the decompression group, an initial period of 6 weeks of compression was completed in each animal before a decompression procedure. Following decompression, animals were sacrificed at 1, 2, 4, 6, 8, 10, and 12 weeks. The operation was performed on the left hindlimb.

Gastrocnemius/soleus muscle complexes were harvested from left and right hindlimbs, sectioned, and stained with synaptophysin or NAChR antibody. Slides were visualized using brightfield microscopy. Three equally sized images were captured from each slide in a systematic fashion for counting of NMJs. A grid was placed over each image to aid counting. A protocol to count areas of NAChR and synaptophysin stain was established and followed by one independent researcher and PS. Results were recorded in identical excel spreadsheets.

Results:

Following compression, areas of synaptophysin stain appeared to steadily increase in muscle from the right limb, while the left compressed limb had an initial decrease at 2 weeks of compression, followed by continued steady increase. After decompression, synaptophysin stain in muscle from the right limb increased at two weeks, decreased until 8 weeks, and then increased until 12 weeks, though no clear trend of increase or decrease was evident. In the left limb, areas of synaptophysin stain increased from 1 to 2 weeks followed by a general decline until 12 weeks. Following compression, areas of NAChR staining in both limbs appeared to show an initial decline, followed by a large increase at 4 weeks, then no general trend thereafter. After decompression, areas of NAChR staining counted from right limb muscle generally increased. In the left limb muscle, a large increase in the number of localized areas of NAChR stain was seen at week 2 after decompression, however, no trend of increase or decrease of NAChR staining was seen.

Discussion:

The generalized increase in synaptophysin following compression is contrary to our hypothesis. This response might represent a biological attempt to compensate for reduced neuronal signaling. Following decompression, the generalized decline in synaptophysin suggests a return towards levels seen at the first week of compression. The large increase in NAChR-labeled NMJs at week 4 of compression may be compensation for decreased neuronal signaling, as more NAChR could potentially increase neurotransmitter sensitivity. The subsequent oscillation at lower numbers of NAChR stained areas in later weeks of compression may represent exhausted cellular resources. After decompression, the large spike in NAChR at week 2 could show the rapid regeneration of NAChR once the compression device is removed.

Overall, operative intervention, whether compressive or decompressive in nature, seems to result in rapid changes to synaptophysin and NAChR within the first 4 weeks. Our small sample size was a limitation, making statistical conclusions difficult. However, the study shows the impact of nerve compression on the neuromuscular junction of innervated muscles. Also, the ability of this structure to recover after decompression surgery. This insight might help healthcare providers evaluate the possibility of early surgical intervention and better functional outcomes in PCN.

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The Role of Transverse Tarsal Arch Collapse in Progressive Collapsing Foot Deformity

Presenter: Eli Schmidt
Mentor: Dr. Cesar de Cesar Netto, MD, PhD
Collaborators: Mattheiu Lalevee, MD, Caleb Ihel, BS, Sam Ahrenholz, BS, Tutku Tazegul, BS, Christain VandeLune, BS, Kevin Dibbern, PhD, Nacime Mansur, MD

Introduction:

A study recently published in *Nature* by Dr. Venkadesan and colleagues demonstrated a previously unrecognized importance of the transverse tarsal arch of the foot (TTA). They showed that the TTA contributes more to the longitudinal stiffness of the foot than the extensively studied medial longitudinal arch (MLA). Moreover, they showed that the evolutionary development of the TTA may be correlated with the evolution of bipedalism as feet developed from flexible flatfeet to a more rigid arched foot.

Given this recent publication, the TTA may also play a role in pathogenesis of modern-day flatfeet, now called Progressive Collapsing Foot Deformity (PCFD). PCFD is mainly described as collapse of the MLA with no consideration of the TTA.

Therefore, the objective of this study was to assess the TTA in the PCFD population. We hypothesized that PCFD will present with TTA collapse in addition to the previously understood MLA collapse.

Methods:

A retrospective review was conducted for 34 feet, 16 with PCFD and 18 control feet. All measurements were performed using weight-bearing CT scans. A novel measurement, the Transverse Arch Plantar Angle (TAPA), was developed to directly measure the TTA. Additionally, the curvature of the TTA was estimated using the equation provided in the abovementioned study. This equation utilizes foot width and length, third metatarsal thickness, and fourth metatarsal torsion to give a torsion-based estimate of the normalized curvature of the TTA.

Results:

PCFD and control groups were comparable for BMI, age, and gender.

There was a significant difference found between groups regarding the TAPA angle (PCFD 111.13° ± 11.29, control 97.02 ± 5.88, $p<0.001$). In contrast, there was no difference found between groups regarding the torsion-based estimation of curvature of the TTA (PCFD 12.76 ± 4.62, control 15.18 ± 5.42, $p=0.25$).

Conclusions:

Our study shows a previously undescribed collapse of the TTA in the PCFD population when measured directly. The non-significant torsion-based results suggest the TTA collapse is due more to a soft tissue failure than an insufficient bone torsion. This newfound understanding of the importance of the TTA should be further explored in the assessment of PCFD.

Using ELISA and IFAT to determine exposure to *Anaplasma spp. in Natal, Brazil*

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Mentors: Christine Petersen, DVM, PhD; Selma Jeronimo MD

Introduction:

Leishmania infantum is an obligate intracellular protozoan parasite tranmitted by sand flies that can lead to visceral leishmaniasis (VL). The fatality rate for untreated VL in the developing world can approach 100% [1]. VL occurs when the parasite infects the internal organs of the patient, most commonly the spleen, liver and bone marrow. In canine reservoir host studies, natural co-exposure to tick-borne diseases, including *Anaplasma* spp., was shown to increase the chances of *Leishmania* infection progressing to clinical illness[2].

Anaplasma phagocytophilium is the causative agent of human granulocytic anaplasmosis. Infection of host granulocytes could have potential immunomodulatory effects, potentially predisposing hosts to develop clinical VL. Very little is known about seropositivity rates in Brazil. *Anaplasma* is of particular interest for this study due to high seropositivity rates (15%) in non-VL patients established by a previous medical student in areas around Natal, Brazil. However, it was suspected that this difference was due to hypogammaglobinemia that occurs during active visceral leishmaniasis.

Hypothesis:

When evaluated via ELISA, the *Anaplasma* seropositivity rate in VL patients is higher than the control non-VL population in Natal, Brazil, however this greatly reduced when a highly specific Immunofluorescence Antibody Test (IFAT) platform is used.

Specific Aims of Study:

1. Use Diagnostic ELISA to establish *Anaplasma* seropositivity rates in VL and non-VL patients from neighborhoods in Natal, Brazil
2. Utilize IFAT to elucidate true *Anaplasma* infection from non-specific antibody binding caused by hypogammaglobinemia.

Method:

1. **Use of ELISA to Determine *Anaplamsa* Exposure Rates in Natal, Brazil**
   Indirect enzyme-linked immunoassay was performed twice for each human sera, using antigen derived from *Anaplasma* infected and uninfected HL-60 cells. The use of uninfected cells established the level of background binding in each of the sera. Sera groups included those with active VL, treated VL, asymptomatic infected/exposed blood bank donors, and blood bank endemic controls.
2. **Screen Sera with IFAT to Determine sensitivity of ELISA and likely true rate of coinfection**
   Immunofluorescence assay was done with human sera brought back to the Iowa from Natal. This assay is more specific, allowing for visualization of the binding antibodies to *Anaplasma* antigen grown in cells. True positivity is able to be differentiated from non-specific binding due to the binding patterns in an *Anaplasma* infection differing from the more uniform staining of non-specific self-biding antibodies. *Rickettsia* slides are also being used to check for possible cross-reactivity.

Results:

Of the plates analyzed using Wilcoxon Paired Sample test, paired ELISA of patients with active VL revealed that there was no statistically significant difference between the two antigens, suggesting that the high prevalence shown previously may be due to hypergammaglobulinemia. ELISA does not seem to be a viable way to analyze *Anaplasma* rates in humans, especially if they have visceral leishmaniasis.

IFAT screening is currently underway. However, initial results seem to show large amounts of non-specific binding in patients with VL. However, this method seems to be able to detect patients with *Anaplamsa* antibodies due to the presence of morula's.

Conclusion/Discussion:

The true *Anaplasma* seropositivity of Natal, Brazil seems to not be able to elucidate using this method of ELISA. However, data needs to be reanalyzed once patient demographics are received in order to address any potential biases. Additionally, IFAT should continue to be used and appears to be a way forward in determining *Anaplasma* seropositivity and its difference in the general population and those who develop VL.

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[2] Toepp, A.J., Monteiro, G.R.G., Coutinho, J.F.V. *et al.* Comorbid infections induce progression of visceral leishmaniasis. *Parasites Vectors* **12,** 54 (2019). https://doi.org/10.1186/s13071-019-3312-3

Interferon-Mediated Protection of Keratinocytes from Ebolavirus Infection

Kristina Sevcik, Wendy Maury

Background/Rationale/Introduction

Interferons have long been recognized to provide an important immune response in the human body and have been utilized in the treatment of a variety of disease conditions. Previous studies in the Maury lab seeking to harness these effects have found that mice infected with lethal doses of Ebolavirus had better survival if given prophylactic interferon gamma (IFNg), and that IFNg treatment inhibited EBOV infection of human-derived macrophages[1]. Further preliminary studies through the Maury lab recognized that EBOV is found on the skin at late stages of infection, traverses skin explants in vitro, and infects keratinocytes and fibroblasts specifically. These studies indicate that EBOV spreads through contact with skin via skin infection later in disease. From these studies, we hypothesized that interferon-stimulation of keratinocytes would provide protective effects against Ebolavirus, and that a profile of interferon-stimulated genes in keratinocytes would reveal the key factors in this response.

Purpose

Given the evidence that IFNs allow for protective effects from infection with EBOV, combined with the presumed role keratinocytes play in infection and viral spread, we sought to investigate the response of interferon-treated keratinocytes to EBOV. Additionally, we sought to elucidate the profile of interferon-stimulated genes (ISGs) in keratinocytes with the potential to further explore what genes play this critical role in immune function.

Method

Cell cultures of primary human keratinocytes were treated with one of the study interferons: IFNα, IFNβ, IFNγ, and IFNλ, of varying concentrations. They were subsequently infected with an rVSV/EBOVgp +GFP model of EBOV. Following incubation, infection levels were assessed via flow-cytometry for GFP to assess response to interferon-treatment. In parallel studies, RNA was harvested from the IFN-treated cells and controls at both 6 and 24 hours using a Qiagen RNeasy mini kit with on-column DNase. The RNA samples were sequenced and analyzed by assessing fold changes of the treatments at the various time points compared to respective control.

Results

IFNα, IFNβ, IFNγ, and IFNλ-treated keratinocytes each displayed dose-dependent protective response to EBOV infection. Upon sequencing, they were found to each share a common 88 genes that were upregulated more than 2-fold compared to controls at both 6 and 24 hours.

Conclusion/Discussion

Interferon-treatment of keratinocytes offers a protective effect against EBOV infection. This protective response is likely produced by the unique set of interferon-stimulated genes generated by each respective interferon treatment. Across treatments, 88 genes were upregulated 2-fold, indicating that these genes play a critical role in this immune response.

1. Rhein BA, Powers LS, Rogers K, et al. Interferon-γ Inhibits Ebola Virus Infection. PLoS Pathogens 2015;11(11).

Virtual and Innovative Personalized Platform for Improving Glycemic Outcomes

Student: Mala Sharma, M2

Mentor: Amy Pearlman, MD

Introduction: Type 2 diabetes is a common diagnosis, as is poor glycemic control in those diagnosed. Between 1999 and 2010, Mohammed et al. found that nearly 50% of patients with Type 2 diabetes did not meet targets for glycemic control, blood pressure, or LDL cholesterol levels. More recent data suggest that the percentage of patients meeting these goals has continued to decrease. Furthermore, high no show rates to primary care and endocrinology appointments also impair the ability to monitor treatment adherence and management of the disease, which can lead to more severe complications. No show visits result in revenue loss for the institution, as well. Despite the difficulties of managing this disease, Diabetes Self-Management Education (DSME) has been shown to improve clinical outcomes. However, due to a variety of factors such as poor reimbursement rates, lack of administrative support, and lack of transportation for patients, these programs are underutilized. Our study aims to determine which organ-specific concerns are most important to patients with poorly controlled diabetes and to determine if educating patients regarding organ-specific concerns via a virtual format can be used to improve follow up adherence and glycemic control.

Hypothesis: Understanding patient-specific priorities when it comes to organ-specific concerns will aid physicians in motivating patients to improve disease monitoring and treatment adherence. The barriers of DSME can be overcome with a virtual, personalized education program and will lead to better glycemic control and fewer no-show appointments to healthcare providers managing diabetes.

Methods: Patients with Type 2 diabetes being managed by a University of Iowa healthcare provider at least 3 months prior to enrollment with most recent HA1c of >8% are eligible to participate. A questionnaire will be administered that will ask participants to rank the following organ functions from most to least important (eyes, brain, heart, gastrointestinal, weight, kidneys, nerves, and genitals) alongside examples of complications in each system due to diabetes (blindness, memory loss, heart attack, gastroparesis, weight gain, kidney failure, neuropathy, and sexual dysfunction). Participants will be randomized into either the control or intervention group. Those in the intervention group will receive short, pre-recorded videos, articles, and quick facts related to their top ranked organ concern via text message every week for three months, in addition to their standard clinical care for diabetes management. The control group will not receive these educational messages and will continue to receive standard clinical care for diabetes management.

Results: Six months after enrollment, HA1c and rates of no-show to diabetes-related healthcare appointments will be assessed to determine efficacy of the digital educational platform in motivating treatment adherence among patients with poorly controlled type 2 diabetes.

Title: Comparison of infection rates post cesarean section with Prevena negative pressure dressing and PICO negative pressure dressing in obese women

Student: Alix Sharp
Mentors: Colleen Stockdale, MD and Abbey Hardy-Fairbanks, MD

Introduction:

Obesity in pregnant women is a worldwide occurrence that is on the rise. It is associated with close to all complications of pregnancy including congenital defects, preeclampsia, gestational diabetes, large-for-gestational age birth weight, preterm or stillbirth, gestational hypertension, suboptimal pregnancy outcomes, maternal and infant death, and sleep apnea. More cesarean sections are performed on obese women, resulting in an increase in anesthetic problems. These women are more likely to undergo cesarean sections due to increased length of labor and more difficulty in monitoring the fetus. The risk of infection, bleeding, and other complications following a cesarean section is also increased in obese women.

Negative pressure wound therapy devices suction to draw off excess fluid to promote wound healing with less risk of infection. Incision wounds in obese patients are known to be more difficult to heal. This makes these women good candidates for the study of the negative pressure wound therapy devices to learn more about post cesarean section incision infections in obese women. There are currently two devices on the market – PICO and Prevena devices. The PICO device has a small pump to suction excess wound fluid while Prevena has a silver permeated sponge to draw excess fluid.

Purpose:

The purpose of this study was to determine how the Prevena negative pressure wound therapy device compares to the PICO negative pressure wound therapy device in post cesarean section infection rates and chorioamnionitis in obese women.

Methods:

Electronic medical records for women who underwent cesarean section at the University of Iowa Hospitals and Clinics from 01/01/2018 to 01/01/2021 were reviewed. Of those, data was collected on women who had a PICO negative pressure wound therapy device and had a body mass index above 30 kg/m^2 and/or had a diagnosis of diabetes, gestational or preexisting. The data collected on these women included demographic information, comorbidities, delivery information, chorioamnionitis diagnosis, as well as pre and postpartum complications. This data from the PICO dressing group were compared to a data set that had been collected on the Prevena dressing using ___ (statistical methods).

Results:

Pending

Conclusion:

Pending

Paramedic Education: The Effects of COVID-19 on Paramedic Clinical Skills

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Abstract

Background: The COVID-19 pandemic led EMS educators to adjust curriculum delivery to ensure students continued receiving required didactic and clinical instruction while adhering to federal guidelines regarding student safety. While didactic courses were preserved with teleconferencing software, limitations on clinical experiences raised potential concerns of overall education quality. The purpose of this study was to compare 1) unit exams scores, 2) first attempt pass rates of the National Registry of Emergency Medical Technicians (NREMT) cognitive exam and 3) self-reported confidence levels in performing Advanced Life Support (ALS) skills between University of Iowa Paramedic students affected by COVID-19 curriculum changes and those not affected.

Methods: This IRB-approved, descriptive, comparison study surveyed former University of Iowa Paramedic students who had a valid email address and successfully completed the program between 2018 and 2021. The one-time, anonymous, self-report survey was available for a 3-week period and asked former students to rate their perceived confidence level in completing ALS skills the day after graduation. Data was analyzed using descriptive statistics, Fisher's Exact test, Welch's t-tests and non-parametric tests when appropriate.

Results: Out of 8 unit exams and 1 final, only two exams showed significant differences of median exams scores between controls and COVID-affected groups (Intro: 90% and 88%, respectively; p=0.035, Trauma: 87% and 91%, respectively; p=0.017). There was no statistically significant difference between control and COVID-affected first-time NREMT pass rates (97% and 96%, respectively; p=1.000). Among the 59 eligible participants, 18 (30.5%) completed the survey (7 control, 11 COVID-affected) and no statistically significant difference was reported in confidence levels in clinical skills (categories of airway, cardiology, medication administration, IV initiation/monitoring, and miscellaneous).

Conclusion: This study indicates that COVID-19 curricular changes did not affect students' ability to pass written certification exams or students' confidence in their clinical skills, suggesting potential strategies for training programs to employ when facing distanced learning constraints. Limitations of the study include the small sample size from one Midwestern paramedic program and potential selection bias. Future research is warranted with larger samples to better understand how the use of the virtual classroom affects paramedic student education.

Assessing the role of SOD2 in the maintenance of corneal-endothelial cell density

Student: Bryce Shonka
PI: Mark Greiner, MD
Collaborators: Jessica Skeie, PhD, Hanna Shevalye, and Tim Eggleston

Abstract

Introduction: Cornel endothelial cells (CECs) are post-mitotic and have limited ability to regenerate. With age, CEC death requires remaining cells to enlarge and cover the gaps in the corneal endothelium.[1] CEC loss is clinically significant as CECs regulate corneal hydration through barrier and pump functions, whereby the passive leakage of fluid through intercellular tight junctions is counterbalanced by Na+/K+-ATPase-mediated pump function.[2] This process requires intact bioenergetic production and substrate utilization.[3] For this reason, CEC loss can result in vision loss through corneal edema and haze.[2] Various research has implicated oxidative stress and mitochondrial dysfunction in the loss of CECs in diseases such as Fuchs endothelial cell dystrophy (FECD) and during hypothermic storage of donor corneal tissue prior to corneal transplantation.[4-9]

Manganese superoxide dismutase (MnSOD) is a mitochondrial enzyme encoded by the nuclear *SOD2* gene,[10] and is a key antioxidant enzyme that reduces superoxide radicals ($O_2^{\bullet-}$) generated by mitochondria to hydrogen peroxide (H_2O_2),[7, 8] thereby preventing the accumulation of reactive oxygen species (ROS). Recently, MnSOD has been shown to be an important antioxidant enzyme for CEC function. MnSOD deficiency has been documented in FECD.[7, 8] Elevated levels of ROS lead to further oxidative damage, cell death, and in the case of FECD, disease progression. Despite this, there is no research evaluating a direct link between MnSOD deficiency and oxidative stress and altered mitochondrial function in CECs. For this reason, we sought to develop a line of cultured *SOD2* knockout (KO) CECs to assess the extent to which MnSOD affects these cellular processes in CECs.

Methods: Utilizing immortalized CECs (B4G12 cell line), *SOD2*-KO CECs were created using CRISPR/Cas9 (OriGene). Cutting of *SOD2* was confirmed via GFP expression. Superoxide was measured using MitoROS-580 assay. Mitochondrial membrane potential was assessed using JC-10 assay. Mitochondrial bioenergetics were assayed using Seahorse XF96 extracellular flux analysis. O_2 consumption was measured and used to calculate ATP-associated oxygen consumption, proton leak, maximal respiration, spare respiratory capacity, and nonmitochondrial respiration. All data were normalized to cell count and analyzed using a one-way ANOVA test.

Results: In assessing the difference between B4G12 cells and *SOD2-KO* cells, we found significant changes in superoxide levels and various markers of mitochondrial bioenergetics. Mean MitoROS levels of 0.5391 and 0.5348 for G1 and G2, respectively, were significantly higher ($p<0.0001$) than the levels measured for B4G12, which had a mean of 0.2978. In assessing mitochondrial bioenergetics, basal respiration was significantly decreased in both the G1 and G2 population ($p<0.0001$ and $p<0.05$). Additionally, ATP production-coupled respiration was significantly decreased in both the G1 and G2 *SOD2*-KO populations ($p<0.0001$ and $p<0.05$). Significant decreases in maximal respiration ($p<0.0001$) and spare respiratory capacity ($p=0.0002$) were only seen in the G1 population.

Conclusions: Our preliminary results indicate that lack of *SOD2* function results in increased superoxide levels in CECs as well as decreased basal respiration, maximal respiration, spare respiratory capacity, and ATP production-coupled respiration. These results are consistent with our hypothesis that lack of *SOD2* function leads to oxidative stress and bioenergetic changes in the mitochondria of CECs. In the future, we plan to continue to culture both populations of knockout cells and to begin puromycin selection to develop a stable line of *SOD2*-KO cells, at which point, superoxide level, mitochondrial membrane potential, and mitochondrial bioenergetics will be reanalyzed. We will also assess whether or not GC4419 (an MnSOD mimetic; Galera Therapeutics) can rescue the negative phenotypic changes observed in CECs lacking *SOD2*, as multiple studies have shown that GC4419 is effective in protecting cells against oxidative damage in the absence of MnSOD.[10, 11]

Title: Development of *Shigella* spp. Soil Recovery Protocol
Student: Megan Sinik
Mentor: Dr. Kelly Baker, Department of Occupational and Environmental Health
Other Collaborators: Alexis Kapanka, Department of Occupational and Environmental Health

Background and Rationale: Globally, one in ten deaths during the first five years of life are due to diarrheal disease, and the burden falls disproportionately on sub-Saharan African and south Asian countries. The Global Enteric Multicenter Study was undertaken to analyze the etiology and populations-based burden of diarrheal disease in children within these afflicted regions. They found the four pathogens most significantly associated with moderate-to-severe diarrhea in children aged 0-24 months in all regions were rotavirus, *Cryptosporidium*, *Shigella* spp. and heat-stable Enterotoxigenic *Escherichia coli* (ST-ETEC). Of these pathogens *Shigella* spp. had the highest attributable fraction for childhood diarrhea across all age strata and study sites. Additionally, the more recent Safe Start Trial revealed that the prevalence of *Shigella* spp. doubles between six and nine months of age, from 4% to 8.2%. Thus, research has demonstrated Shigella infections are both prevalent and associated with disease within affected areas. However, more research is needed to determine how *Shigella* spp. are transmitted from the environment to the child, whether that be through soil, animals, water, caretakers, etc. so strategies can be developed to prevent infection. The aim of this project is to develop a protocol for detection and quantification of *Shigella* spp. from soil, to allow further elucidation of the pathways between environment, child, and disease presentation. Three specific variables will be tested throughout the development of the protocol: time for pre-enrichment, Stomacher or hand-mash manipulation, and MacConkey or XLD agar for plating.

Method: Since samples will need to be pre-enriched at warm conditions to optimize bacteria recovery, we chose to utilize the Most Probable Number method for gaining a quantitative estimation of contamination based upon presence and absence data. In practice, dilutions would be made of contaminated soil, pre-enriched, and then plated and read 24 hours later to determine at what dilution level the bacterial detection disappears. For protocol validation, autoclaved soil was spiked with five dilutions of Shigella liquid culture, to replicate contaminated soils at distinct bacteria colony-forming unit/gram ratios. The soil was added to Stomacher bags with Buffered Peptone Water, and spiked with 10^4, 10^3, 10^2, 10^1, or 10^0 concentrations of *Shigella* spp. liquid culture. These bags were sealed and then pre-enriched for 3-5 hours at 37 C. Two different methods of recovery were used to compare whether the Stomacher machine would improve soil recovery over hand-mashing. One bag for each concentration level was shaken and then hand manipulated for mixing, and the other was put in the Stomacher machine. Duplicates were then plated, followed by a 24-hour incubation at 37 C. After this time, plates were verified for phenotype morphology, and colonies were counted to determine presence/absence data.

Results and Conclusion: Given that *S. sonnei* is commonly associated with foodborne outbreaks and transmission, and generally higher environmental stability, we found it easier to consistently recover than *S. flexneri*. We found a 5-hour pre-enrichment time, in comparison to 3 hour and 4 hours, allowed recovery of lower concentrations more consistently without overgrowth. There was no measurable difference between recovery capabilities of the Stomacher and hand-mash manipulation to warrant the purchase of a Stomacher machine. The MacConkey allowed for more consistently detected growth at 10^1 cfu/gram.

Conclusion: We were able to address a gap in the current literature through the development of a new protocol for quantifying Shigella spp. from soil for exposure assessment. The main limitation of the protocol was variability between duplicates of the same concentration. In the future, filtered bags should be used to plate a more homogenous sample. Additionally, more research should be done on XLD and MacConkey use in the field, as XLD would be preferred given its more selective nature.

Relationship Between Anesthetic Type and Fetal Outcomes Following Emergent (Grade 3) Cesarean Delivery

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Introduction: The current classification system for urgency of cesarean delivery at UIHC labor and delivery unit spans grades 0, 1, 2, and 3. The grading system is based on published guidelines from the Royal College of Obstetricians and Gynecologists in the United Kingdom. The goal of a uniform grading system ensures all members of the team have a common understanding of the degree of urgency of the procedure for that specific patient. The grade 3 cesarean delivery is the presence of an immediate threat to the life of the woman or fetus. Therefore, a short decision-to-delivery interval is targeted. In cases of fetal compromise during labor, obstetricians may request general anesthesia to facilitate immediate delivery of the baby via cesarean section even in women with a functional labor epidural analgesia. It is assumed that the time to onset of epidural anesthesia will delay delivery and further compromise the fetus. However, the available data is inconclusive regarding this assertion and does not consider the added risks of performing a general anesthetic in a pregnant woman compared to the general population. These risks include difficult airway management, aspiration, and intraoperative awareness.

Purpose: The goal of this study is to evaluate the relationship between the choice of anesthetic for grade 3 cesarean delivery and fetal outcomes. The primary outcome measure assessed is the fetal umbilical cord arterial pH. Secondary outcome measures include fetal umbilical cord arterial base deficit, 5-minute APGAR scores, and neonatal intensive care unit (NICU) admission. We hypothesized that the use of epidural anesthesia for intrapartum grade 3 cesarean delivery in women with functional labor epidural catheters is not associated with poorer neonatal outcomes.

Methods: This study was a retrospective chart review of all urgent cesarean deliveries performed at UIHC from 2016 to 2021. All deliveries labeled emergent were pooled and sorted to identify grade 3 deliveries. Inclusion criteria: grade 3 cesarean section, labor epidural analgesia. Exclusion criteria: multiple gestation, maternal indication for CD, and epidural converted to GA prior to delivery of neonate. Data extracted from the medical records included maternal demographics, intraoperative vital signs, anesthesia techniques and drugs administered, Apgar scores, umbilical arterial pH, base deficit, and neonate admission to the intensive care unit. Maternal characteristics, intraoperative variables, and anesthetic techniques were tested for association with umbilical cord arterial pH. A multivariate regression analysis was then performed to identify covariables associated with umbilical cord arterial pH.

Results: In total, 193 patients were analyzed for the study receiving either regional anesthesia (n = 117) or GA (n = 76). Eight patients were excluded from the study due to insufficient data or exclusion criteria. Univariate analysis showed no association between umbilical cord arterial pH and anesthesia technique ($p = 0.51$) but did show an association with minimum systolic blood pressure (SBP) ($p < 0.001$). It also showed an association between NICU admission and anesthesia technique ($p = 0.02$). On multivariate analysis only the minimum SBP was predictive of a low umbilical cord arterial pH ($p < 0.001$, $\beta = 0.002$). Lastly, birth weight was predictive of NICU admission ($p = <0.001$, $\beta = -2.01$).

Conclusions: Our results indicate regional anesthesia for grade 3 cesarean delivery is not associated with poorer neonatal outcomes. Although a larger sample size may be required to confirm these findings, it does suggest that epidural anesthesia should be considered for grade 3 cesarean deliveries.

Correlating Mental Health Disorders with Bleeding Rates in Hemophilia

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PURPOSE: Hemophilia is a genetic bleeding disorder caused by a mutation in clotting factors, factor VIII (hemophilia A) or factor IX (hemophilia B) required for hemostasis. People with hemophilia (PWH) must take preventative measures to control their predisposition to hemorrhage, including pharmacologic treatment (factor VIII or IX concentrate). Our recently published meta-analysis identified significantly higher rates of depression, anxiety, and attention deficit hyperactivity disorder (ADHD). Based on our meta-analysis, PWH are nearly 2.5 times more likely to experience depression, 1.75 times more likely to experience anxiety, and 3.5 times more likely to experience ADHD. Our study aims to evaluate the impact of mental health disease on adult and pediatric patients with hemophilia. Our aims were to quantify and evaluate the number of PWH with MHD including depression, anxiety and/or ADHD, as well as the number of medications used by each population. There is a critical need to better understand the relationship between bleeding control and mental health status, as this is an important domain in overall quality of life.

METHODS: We conducted a retrospective chart review of hemophilia patients and control patients without hematologic comorbidities. Hemophilia subjects were obtained though the Iowa Hemophilia and Thrombosis Center database and control subjects were obtained using TriNetX. Using REDCap, we built a data collection base and patient demographic data was auto-populated using the HEDI database. Variables analyzed included type of hemophilia, mental health diseases, co-morbidities, emergency room visits related to MHD, and medications. Two independent reviewers performed chart review and data entry. Statistical analyzed was performed using GraphPad Prism.

RESULTS: We found that PWH demonstrated higher rates of total MHD. PWH also had more emergency room visits related to MHD. We plan to analyze the annualized bleeding rate (ABR) in hemophilia subjects with and without MHD. We anticipate the ABR to be increased in patients with MHD. The number of medications for MHD had no statistical difference between PWH and controls.

CONCLUSIONS: Our previous meta-analysis demonstrated higher rates of MHD (depression, anxiety, and ADHD) in PWH compared to the general population. Our current study indicates PWH have more ER visits related to MHD indicating that hemophilia exaggerates the negative effects of MHD. We anticipate that PWH who experienced MHD will also have higher bleeding rates compared to those without MHD. To date, our data suggest MHD correlates with worse outcomes of hemophilia.

Characterization of the efficiency of DAF in regulating nephritic factor stabilized complement convertases in patients with C3 Glomerulopathy

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Background: Nephritic factors (Nefs) are acquired immunoglobulins that dysregulate the complement system by binding to and stabilizing the critical central enzymatic complexes known as the C3 and C5 convertases. Normally, these convertases are transient serine protease complexes responsible for cleaving complement C3 into the active form C3b, and the anaphylatoxin C3a. Stabilization of these complexes by Nefs allow them to persist in the serum and prolong complement activation. Stabilization drives C3 deposition onto glomerular tissue – the hallmark of the renal disease C3 Glomerulopathy (C3G). Ongoing inflammation incites scarring and ultimately end-stage renal disease (ESRD) in the majority of affected individuals. Several naturally occurring regulators (CR1, FH, DAF, MCP) are responsible for the homeostatic control and deactivation of these enzyme complexes under normal conditions, but little is known about the efficacy of these regulators when Nefs are present in patients with C3G. Previous work by the Molecular Otolaryngology and Renal Research Laboratories (MORL) identified a patient (MPGN2-441) from a cohort of 25 nephritic factor-positive serum samples whose Nef-stabilized convertases were completely de-stabilized (regulated) by DAF once the acute phase of disease had passed. This finding suggested that Nef function and response to regulators changes over time. The phenomena of a change in Nef character being associated with an improved clinical phenotype has not been reported in the literature. If present in a larger population, the identification of this phenomena may have prognostic import.

Purpose: The goal of this study was to characterize the capacity of DAF to regulate C3Nef-stabilized convertase complexes in a larger cohort of C3G patients. We predicted that other C3Nef-stabilized convertases would be similarly regulated by DAF, and that this, along with titer, should be considered as a feature of nephritic factor pathogenicity.

Methods: Purified IgG from 18 Nef-positive patients at three separate time points each were characterized using a surface plasmon resonance (SPR)-based nephritic factor assay (Biacore X100) previously adapted by MORL.[1] In brief, Nef-stabilized convertase was created by injecting Factor B, Factor D, and IgG over C3b stabilized on a CM5 chip. The nascent Nef-convertase complex was then exposed to a DAF injection and decay of the complex was measured using custom report points provided by Biacore BiaAnalysis software. Quantitative analysis of the report points determined the sensitivity of C3Nef-stabilized convertase complexes to DAF-mediated decay.

Results: In our analysis of 18 patients, 10 (55.6%) showed significant increases in DAF sensitivity over time. No patient in our cohort matched the proband's phenotype in terms of complete regulation of C3Nef-stabilized convertases by DAF. Although not the focus of the study, we observed that the stabilizing activity conferred by the Nefs that improved in DAF sensitivity generally decreased over time (70%, n = 7).

Conclusion: More than half of subjects trended toward a more regulated state (DAF sensitive state) over time. This, combined with a relative reduction in Nef stabilizing activity over time, suggests that multiple Nef characteristics are likely to be involved in the pathogenicity of these acquired proteins. Whether these changes in Nef character are correlated with a change in clinical outcome is under investigation. The limitations of our study include variability of measures as compared to disease onset, and the short follow up time in many subjects.

Reference:

1. Paixão-Cavalcante D, López-Trascasa M, Skattum L, et al. Sensitive and specific assays for C3 nephritic factors clarify mechanisms underlying complement dysregulation. *Kidney Int*. 2012;82(10):1084-1092. doi:10.1038/ki.2012.250

Title: Effectiveness of Early Improvement as a Predictor of Clinical Outcomes in 10 Hz rTMS and iTBS Treatment for Major Depressive Disorder

Authors: Nathen A. Spitz, Patrick Ten Eyck, Chaorong Wu, Krystal Nizar, Aaron Boes, **Nicholas T. Trapp**

Background and Purpose:
Few studies exist directly comparing the ability to predict depression treatment response between intermittent theta-burst stimulation (iTBS) and 10 Hz repetitive transcranial magnetic stimulation (rTMS) in the treatment of major depressive disorder (MDD). Our study sought to test the hypothesis that early clinical improvement could predict ultimate treatment response in both iTBS and 10 Hz rTMS patient groups, and that there would not be significant differences between the non-inferior therapy modalities across a variety of improvement criteria.

Methods:
Retrospective analyses of 105 participants with MDD that received 10 Hz rTMS (n=68) and iTBS (n=37) investigated clinical response to treatment using PHQ-9 (Patient Health Questionnaire 9) scores. As our primary analysis, percent changes from baseline to treatment 10 (t_{10}) as well as final treatment (t_f) were used to calculate confusion matrices including sensitivity, specificity, and negative predictive value (NPV) to assess predictive capability of early treatment improvement on final treatment response. Treatment non-response was defined as <50% according to the literature, and population, data-driven response criteria established via kernel density estimation (KDE) was defined as <40% for 10 Hz and <45% for iTBS. Comparisons were made using two-tailed proportional difference tests.

Results:
Participants with <20% improvement at t_{10} had a NPV for 10 Hz rTMS and iTBS at 80.0% and 65.0%, respectively: $z = 1.23$, $p = 0.22$. When the criterion was decreased to <10% improvement, the NPV for 10 Hz and iTBS decreased to 62.9% and 50.0%: $z = 0.93$, $p = 0.35$. Lastly, at <0% improvement the NPV for 10 Hz and iTBS decreased further to 45.7% and 35.0%: $z = 0.77$, $p = 0.44$. Subsequently, using the KDE data-driven, population defined criteria for response for 10 Hz rTMS at >40% and >45% iTBS, using the same parameters, we determined the NPV at the same three cut-offs. At <20% improvement at t_{10}, the NPV for 10 Hz rTMS and iTBS were 83.9% and 68.4%, respectively: $z = 1.28$, $p = 0.20$. Then at <10% improvement the NPV for 10 Hz and iTBS decreased to 67.7% and 52.6%: $z = 1.07$, $p = 0.28$. Lastly, at <0% improvement the NPV for 10 Hz and iTBS decreased further to 48.4% and 36.8%: $z = 0.80$, $p = 0.44$.

Conclusion:
Patients who fail to achieve at least 20% improvement by session 10 in both 10 Hz rTMS and iTBS groups have ~70% chance of non-response to full courses of treatment. With no statistically significant differences between the predictive capacities of the two modalities across an array of improvement criteria, identifying patients at risk for non-response to treatment affords psychiatrists greater opportunity to adapt treatment strategies to optimize outcomes. This study was funded by the Department of Psychiatry at the University of Iowa and University of Iowa Clinical and Translational Science Award.

Title: IRG1 potentially alters CMP-001 treatment anti-tumor microenvironment
Student: Yutao Su
Mentor: Dr. Carlos Chan

Background:
Peritoneal carcinomatosis (PC) is a common and deadly metastatic spread from gastrointestinal and pancreaticobiliary cancers. Between 2009 and 2015, metastatic disease was present in 18% of hepatobiliary, 21% of colorectal and 52% of pancreatic cancer patients at the time of diagnosis. Five-year survival of patients with metastatic disease remains poor with 2% in hepatobiliary cancers, 3% in pancreatic cancers and 14% in colorectal cancers. While some patients can undergo aggressive surgery and systemic therapy, many patients are not candidates for any treatment. Due to the aggressive nature of this disease and lack of effective therapy, pursuit of novel therapeutic approaches is essential to battle with this deadly disease.

We have recently shown CMP-001, a virus-like particle containing TLR9 agonist CpG-A DNA, triggers a type I interferon release from plasmacytoid dendritic cells, leading to a cascade of anti-cancer immune response by converting a “cold” to “hot” immune tumor micro environment (TME) in the peritoneal cavity. However, response to CMP-001 also includes upregulation of genes such as IDO and IRG1 that negatively regulate the immune response. In particular, IRG1 is an enzyme that converts cis-aconitate to itaconic acid which then activates pathways that include ATF3 and NRF2 that are anti-inflammatory.

Hypothesis:
While CMP-001 has been effective on its own in reducing tumor growth and increasing immune cell infiltration, we wanted to determine how the IRG1 pathway might influence the immune response to CMP-001. We hypothesized that treating cells with the IRG1 downstream product (itaconic acid) would suppress the CMP-001 response. Similarly, IRG1 knockout was predicted to improve immune response to CMP-001 treatments.

Methods:
To determine whether overactive IRG1 pathway could dampen the response to CMP-001, we harvested ascites fluid from mice exposed to PANC1 (a mouse pancreatic cell line), stimulated with CMP-001, and treated with 4-octyl-itaconic acid, an alternative form of itaconate that more easily penetrates cells. Cells were then assessed for expression of various markers of inflammation including IP10, TNF-alpha, and IL-6 through qPCR. We also performed a survival study comparing IRG1 knockout mice with WT mice both treated with PANC1 cells and CMP-001.

Results:
We found that levels of IP10 were drastically reduced in mice treated with both 4-octyl-itaconic acid and CMP-001 compared to CMP-001 alone, almost down to baseline. We also found that IRG1 knockout mice survived for longer when given CMP-001 than did wild type mice.

Conclusion:
Our results indicate that the IRG1 pathway interacts with the CMP-001 response. IRG1 may potentially improve the CMP-001 created anti-tumor microenvironment.

Identification of phase amplitude coupling in the human hippocampus during episodic memory processing

Student: Danial Syed M4
Mentor: Dr. Matthew Howard, Neurosurgery

Rodent models of episodic memory posit that phase-amplitude coupling (PAC) is necessary for the spatial organization of neuronal ensembles critical for associative encoding. Here, we used a bispectral analysis to document PAC occurrence in neurosurgical patients performing a free recall memory task. Local field potentials recorded from intracranial electrodes placed for seizure localization offer a unique opportunity to record high fidelity signals from the brain to study memory (1,2,3). Memory encoding is strongly correlated with PAC interactions, specifically coupling between theta and high gamma activity in the rodent hippocampus. Conventional measures of PAC are windowed bispectral estimators, amounting to narrow smoothings of the bispectrum (4). They are "blind" in that a statistic (such as a modulation index) is calculated using pre-established frequency bands. PAC that matches the standardized bands will be detected, but a broad representation of PAC incidence in the signal is not obtained; a direct analysis of the bispectrum can be used to observe the full picture. We used a visual inspection of the bispectrum to document PAC instances in the human hippocampus. We were particularly interested in documenting the dominant frequency of the slow oscillation, as well as anterior/posterior hippocampal differences in PAC. These findings were aggregated to identify the distribution of PAC frequency bands for each region. Bispectral analysis results were regressed onto trial windows to identify PAC correlated with successful memory encoding. 1709 PAC instances were visually identified over 247 electrodes. 429 PAC instances were found to be correlated with successful memory encoding. The anterior and posterior hippocampi both exhibited a 1-3 hz predominance of the PAC slow oscillation. The posterior hippocampus exhibited a significance fast oscillation predominance in the 80-100 hz range. Additionally, the posterior hippocampus demonstrated significantly increased bispectral activation during both memory encoding and retrieval. Overall, our PAC distribution analysis allows an increased understanding of neuronal signaling frequencies relevant to memory. We found the predominant slow oscillation to be slower in humans relative to rodent models. Finally, we identified regional differences in hippocampal PAC which suggest that the posterior hippocampus plays an especially important role in episodic memory.

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Dosimetric comparison of a JEI-Deep Logismos algorithm to physician-drawn contours for radiation treatment of laryngeal and oropharyngeal cancers

Student: Tutku Tazegul, M2 Mentor: Carryn Anderson, MD

Introduction/Purpose

Despite the frequent use of radiation therapy in the treatment of laryngeal and oropharyngeal squamous cell carcinoma (SCC), manual delineation of targets is complex and recognized as a source of inconsistency. Potential solutions for this inconsistency include using enhanced quantitative imaging and algorithmic determination of targets. In this study, we evaluated the difference in radiation therapy plans for laryngeal and oropharyngeal SCC patients, comparing physician-drawn contours to just-enough-interaction (JEI)-Deep Logismos, a semi-automated tumor delineation algorithm. The specific aim of this project was to evaluate whether a JEI-Deep Logismos algorithm-driven head and neck radiation treatment plan maintains tumor control while decreasing dose to normal tissues when compared to standard, manual contouring and to evaluate consistency amongst users comparing the JEI approach to the standard.

Methods

Patients treated with curative-intent chemoradiation for laryngeal and oropharyngeal SCC were retrospectively analyzed. Each patient previously had PET/CT imaging for simulation of radiation therapy treatment, manual contouring performed by an expert head and neck radiation oncologist, and radiation dose planning performed in the software Pinnacle. The PET/CT images of each patient were uploaded into 3D Slicer, a computer program with the JEI-Deep Logismos algorithm, to generate new three-dimensional tumor delineations. The JEI contours were created separately by an expert head-and-neck radiation oncologist and a novice user to assess the software's ease and consistency of use across different expertise levels. Both users had clinical information and previous procedural reports, as well CT and MRI imaging, available as additional resources to aid in semi-automatic contouring. The JEI contours were then exported to Pinnacle and modified for better tumor coverage and avoidance of normal tissues; original and modified contours were saved separately and both included for analysis. New radiation therapy treatment plans using the JEI contours were then generated by a dosimetrist. Tumor delineation volumes, clinical target volumes, and dosimetric information for both target- and normal-tissues were compared across all four plans.

Results

For all patients in this study, original gross tumor volumes (GTVs) were different in size when compared to the GTV_{JEI} contours. This indicates that the JEI software alone did not adequately detect gross tumor when compared to the original manual contours utilizing CT, PET, MRI and clinical examination information. The modified GTV_{JEI} contours ($GTV_{JEI,mod}$), however, were similar in size and coverage to the original contours. Notably, GTV_{JEI} and $GTV_{JEI,novice}$ were remarkably similar, indicating high consistency of the JEI algorithm across different expertise levels. Clinical target volumes varied in size and coverage, likely due to elective coverage of local nodal disease in the original and manual JEI plans. Of note, the $CTV5600_{JEI,auto}$ and $CTV5600_{JEI,novice}$ plans show similarly sized volumes, again highlighting the consistency of the method. Dosimetric comparison of three select tissues, (the spinal cord maximum dose, pharynx mean dose, and contralateral parotid mean dose), showed that the JEI method in all cases provided equivalent or reduced dose when compared to the original, manual plan. This was true for plans created using contours from both expert and novice users. Select gross tumor and clinical target volumes, and normal tissue doses, are shown in the table below.

	Volume (cm3)											
Research Identifier	Original GTV	GTVjei	GTVjei mod	GTVjei novice	Original CTV7000	CTV7000jei novice	Original CTV6300	CTV6300jei novice	Original CTV5600	CTV5600jei auto	CTV5600jei man	CTV5600jei novice
1	44.6394	54.7429	59.1787	54.7429	133.773	77.1525	80.8165	144.528	77.4766	325.885	286.739	295.735
2	6.18159	7.61618	6.28656	7.61618	27.4137	18.8184	52.7321	36.3716	340.483	97.6167	166.84	98.1792
3	76.2646	94.0296	94.0296	95.5759	170.791	225.444	333.624	376.802	45.7376	628.456	447.635	625.481
4	53.18	42.4967	52.8661	45.1323	181.964	87.7271	108.776	139.218	64.2787	346.732	266.004	265.86
5	57.6399	26.1143	57.9334	25.4302	90.2123	61.0512	274.921	125.835	113.936	327.37	201.531	326.11
	Dose (cGy)											
	Spinal cord max				Pharynx mean				Contralateral parotid mean			
Research Identifier	Original Plan	JEI auto plan	JEI manual plan	JEI novice plan	Original Plan	JEI auto plan	JEI manual plan	JEI novice plan	Original Plan	JEI auto plan	JEI manual plan	JEI novice plan
1	4281.7	4389.8	4226.2	4308.1	4934.8	4634.5	4189.4	4733.5	2482.7	900.1	868.2	581.4
2	4191.4	1552.6	1616.4	1490.2	5008	1229	1683	1216.8	699	78.5	110.8	74.6
3	3712.6	3862.7	3837.6	3912.4	4499.4	4748.7	4139.9	4443.6	2473.3	2601.6	1945.1	2649.8
4	4349.5	4282.6	3734.2	4325	4899	3080.1	3068.4	3282.6	1777.7	535.5	527.8	536
5	3994.7	4023.4	3874.6	4125	5118.6	4783.8	4648.1	4908.7	1672.2	513.2	507.7	294.6

Conclusion

A primary concern in radiation treatment of head and neck squamous cell carcinoma is the balance between overdosing, which can lead to tissue toxicity and numerous long-term sequalae, and underdosing, which can lead to tumor recurrence. Our study demonstrates that the algorithmic JEI-Deep Logismos method can improve the consistency of target delineation for laryngeal and oropharyngeal SCC and may provide equivalent or decreased dose to surrounding normal tissue. For adequate disease coverage, manual modification of the JEI contours may be needed. This method will be further explored with a larger cohort of patients.

Quantifying ankle arthritis using a 3D Hounsfield Unit (HU) weight-bearing computed tomography (WBCT) algorithm

Student: Tutku Tazegul, M2 Mentor: Cesar de Cesar Netto, MD, PhD

Background: Treatment of ankle osteoarthritis (AO) varies depending on the severity and distribution of the degeneration. Staging is usually based on subjective analysis of conventional two-dimensional (2D) radiographic evaluation, with reported questionable reliability. The purpose of this study was to develop and describe a novel software-based three-dimensional (3D) Hounsfield Unit algorithm to objectively quantify AO using weight-bearing computed tomography (WBCT) images. Our hypothesis was that the developed 3D HU algorithm would objectively demonstrate significant differences in joint space width between healthy controls, and AO patients.

Methods: In this IRB-Approved case-control study, we analyzed 20 patients with AO and 20 healthy controls that underwent WBCT of the foot and ankle. Conventional 2D radiographs of the AO and control ankles were graded using the standard subjective Kellgren-Lawrence (KL) classification system by consensus of two fellowship-trained orthopedic foot and ankle surgeons. For each ankle, a 20x20x20mm cubic volume of interest (Figure 1) was defined and centered in the tibiotalar joint space. Within the 3D cube, four linear projections perpendicular to the articular surface of the distal tibia were selected to sample the entire HU distribution within that line (Figure 2). Each line collected image intensity data across the transition of distal tibial cancellous and subchondral bone, the joint space, and talar subchondral and cancellous bone, in that order (Figure 2). The HU intensity profiles were then recorded, and graphical plots were generated for each line (Figure 2). These plots were used to calculate the joint space width (JSW) and contrast. JSW was defined as the distance between the subchondral bone of the distal tibia and talar dome, indicated in the plots by the two points with maximum HU intensity values (peaks). Contrast, the ability to distinguish between differences in image intensity, was calculated as $(I_{max,avg} - I_{min})/(I_{max,avg} + I_{min}) * 100$, where $I_{max,avg}$ is the average of the two maximum intensity points (subchondral bone), and I_{min} is the minimum intensity (joint space). JSW and contrast were compared between AO and control ankles. Continuous data was assessed by the Shapiro-Wilk test for normality and categorical/ordinal data were described in percentages. Comparisons between AO and control patients were performed using paired t-tests or paired Wilcoxon. Significance was considered for p-values <0.05.

Results: AO and control groups were demographically similar in sex and body mass index, but not age. KL classifications were as follows: 12 patients - grade 0, nine - grade 1, nine - grade 2, seven - grade 4, and three - grade 4. All control patients were graded as KL 0 or 1. All AO patients were graded as KL 2, 3, or 4, except for one KL 1. Average JSW was 3.89mm [95%CI: 3.12-3.77] for control and 3.44mm [3.57-4.22] for AO, with no significant difference based on arthritis status alone. Average contrast was significantly different with 62.81 [56.82-78.79] for control and 72.88 [66.90-78.87] for AO (p=0.02). When stratified by KL, the average JSW was 3.75mm [3.39-4.11] for KL 0, 4.03mm [3.61-4.45] for KL 1, 4.55mm [4.13-4.97] for KL 2, 2.62mm [2.14-3.10] for KL 3, and 2.07mm [1.34-2.80] for KL 4. Results were significant for all pairs except KL 0 vs 1, KL 1 vs 2, KL 0 vs 2, and KL 3 vs 4. Contrast displayed a similar pattern of significance. Of note, multiple projections in the severe AO cases (KL 3 and 4) had JSW and contrast values of 0 due to complete joint space loss (Figure 3).

Conclusions: In this case-control study we developed a novel 3D HU software-based algorithm to quantitatively assess the severity of AO. We found significantly decreased average contrast but not JSW when comparing AO patients to healthy controls. Significant difference was also noted when comparing patients with mild (KL 1-2) and severe AO (KL 3-4). Our hope is that this novel AO grading algorithm can represent a more accurate imaging tool to stage AO in different areas of the joint, allowing assessment of progression of joint degeneration and potentially serving as base for a more robust and precise AO classification system.

Figure 1

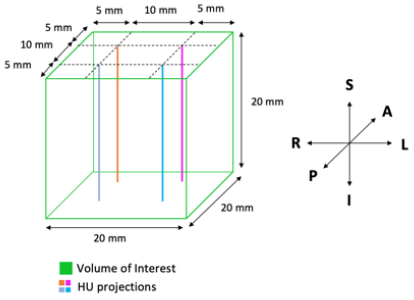


Figure 2

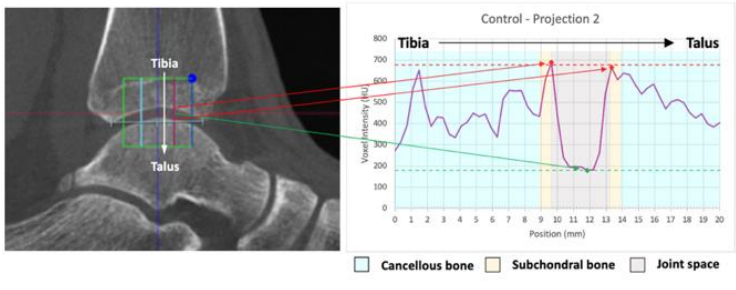
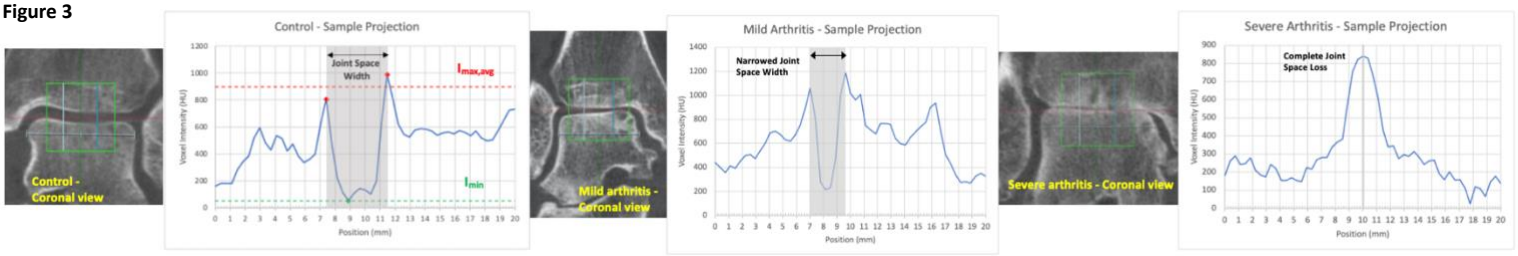


Figure 3



Maternal Characteristics in a Prospective Study on the Impact of Depression on Infant Heart Development

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BACKGROUND: More than 18% of women experience depression while pregnant and approximately 10% of pregnant women take selective serotonin reuptake inhibitors (SSRIs). Depression has been associated with adverse pregnancy outcomes including premature birth, restricted intrauterine growth, and low birth weight. In addition to these issues, SSRI use during pregnancy is linked to an increased risk of congenital heart disease and persistent pulmonary hypertension. Data related to the cardiovascular outcomes of infants born to depressed mothers is lacking. To increase clarity regarding the impact of maternal depression on infant cardiac outcomes, we aim to execute a prospective study in which we examine outcomes for depressed pregnant women treated with either SSRI therapy or psychotherapy, compared to outcomes for non-depressed pregnant women.

PURPOSE: Describe the demographics and mental health status of currently enrolled expectant mothers as part of a preliminary data review.

METHODS: Our study was approved by the University of Iowa Institutional Review Board, and subjects were recruited from self-referral, obstetric clinics, and the Women's Wellness & Counseling Service. Enrolled pregnant women aged 18-45 years who met inclusion criteria completed validated interviews or surveys every 4 weeks to assess mental health including: 1) baseline Structured Clinical Interview for DSM 5 (SCID) disorders and 2) Hamilton Depression Rating Scale (HDRS), Beck Depression Inventory (BDI), and Generalized Anxiety Disorder 7 (GAD-7) scale surveys. Subjects also reported the impact of the COVID-19 pandemic on their overall wellbeing. Women were classified as depressed based upon SCID criteria for current Major Depressive Disorder (MDD) or past MDD being actively treated.

RESULTS: Fourteen women were categorized as controls and 7 were categorized as depressed (4 on SSRI medication, 3 in the intention-to-treat psychotherapy group). There were no significant demographic differences between these two groups (marital status, education level, employment, maternal co-morbidities or other history with cardiovascular conditions); however, as expected, there were differences in the HDRS (Control 2.5 ± 3.6, Depressed 10.2 ± 5.1, $p < 0.01$), GAD-7 (Control 1.5 ± 3, Depressed 8.0 ± 4.6, $p < 0.01$), and BDI (Control 3.0 ± 4.4, Depressed 16.6 ± 8.9, $p < 0.01$) scores between groups. There were also differences in the Covid-19 survey responses with the depressed group reporting less social support ($p= 0.04$) and worse mental health during the pandemic ($p= 0.04$). The only difference between the SSRI and intention-to-treat psychotherapy group was the BDI score (SSRI 12.2 ± 7.5, Psychotherapy 22 ± 10.2, $p=0.01$).

CONCLUSION: Our preliminary data show no demographic differences between depressed and non-depressed women that could confound fetal development. Our data demonstrate similar levels of depression and anxiety in the depressed groups and support the use of the SCID as the gold standard for identifying depression. We anticipate that this study will be beneficial in evaluating the role of maternal depression and treatment effects on infant cardiovascular development.

Improvement in surgical stabilization of critical abdominal injuries prior to transfer: A measure of trauma system improvement

Chandler Tinsman, Michele Lilienthal, RN; Colette Galet, PhD; James Torner, PhD; Dionne Skeete, MD

Background and Purpose. Unintentional injury is the 3rd leading cause of death overall in the US and the leading cause for people under 45 years old. Additionally, injuries in rural areas tend to have worse outcomes when compared to injuries in urban settings. To combat this disparity, the State of Iowa established an integrated trauma system in 2001. Integrated trauma systems have been shown to decrease mortality and improve patient outcomes. Previous literature has shown that the implementation of the Iowa trauma system reduced mortality for patients with traumatic brain injury, however no study has yet examined the impact of the Iowa trauma system on abdominal injuries. We hypothesized that maturation of the Iowa trauma system would lead to more laparotomies for the stabilization of time-critical abdominal injuries prior to transfer to a higher level of care and better outcomes for patients. Herein, we evaluated the rate of surgical stabilization prior to transfer to UIHC as well as patient outcomes. An increase in surgeries prior to transport as well as improved patient outcomes would suggest that the Iowa trauma system is providing effective care.

Methods. The University of Iowa Trauma Registry was queried to identify all patients transferred from Iowa hospitals and admitted to UIHC from 01/01/2010 through 12/31/2020 who underwent exploratory laparotomy either before transfer or within 4 hours of arrival at UIHC. Subjects were excluded if they were transferred directly to UIHC from the scene of the trauma, if the exploratory laparotomy was performed for non-trauma reasons, or if they were transferred for reasons other than trauma. Rates of exploratory laparotomy as well as other categorical variables were compared using a Chi-Square test. All continuous variables were analyzed using Mann-Whitney test. $P < 0.05$ was considered significant.

Results. A total of 213 patients were included; 63 had exploratory laparotomy performed before transfer and 150 after. There was no significant difference in the proportion of exploratory laparotomy before and after transfer when comparing the first period (2010-2015) to the second period (2016-2020) ($p = 0.314$), nor was there any significant difference in outcomes. We did, however, observe an increase in the proportion of laparotomies performed before transfer for patients with severe abdominal injuries (57.1% vs. 30.6%, $p = 0.011$). There was also an increase in the proportion of damage control laparotomies (23.6% vs. 43.9%; $p = 0.02$) as well as in multi-component blood product usage at referring hospitals. The time from injury to laparotomy for patients stabilized prior to transfer significantly decreased from the first to the second period (2h11min ± 55min vs. 1h47min ± 1h, $p = 0.04$).

Discussion. The increase in surgical stabilization of severe abdominal injuries prior to transfer along with the decreased injury-to-OR time of patients stabilized at the outside hospitals suggest improvement in the identification and stabilization of critical patients prior to transfer to UIHC. This is important as these injuries are time-sensitive, and a short time-to-OR is paramount. We also observed a significant increase in usage of blood products at outside hospitals and increased utilization of damage control techniques over time. These findings suggest a shift in the approaches to surgical stabilization and resuscitation efforts at level III and IV trauma care facilities. Early surgical intervention, damage control surgeries, and ratio-driven transfusion have all been shown to improve survival and patient outcomes. Taken as a whole, the increased identification and stabilization of critical injuries along with the shift toward providing more ratio-driven transfusions and using more damage control surgical techniques signal a maturation in the Iowa trauma system and focus on evidence-based clinical practice. Interestingly, this shift has not been accompanied by a decrease in mortality or improved outcomes. A larger, state-wide, study of all trauma patients is warranted to evaluate the impact of the changes on surgical care and to implement further changes to maximize our trauma system efficiency.

DEFORMITY CORRECTION IN END-STAGE ANKLE OSTEOARTHRITIS USING A LATERAL TRANS-FIBULAR APPROACH TOTAL ANKLE REPLACEMENT: A WEIGHT-BEARING CT STUDY

Christian VandeLune, BS; Cesar de Cesar Netto, MD, PhD.

Background: Ankle osteoarthritis (AO) is often due to prior trauma and frequently presents with joint deformity. Total ankle replacement (TAR) has been shown as an excellent surgical option to reduce pain, improve patient outcomes, and preserve ankle joint range of motion. It has been hypothesized that when compared to the standard anterior approach TAR, the lateral trans-fibular approach TAR could potentially allow for improved multiplanar deformity correction. However, the overall three-dimensional (3D) correction of foot and ankle alignment following this specific procedure has not been performed in the literature.

Aims/Hypothesis: The aims of this study were primarily to assess and compare pre- and post-operative 3D, sagittal and coronal plane foot and ankle alignment in patients that underwent lateral trans-fibular approach TAR for treatment of end-stage AO, and secondarily to assess clinical improvement based on patient reported outcomes (PROs). Our hypothesis was that significant amount of 3D deformity correction and improvement in PROs would be observed.

Methods: This IRB-approved, retrospective comparative cohort study included 14 consecutive patients (14 feet/ankles; 7 males/7 females; 5 right side and 9 left side) that underwent lateral trans-fibular approach TAR for end-stage AO. Demographics, comorbidities, associated surgical procedures and complications for included patients were investigated. All patients had received pre- and post-operative WBCT imaging on the affected foot and ankle. Using multiplanar reconstruction of WBCT images, 3D landmark coordinates (on X, Y, and Z planes) were manually found by a single observer, and an automatic calculation of the Foot and Ankle Offset (FAO) was given by the utilized software (CubeVue; CurveBeam®). The coordinates were the weightbearing points of the first metatarsal and fifth metatarsal heads, calcaneal tuberosity, that together represent the tripod of the foot, and by the central apex of the talar dome, representing the center of the ankle joint. The same observer measured traditional measures of coronal and sagittal plane ankle alignment: Talar Tilt Angle (TTA), Hindfoot Moment Arm (HMA), and Lateral Talar Station (LTS). Examples of Measurements performed are demonstrated in Figure 1. PROs were collected preoperatively and postoperatively at the latest clinical follow-up. Continuous data was assessed by the Shapiro-Wilk test for normality, and variables were compared using paired T-tests or paired Wilcoxon. P-values of less than 0.05 were considered significant.

Results: Patient's average age and BMI were respectively 63.2 years (range 43 to 83) and 32.48 kg/m^2 (range, 21.25 to 47.75). All patients demonstrated significant amount of averaged deformity correction in all measurements performed (Figure 2): the FAO improved from 7.73% to 3.63% (p=0.031); HMA decreased from 10.93mm to 5.10mm (p=0.036); TTA decreased from 7.94mm to 1.45mm (p=0.002); and the LTS improved from 5.25mm to 2.83mm (p=0.012). Some of the PROs measured also demonstrated significant improvement postoperatively, with the Tampa Scale for Kinesiophobia (TSK) improving from 41.14 to 33.00 (p=.0164) and the Foot and Ankle Ability Measure (FAAM) Sports Score improving from 20.78 to 40.60 (p=0.0168). The average follow-up time was 6.75 months with a range of 3-14 months. No significant changes on Foot Function Index (FFI) (46.87 to 39.28, p=0.51) or FAAM Daily Living (58.69 to 71.01, p=0.125) were observed. No direct correlation between deformity correction and PROs improvement was observed.

Conclusions: In this retrospective comparative cohort study, we demonstrated significant improvement in 3D, sagittal and coronal plane alignment following lateral trans-fibular approach TAR for end-stage AO. We also observed significant improvements in some of the measured PROs, more specifically the Tampa Scale for Kinesiophobia (TSK) and the Foot and Ankle Ability Measure (FAAM). However, no direct significant correlation was found between alignment correction and PROs improvement. The results of our study suggest that lateral trans-fibular approach TAR has the ability to significantly correct deformity, decreasing pain and improving function. Additional prospective and comparative studies are needed to support/confirm the results of this study.

Figure 1

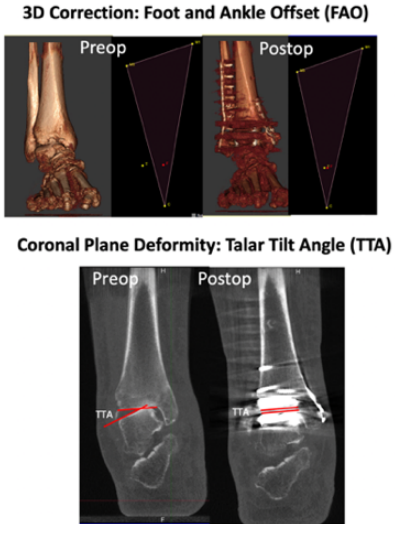
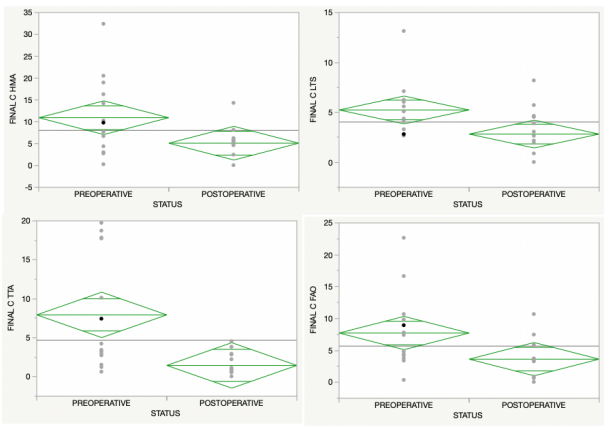


Figure 2



Functional and Patient Reported Outcomes after Successful DAIR for Periprosthetic Joint Infection of Total Knee Arthroplasty

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

Introduction

Periprosthetic joint infection (PJI) is a devastating complication in patients who have undergone primary total knee arthroplasty (TKA). Although the risk of PJI is relatively low, it is the leading cause of revision TKA in the United States. There is active debate regarding the utility of Irrigation and Debridement, Antibiotic therapy and component Retention (DAIR) as a treatment for acute PJI. Variable results for DAIR have been published regarding rates of infection resolution with little to no data investigating functional outcomes.

Study Aims

The purpose of this study was to establish a defined success rate for DAIR procedures in the treatment of acute PJI, as well as investigate patient reported functional outcomes (PROs) following successful DAIR. Our hypothesis was patients who had a successful DAIR surgery would have non-inferior functional outcomes when compared to a nested cohort of primary, uncomplicated TKAs.

Methods

Upon institutional review board approval, a retrospective review was performed to identify all patients who underwent DAIR for treatment of acute PJI at a single institution from 2008-2020. Patients were included in the study if they underwent irrigation and debridement of an acutely infected TKA with modular component exchange and treatment with intravenous antibiotic therapy. Failure of DAIR was defined as undergoing a subsequent surgery for the treatment of PJI. Kaplan Meier survival analyses evaluating durability of DAIR were performed. Patients with successful DAIR procedures, and their same TKA still in place, were sent Knee Injury and Osteoarthritis Outcome Score for Joint Replacement (KOOS-JR), Patient Reported Outcome Measurement Information System 10 (PROMIS-10), and Pass Knee surveys to assess functional outcomes. The DAIR cohort outcomes were compared to a separate cohort of uncomplicated TKAs with KOOS-JR and PROMIS-10 scores already on file in the institution record base.

Results

In total, 244 patients had a DAIR procedure. The median follow-up time for all cases was 5.9 years (Range 1-12 years). 74% of patients in the DAIR cohort did not require any later surgery for PJI. The rate of survival without subsequent operation for infection was 86.1% at 0.5 years, 80.0% at 1 year, 77.1% at 2 years, and 74.4% at 5 years. Functional outcomes data was obtained from 73 successful DAIR cases. The median follow-up time for this cohort was 4.5 years in comparison to 2.6 years for the control TKA group. No difference was observed in KOOS-JR or PROMIS-10 Physical Health scores when comparing the DAIR cohort to the control TKA group ($P>0.05$). Interestingly, PROMIS-10 Mental Health scores were significantly lower in the DAIR cohort compared to the primary TKA cohort (45.9 vs 50.1, $P<0.05$). PASS was achieved by 75% of the DAIR cohort.

Conclusion

Our data demonstrates that 74% of acute PJI cases treated with DAIR were successful in treating the infection out to 5 years. Additionally, knee function and overall physical health outcomes in successful DAIR procedures can restore knee function to a level similar to that of a primary, uncomplicated TKA. However, clinicians must consider the psychological impact of patients with PJI treated with DAIR, given that these patients had significantly lower mental health scores than the primary TKA cohort.

Gender Disparity in Ophthalmology Resident Surgical Case Numbers

Abby Walling; *Mentor: Jaclyn Haugsdal; Other team members: Lindsay De Andrade, Erin Shriver*

Introduction: In the past decade, the number of female ophthalmologists has significantly increased, from women representing 16% of practicing ophthalmologists in 2007 to 24% in 2011 (1). However, discrepancies between females and males still exist in medical practice. Gender-based discrimination is widespread and experienced by 87% of medical students, 88% of residents, and 91% of practicing physicians (2). Recently a study of 24 residency programs found that there is a significant difference in the number of surgeries performed by male and female ophthalmology residents, even when corrected for parental leave (3). Other studies have found a broad range of barriers for female physicians, including a historically male dominated culture and family conflicts that make it difficult to maintain a work-life balance (4). However, there is a lack of knowledge about the barriers that women experience in ophthalmology residency.

***Purpose*:** In our study, we are focusing on the University of Iowa Department of Ophthalmology and Visual Sciences to determine if there are disparities in surgical numbers, why there are disparities, and what are the barriers (perceived or real) for female residents at the University of Iowa. Based on previous studies, we hypothesized that female residents would have a lower number of surgeries, even when corrected for absentee days (2). We also hypothesized that, based on survey results, a significantly greater number of women will "agree" or "strongly agree" that they have experienced gender-based barriers while completing their residency training. By focusing on the University of Iowa, we aim to use this data to create personalized residency program interventions to address the barriers and make this program more equitable.

Methods: Our study includes a retrospective data review and a survey to combine numerical gender discrepancies and potential subjective reasons for the objective differences. For part one, we analyzed data of 65 University of Iowa Ophthalmology residents from 2010 to 2020. We identified statistical differences in surgical numbers as stratified by their schedule, absentee days, and subspecialty training. The second part of the study involved sending a survey via email to 95 individuals: 15 current ophthalmology residents, 50 alum graduating from the residency program in the last 10 years, and 30 current clinical ophthalmology faculty. The emails were obtained through a department directory and the distributed survey was both voluntary and anonymous. The survey began with collecting demographic information, followed by statements about gender discrimination for the individual to indicate their level of agreement. Based on previous studies, many potential barriers were included in the study, such as exclusion from the male-based culture, lack of female role-models in the field, and domestic duties (5, 6, 7). The survey results were aggregated and compared to the quantitative difference in surgical numbers based on gender, as stratified by several variables. Informed consent was obtained for every survey participant. This study was approved by the University of Iowa IRB and adheres to the Declaration of Helsinki.

Results: Based on the surgical data analysis, overall, female residents performed significantly fewer cataract surgeries than male residents during their PGY-4 year of the program. When corrected for the location of the rotation where these surgeries were performed, the biggest disparity came from the VA rotations. The University of Iowa Hospitals and Clinics cataract surgery rotations demonstrated relatively equal numbers between genders. However, the difference in surgical numbers was only significant if the rotation at the VA was their first rotation. Lastly, there were no significant difference in the number of absentee days between male and female residents. For the survey, 27 male and 10 female residents or alumni responded. Significantly more females than male residents answered that they were treated differently and felt discriminated against by patients and attending physicians due to their gender. Significantly more females perceived the organizational structure was inclined to support the opposite gender and felt that they were at a disadvantage due to lack of mentors of their gender. However, there was no significant difference in the number of females versus males who were satisfied with their career, found it difficult to maintain a balance between work and family life, felt supported by friends and family, or felt that their role as a parent limited their career advancement. There were multiple comments from survey respondents who felt that discrepancies in surgical numbers were present because males are more confident and aggressive in seeking out cases.

Conclusion: From the data obtained in this study, female ophthalmology residents are experiencing both objective and subjective discrimination. Female ophthalmology residents at the University of Iowa do have significantly lower surgical numbers than male counterparts overall. However, further analysis showed that this difference only holds if the female residents were at the VA for their first rotation. The VA rotation offer the residents more autonomy in adjusting their surgical case load than their rotations at the University of Iowa. Based on the comments from the survey, it is speculated that especially during the first rotation of the PGY-4 year male residents might have been more confident than females to increase their surgical case loads. This difference disappears as female residents gain experience duirng the program, illustrated by the fact that there is no longer a significant difference in surgical numbers if the resident is at the VA for their last rotation. Importantly, the difference in surgical numbers is not because females take more time off for family reasons, since both males and females had a similar number of absentee days. The survey responses illustrated that female residents experience subjective discrimination from patients and also attending physicians. These women feel that lack of mentorship and organizational support put them at a disadvantage. This illustrates that increasing female representation in leadership positions may help female residents feel more accepted in their roles. Additionally, addressing patient-initiated gender discrimination, for example by using toolkit developed by Lauren Hock, may assist with reversing the male dominated culture (6). Finally, organizational changes in the rotations may improve the female residents' level of confidence to feel embolden to increase their surgical case load, thereby decreasing the gender-based disparity in surgical numbers.

Cherry-Picking in the UIHC Emergency Department: A qualitative study from the perspective of attendings, APPs, and residents.

Max Wei, Uche Okoro, Mimi Williams, PI: Paul Van Heukelom

Background:
The concept of cherry-picking is well understood throughout emergency medicine. While this is true, a preliminary study on cherry-picking in the UIHC ED has demonstrated statistically significant evidence of its occurrence among providers. However, the reasons why health care providers cherry-pick patients at UIHC ED are not clearly understood.

Objective:
To determine factors that motivate health care providers to cherry-pick patients in the UIHC ED.

Methods:
Semi-structured qualitative interviews were conducted on current UIHC ED attendings, APPs, and residents. Eighteen participants, six from each category participated in this study. Grounded theory and thematic analysis were used to analyze the transcripts.

Results:
Eight major themes emerged among the transcripts: 1) end of shift, 2) specific cherry-picked chief complaints/demographics, 3) education potential, 4) prioritizing highest acuity, then longest wait, 5) procedure opportunities, 6) current workload, 7) competency, 8) quick dispositions. Among chief complaints and demographics, psychiatric patients, chronic pain, and frequent flyers were least likely to be cherry-picked, while patients with procedures, chest pain, or required airway were most likely to be cherry-picked.

Conclusions:
All participants indicated that cherry-picking does occur at the UIHC ED and there are specific chief complaints and demographics that are cherry-picked. Due to the academic nature of UIHC, educational value of patients, procedure opportunities, current workload, competency, and quick dispositions are additional factors that play a role in the selection of patients. This information may be used for clinical operational changes at the UIHC ED to improve patient care. Future work analyzing the responses of providers in a community hospital setting may provide further insight on the phenomenon of cherry-picking.

Identifying Trafficking Victims in the Hospital via the use of an Abuse Screening Tool

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Mentor: Shannon Findlay, MD, MPH, CTropMed
Collaborators: Kari Harland, MPH PhD, Katy DeMeulenaere, BSW

Abstract:
Background: In 2019 there were 98 cases of human trafficking reported by the National Human Trafficking Hotline in the state of Iowa. Surveys of human trafficking victims have shown that between 68-88% of victims were seen by healthcare providers during the period of their exploitation. In attempt to increase human trafficking victim identification, UIHC added three questions specific to human trafficking to their hospital-wide abuse screening tool.

Objective: This project sought to estimate the prevalence of human trafficking among all patients who screened positive on the abuse screening tool.

Methods: On March 31st, 2021, screening questions specific to human trafficking were added to a hospital-wide abuse screening tool which was administered by nurses to all inpatient and ED patients. The questions added to the abuse screening tool include the following: Are you currently being forced to engage in sexual activity, are you being abused or threatened in your work or home environment, and are you being forced to work. Data was collected between March 31st and August 2nd, 2021. Statistics were collected via SAS on frequency, proportions, and means of demographic information of patients who screened positively in the abuse screening tool, and patients with concern for human trafficking who were identified outside of the screening tool.

Results:
During the project period, 77 individuals screened positive in the abuse screening tool. The average age of individuals with positive screens was 37.4 years. Of the 77 positive screens, 3.8% (n=3) were identified as individuals affected by human trafficking. All three were exploited by sex trafficking. Two of these individuals had positive responses to all three human trafficking screening questions, and one responded only to the question, "Are you being abused or threatened in your work or home environment?" The age range of these individuals identified by the screening tool was 31-45 years old. There were five patients identified as individuals affected by human trafficking outside of the abuse screening tool. Two of these patients screened negative in the tool, two were unable to answer the questions, and one patient was never screened. Four of these patients were exploited by sex trafficking and for one patient, the trafficking type was unable to be determined. The age range of these individuals identified outside of the screening tool was 17- 41 years.

Conclusions: Based on these results, it is undetermined whether the three questions added to the abuse screening tool aided in the identification of individuals affected by human trafficking. While three patients were identified by the abuse screen as a whole, all of these patients responded yes to other (non-human trafficking related) questions in the screen. It is possible that these patients would have been identified without the human trafficking questions on the tool. Furthermore, the five patients identified as individuals affected by human trafficking outside of the screening tool demonstrates that sometimes, screening tools may not be the most effective method for human trafficking identification. Rather, educational efforts and the implementation of training in the subject of human trafficking could prove more successful in human trafficking identification.

Assessing cognitive performance in bipolar disorder and effects of cerebellar TMS

Rebecca Wen BA, Victória A. Müller Ewald PhD, Nicholas Trapp, MD, MS

Background

Cognitive impairment is a prevalent concern among individuals with bipolar disorder (BP), including impairments in time perception. However, few physiologic biomarkers of cognitive performance exist in this population. Identification of such biomarkers could serve as a potential treatment target in psychiatric clinical trials. One promising biomarker is the interval timing task (ITT), which engages cerebellar-frontal brain circuitry. Previous studies suggest that cue-induced delta frequency power in the cerebellum during a timing task is positively correlated with cognitive performance, and that in schizophrenia (SCZ), this delta power is reduced for individuals with poor cognitive performance. Given the genetic similarities and similar cognitive deficits between patients with SCZ and BP, we predict a positive correlation between cue-induced delta power during a timing task and task performance in bipolar subjects. Furthermore, cerebellar intermittent theta burst stimulation (iTBS) may be useful in improving cognitive performance in SCZ. We predict that cerebellar iTBS could also improve cognitive function in patients with BP.

Objectives

The primary objective of this study was to assess the relationship between EEG cue-induced delta frequency power in the cerebellum during a timing task and cognitive performance. The second objective of this study was to assess the effect of cerebellar iTBS compared to sham iTBS on cognitive performance in a population of patients with bipolar disorder.

Methods

To assess the relationship between EEG power and cognitive performance, subjects were rank ordered based on baseline scores on the ITT, Flanker inhibitory control task (FICAT), and fluid cognition. Top performers (top third percentile) and bottom performers (bottom third) were grouped, and time frequency plots were averaged. T-tests were performed in a point-by-point manner.

To address our second objective, subjects were randomized to receive either 10 treatments of iTBS (50 Hz triphasic burst of TMS pulses in a 5 Hz pattern, 2 seconds of stimulation with an 8-second intertrain interval) or sham. Cognitive tests including the National Institutes of Health Toolbox Cognition Battery (CB) were performed before and after 10 treatments. An ITT was also performed while recording 64-channel EEG customized to include 3 cerebellar recording electrodes. To assess change in performance on CB after iTBS or sham, scores were normalized to represent a change from baseline. T-tests were performed on baseline normalized scores between active and sham groups. To assess change in performance on ITT, t-tests were performed on baseline normalized CV scores, a measure of response variability or timing error.

Results

For our primary outcome, cue-induced cerebellar EEG power in the delta frequency was not associated with cognitive performance. For our secondary outcome, there was no statistically significant difference in CB or ITT performance between subjects who received 10 TMS treatments compared to sham ($p>0.05$ for all measures).

Discussion

Contrary to our predictions, cue-induced cerebellar EEG power in the delta range during an interval timing task was not associated with cognitive performance on that task or more generally. In fact, there was a trend towards a negative correlation, where lower delta power correlated with higher cognitive performance. This contrasts with the opposite relationship identified in patients with SCZ and suggests that cognitive biomarkers in BP are not similar to those in SCZ. We also predicted that iTBS could improve performance on cognitive tasks in BP patients. However, there was no statistically significant difference in performance on cognitive tasks in bipolar patients receiving cerebellar iTBS compared to sham. Future directions include recruiting more patients to increase power and considering other TMS treatment protocols that may have more robust effects on ITT cue-induced EEG biomarkers.

Title: Characterization of Sialoglycoconjugates in the Retina and Choroid through Neuraminidase Treatment and Lectin Labeling
Presenter: Piper Wenzel
Mentor: Robert F. Mullins, PhD

The choroid is a layer of the human eye containing the choriocapillaris, a rich vascular network that sustains the photoreceptors of the retina. When there is loss or breakdown of the choriocapillaris, retinal degenerative diseases can result, such as age-related macular degeneration (AMD). The glycoconjugate structure and extracellular matrix components of the choroid are not well understood. This study sought to characterize the glycoconjugates in the choroid of human donor eyes without AMD. Human donor macular tissue was collected and sectioned. One section per slide was treated with neuraminidase and then slides were incubated at 37°C for 18 hours. After incubation, the tissue sections were labeled with one of the 37 biotinylated lectins studied followed by Avidin Texas Red. An Olympus BX41 microscope with a SPOT RT3 camera was then used to capture images of the tissue. The lectin signal in various retinal and choroidal structures in the neuraminidase-treated section was evaluated and compared to the section without neuraminidase treatment. Of the 37 lectins studied, 13 showed no labeling in the choriocapillaris in the tissue sections with or without neuraminidase treatment. Nine lectins showed equal signal brightness with and without neuraminidase treatment. Six lectins had an increased signal in the neuraminidase-treated section (i.e., possessed carbohydrate epitopes masked by sialic acid) and nine lectins had a decreased signal in the neuraminidase-treated section. Further studies were performed on two lectins that showed increased binding following neuraminidase pretreatment, MPL and EEL, to evaluate if they bind to O-linked glycoproteins by treating tissue sections with O-glycosidase. The study found that MPL binds to O-linked glycoproteins whereas EEL likely binds to N-linked glycoproteins or glycolipids. The results from this study provide an initial characterization of the extracellular matrix of the human choroid. Future experimentation could be done to further identify the specific glycoproteins and compare the composition of the extracellular matrix in human eyes with and without AMD. Differences in composition could reveal more about the pathogenesis of AMD.

Treatment of Low Back Pain in Family Medicine and Internal Medicine

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Introduction: Low back pain (LBP) is a common reason for seeking healthcare and disability in the United States. There is a push for non-pharmacological treatments of low back pain. It has proven to be a challenge to find a medication that is powerful enough treat the pain while also reducing the side effects and complications. The negative side effects and risks associated with opioids and their limited efficacy with chronic pain has many concerned that opioids for low back pain are prescribed too often in the primary care setting.

Purpose: The purpose of this study was to identify how low back pain is treated in the primary care setting at the University of Iowa. We assessed differences in how LBP is managed in family medicine and general internal medicine. It is important to know how low back pain is treated and varies within the primary care settings to recognize any gaps that may exist in the delivery of care and to develop interventions to improve care.

Methods: This study was a retrospective chart review that examined patients seen in calendar year 2020. After IRB approval, we downloaded information from Epic for a total of 400 patients with LBP as one of their top three diagnoses during a visit. 200 were randomly selected from family medicine and 200 from internal medicine. Three patients from family medicine and three patients from internal medicine did not meet the inclusion criteria and were excluded. Specific variables related to LBP were downloaded from Epic and through manual chart review. Differences in treatment modalities between departments were identified using Chi-square tests or t-tests with a two-sided p-value of 0.05.

Results: Family medicine patients were younger with a mean age of 51.0 vs 60.3 in internal medicine ($p = <0.001$).The sex mix of the clinic patients showed no differences. There was no significant difference in opioid prescriptions for LBP with 11.7% in family medicine and 9.1% in internal medicine ($p = 0.409$) and 10.4% overall. Family Medicine recommended significantly more NSAIDs (26.4% vs 15.7% $p = 0.009$), acetaminophen (24.4% vs 15.2% $p = 0.023$), and muscle relaxants (26.4% vs 13.7% $p = 0.002$) than general internal medicine. Physical therapy was used 29.2% of the time with no significant difference between family medicine and internal medicine (33.0% vs 25.4%, $p = 0.096$). X-ray was the most common imaging ordered (19.5% overall), with the only significant difference between the departments being MRI. Family Medicine was less likely to order lumbosacral MRI than Internal medicine (1.5% vs 6.6%, $p = 0.011$).

Conclusion: LBP was largely treated similarly in the two specialties, with no difference in opioid prescription, x-ray of the lumbar spine, or referral to PT. NSAIDs, acetaminophen, and muscle relaxants, were more likely to be recommended in family medicine. MRI was more likely to be recommended in internal medicine.

Results of a SARS-CoV-2 Serosurvey among University of Iowa Hospitals and Clinics (UIHC) Employees

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Background: The novel acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a global pandemic of coronavirus disease 2019 (COVID-19). SARS-CoV-2 was first identified in Wuhan, China, and is the only coronavirus to have caused a pandemic. Healthcare workers (HCWs) are at an increased risk of contracting COVID-19 given their proximity to and interactions with patients. Numerous groups have assessed seropositivity rates among HCWs and the duration of seropositivity. However, the results of published studies conflict and few studies have assessed seropositivity rates among HCWs in rural areas, as well as change in antibody titers over time.

Purpose: The purpose of this study is to assess SARS-CoV-2 seropositivity rates over time among UIHC employees with and without a history of COVID-19 at baseline, identify possible sources of exposure in the hospital and community, describe employees' infection prevention practices, and evaluate employees' perceptions towards COVID-19. To address these goals, the UIHC Healthcare Worker Serosurvey Study is following a cohort of 300 HCWs for one year. My project will: 1) describe the cohort at baseline and 3 months; 2) determine the rate of seroconversion during the 3-month period; and 3) identify possible sites of exposure in the hospital and community. We hypothesized that employees at the UIHC will have a low seroconversion rate.

Methods: For this prospective cohort study, we invited all UIHC and UI Carver College of Medicine (UICCoM) employees ≥18 years of age to complete a screening survey. We invited all employees with laboratory confirmed COVID-19 or who indicated that they had COVID-19 to participate. We used a random number generator to select the remaining participants until we had a cohort of 300 employees representative of the population. Participants completed a baseline survey and follow up surveys at 3, 6, and 9 months. They submitted blood samples for COVID-19 antibodies at 0, 3, 6, and 9 months. The laboratory uses both the Roche (detects anti-nucleocapsid antibodies [anti-N] produced during natural infection) and Diasorin (detects anti-spike [anti-S] antibodies produced by vaccines or natural infection) assays to detect SARS-CoV-2 antibodies.

Results: 288 employees have completed their baseline visit and 202 employees have followed up at 3 months. Among the baseline cohort, 70.1% are female, 92% are Caucasian, 68.8% have a patient care role, and the mean age is 41.1 ± 12.5 years. Seventy (36.5%) participants reported a previous positive PCR COVID-19 test, and 63 (90%) of them had anti-N at baseline. Fifty-seven of these 70 participants have followed up at 3 months and 54 (94.7%) had anti-N. Given that we enriched the population for employees who contracted COVID-19, 29.2% of participants had anti-N at baseline. At 3 months, 33.7% had anti-N and 44 (21.8%) employees had acquired anti-S. Five (2.5%) of the 202 employees who did not have anti-N at baseline had acquired it at 3 months. None of the variables we evaluated were associated with having anti-N antibody.

At baseline, 9.47% of participants reported having interacted with ≥ 1 person with COVID-19 in the community, and 59% of these exposures occurred in homes where PPE was rarely worn. Whereas, 49.65% of participants reported having ≥ 1 interaction with a person at the UIHC who had COVID-19, but the frequency of reported use of appropriate PPE when caring for infected patients was 6.95 for masks and 6.78 for face shields (score of 7 = always). More than 80% of the cohort at baseline and 3 months felt they were not likely to contract COVID-19 in the community or at the UIHC, and > 60% at baseline agreed that they avoid risky situations and play it safe.

Conclusions: The seroconversion rate among this risk averse group of HCWs was low. Consistent with the literature,[1,2] a high proportion of participants who reported a previous COVID-19 diagnosis had anti-N antibody at baseline and at 3 months, but the positivity rate was not 100%. The proportion of participants who had anti-S antibody increased from baseline to 3 months as vaccines became available. Few participants were wearing PPE during known COVID-19 exposures in the community, but reported PPE use during interactions with persons who had COVID-19 at the UIHC was substantially higher. We will extend these results as participants complete their 3, 6, and 9 month follow up surveys and antibody testing.

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CT-P/A Results and Evaluation considerations for Emergency Providers (CREEP)

Cal Zahn (research fellow), Nick Kluesner (mentor), Hayden Smith, Jonathan Hurdelbrink, Clint Hawthorne, Cal Hansen, Steven Craig, Ryan Holdsworth, Suzie Justo-Roth, Victoria Cunningham

Background: In the United States, patients presenting to the Emergency Department (ED) with acute stroke symptoms are assessed to determine eligibility to receive intravenous thrombolytics and/or mechanical thrombectomy. These patients' history and clinical features play a role in the assessment and determination of treatment options. Research has yet to define a set of clinical criteria that adequately inform a provider's decision to order computed tomography perfusion and angiogram (CT-P/A) to acquire evidence for mechanical thrombectomy when ischemic stroke is in the differential diagnosis. As technologies improve and neuro-interventionalists look to expand the use of thrombectomy to previously ineligible patients, emergency providers need to be mindful to avoid diagnostic indication creep related to CT-P/A.
Purpose: To review the use of CT-P/A in adult patients presenting to the ED with acute stroke findings and evaluate existing clinical criteria for ordering CT-P/A.
Methods: A retrospective study was conducted based on patients receiving a CT-P/A when presenting to the Iowa Methodist Medical Center (IMMC) ED during September 2019 to June 2021. Clinical variables of interest were the patient's last known normal time in relation to their ED presentation, initial recorded National Institute of Health Stroke Scale (NIHSS), and whether symptoms were explicitly suggestive of a cortical stroke. The perfusion variables of interest describe the presence and size of the infarct core and ischemic penumbra caused by a potential occlusion, and the angiography variables of interest describe the presence and location of the potential occlusion. These variables were used to examine whether the patients would have met criteria to undergo thrombectomy within the current landmark studies in the field (i.e., DEFUSE3 and DAWN) compared to their true course of treatment. Patients who were deemed eligible for thrombectomy were transferred for evaluation and potential treatment.
Results (interim): From the introduction of CT-P/A technology at IMMC in September 2019, the percentage of all ED patients receiving CT-P/A each month increased from 0.6% to 1.6% in June 2021. In total, 718 patients received a CT-P/A during the 22-month study period. The average monthly recorded NIHSS for these patients increased from 6.4 to 6.7 during this time, with 81.5% of these patients not having a detectable blood vessel occlusion on imaging. 43.2% of patients receiving CT-P/A presented with explicit cortical stroke features on physical exam (i.e., hemispatial neglect, visual field deficit, gaze preference, aphasia), whereas of the 105 patients transferred for further management, 85.7% presented with explicit cortical features. Of the 73 patients known to undergo thrombectomy after presentation, 71.2% of the procedures were deemed "successful." The comparison of these results to the thrombectomy criteria discussed in the previous literature is forthcoming.
Discussion: The presented final study results will help understand the utility of CT-P/A, especially in appraising it for use in patient populations that fall outside of the treatment criteria used in current thrombectomy literature. The study will also be valuable to institutions interested in using CT-P/A as a diagnostic tool as well as those institutions already using it to ensure that CT-P/A studies produce adequate return on investment in relation to the increased workload.