2017 Student Research Forum
Poster Abstracts

(Alphabetical By Student Last Name
and Numerical By Poster Display)
DISADVANTAGE INDICES: A WAY TO MEASURE NEIGHBORHOOD DISADVANTAGE

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Support: Department of Medicine Shapiro Summer Research Program

Background: Disadvantaged neighborhoods are associated with increased risks of poor health outcomes, including earlier death. Yet, quantification and identification of neighborhood disadvantage for the US is challenging. European nations use multi-component, geographic based indices to quantify disadvantage. These typically measure the relative disadvantage of a neighborhood using various characteristics such as level of employment, education, overcrowding, and access to services measured at a granular level, such as census block group. Indices such as these have been created for decades and are integral to research in many different fields, yet no consensus exists for the creation of such indices, especially in the US. New options in the current era may improve prediction power, but no systematic review of measure construction and use has been conducted. Methods: A systematic review of all uniquely created disadvantage indices in the peer-reviewed literature was conducted. A set of search terms was applied to databases returning over 3,000 articles. Over 125 articles met inclusion criteria, which included the following: must describe the creation of a unique index on a neighborhood or neighborhood-equivalent scale and English language paper available. Additionally, government-released technical papers were included if they met inclusion criteria. For each identified index the following information was collected: categorical domains, variables, scale, and statistical methods utilized. Results: 125 unique domains, 1,000 variables, 60 scales, and 40 statistical methods were recorded and each item was linked to each index employing it. Conclusions: Next steps include compiling and quantifying the domains, variables, scales, and statistical methods. For example, all 1,000 unique variables will be consolidated into groups consisting of similar variables and then quantified. This summary of the numerous disadvantage indices in existence will be used to establish history of practices and explore various methods employed. Eventually, this research will be used in the development of an improved US metric with increased prediction power, further facilitating research using neighborhood disadvantage, as well as targeting the delivery of limited resources.
USE OF STATINS IN COMBINATION WITH ANDROGEN DEPRIVATION THERAPY IN PATIENTS WITH ADVANCED PROSTATE CANCER: IMPACT ON ONCOLOGICAL OUTCOMES

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Support: Shapiro Summer Research Program; Department of Surgery T35 DK062709; Department of Urology

Background: Statins are thought to possess anti-neoplastic properties related to their effect on cell proliferation and steroidogenesis. De-regulation of androgen synthesis is crucial in the development of castrate resistant prostate cancer suggesting a possible role for statins in preventing progression of prostate cancer. Our goal was to assess the role of statin therapy on oncologic outcomes in patients with advanced prostate cancer being treated with Androgen Deprivation Therapy (ADT). Methods: The national VA database was used to identify men diagnosed with prostate cancer who were treated with ADT for at least 6 months. Our cohort was stratified based on statin use of at least 6 months duration during the same time period. Primary outcomes measures included prostate cancer specific survival (PCSS), overall survival (OS) and skeletal related events (SREs). Results: A total of 87,346 patients on ADT were included in the study cohort, of which 53,360 patients used statins and 33,986 did not. Statin users were younger in age (median 73 vs. 76, p<0.001), more likely to have Charlson Comorbidity Index >3 (3.1% vs 2.5%, p<0.001) and more likely to have a high grade (Gleason score 8-10) cancer (12.3% vs. 10.9%, p<0.001). Statin users had longer OS (median 6.50 and 3.95 years in the statin and non-statin group, p<0.001) and decreased death from prostate cancer (9.0% and 12.7%, p<0.001). Statin use was not associated with SREs (9.8% and 9.3% in the statin and non-statin group, p=0.011). On multivariable Cox proportional hazards analysis, statin use was an independent predictor of OS (HR = 0.69, CI 0.66-0.72; p<.001), PCSS (HR 0.58, 95% CI 0.54-0.63; p<0.001), and SREs (HR 0.64, 95%CI 0.57-0.73; p<0.001) while controlling for age, race, CCI, PSA, and Gleason score. Conclusion: Statins are widely available, low risk medications with increasing evidence of anti-neoplastic properties in the setting of prostate cancer. Our study adds to the limited existing literature on the role of statins in progression of advanced prostate cancer and is the largest study to date to look at statin use specifically in the setting of ADT. Statin use in conjunction with ADT was associated with improved overall survival and decreased death from prostate cancer. Statins offer a promising adjunct to ADT and require further prospective studies.
RADIOFREQUENCY ABLATION AND PULSED RADIOFREQUENCY FOR TREATING PERIPHERAL NEURALGIA

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Support: Shapiro Summer Research Program, Department of Anesthesiology

Background: Chronic pain of peripheral nerves is a common complaint in the clinical setting. Treatment with pain medications tends to provide temporary and incomplete relief. Radiofrequency Ablation (RFA) and Pulsed radiofrequency (PRF) have the potential to provide better pain relief for a longer duration. RFA/PRF are used to ablate the nerves that conduct pain after these nerves are identified by nerve blocks. The purpose of this study is to determine the effectiveness of RFA and PRF in providing pain relief and the duration of the relief through a retrospective chart review. Methods: We collected pain scores before and after RFA/PRF, % relief from the procedure, and duration of pain relief for 16 patients. Out of 16 patients, we performed analysis for 14 patients because 2 patients did not show up to pain clinic for follow up. We performed the statistical analysis using SPSS22 software. We used paired t-test to compare pre- and post-procedure pain scores, with a P-value <0.05. Results: 80% of the patients in our study reported pain relief. The average pain scores decreased from 6.3 ± 2.3 before RFA/PRF to 3.6 ± 2.7 after RFA/PRF (P=0.03). The average improvement was 60.8% ± 35%. The average duration of relief was 128.8 ± 106.8 days. Conclusion: Our study shows that RFA and PRF can be useful in the clinical setting to provide long-term pain relief from peripheral pain. Both procedures provide better pain relief for longer duration than other conservative modes of treatment. Although RFA and PRF are more invasive than other conservative treatments, our study found that they are both safe to use and the patients in our study did not experience complications from the procedure.
DEVELOPMENT OF AN ASSAY TO STUDY ATP DEPENDENT MITOCHONDRIAL POTASSIUM CHANNELS

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Support: Shapiro Summer Research Program; NIH R56HL057414-15A1 (Makielski)

Introduction: ATP dependent potassium channels (K\textsubscript{ATP}) are found in many excitable tissues including the pancreas, heart, and skeletal muscle. In myocytes, K\textsubscript{ATP} channels are crucial in regulating membrane potential during times of stress. When ATP levels are high such as during normal metabolism, ATP is bound to the SUR2 regulatory subunit and closes the inwardly rectifying sarcolemmal Kir6.X pore. In times of cardiac stress, ADP binds and the channel closes leading to a smaller rectifying current which causes shorter and diminished action potentials which require less energy expenditure thereby protecting the cell. A similar K\textsubscript{ATP} is thought to be present on the mitochondrial membrane (mitoK\textsubscript{ATP}). Although the exact structure still needs to be elucidated, the mitoK\textsubscript{ATP} regulatory subunit likely has a similar structure to the sarcolemmal K\textsubscript{ATP}. In order to study the specific protein make up of this channel, an assay to determine the flux of potassium through this channel is needed. A thallium flux assay based on the principles outlined in Wojtovich et al (2010) was developed.

Methods: Mitochondria were isolated from adult B6J male mice following the procedure outlined in Wojtovich et al (2010). Mouse hearts were extracted from the mice and immediately diced and homogenized and then put through differential centrifugation to isolate the mitochondria. The pellet was resuspended and incubated in BTC-AM dye and then washed after 30 minutes. The dye loaded mitochondria are diluted and read in a Cary Eclipse fluorometer. Thallium was used as a surrogate for potassium and was added to the cuvette with incubated mitochondria 30s after a run was started. Changes in fluorescence could be understood as changes in Thallium flux through the mitochondrial membrane.

Conclusion: Although many different approaches to the assay were tried, a measurable flux through the channel was never observed. Changes to the composition of the buffer used to isolate the mitochondria such as adding low concentration ATP or phosphatidylinositol phosphates which are known to help stabilize mitochondria and prevent mitoK\textsubscript{ATP} channel run down were ineffective in producing flux. In addition, the speed of the isolation was lowered and the concentration of mitochondria used in fluorometry were varied with no success. Further research is needed to validate the methodology of thallium flux assays for use in the study of mitoK\textsubscript{ATP} in mouse models.
BARRIERS TO USE OF LONG ACTING REVERSIBLE CONTRACEPTION IN WISCONSIN

Melyssa Baron, Sarina Schrager, MD, Beth Potter, MD

Background: Unplanned pregnancies are a serious health concern in Wisconsin. Increasing access to contraception is a proven method to reduce unplanned pregnancies while giving patients greater agency. Long acting reversible contraception methods (LARCs), such as subdermal implants and intrauterine devices (IUDs), are among the most effective contraception methods and have high patient satisfaction. The goal of this project is to understand the barriers to and benefits of LARC use in Wisconsin. Methods: A review of LARC initiatives throughout the country and within Wisconsin was performed. Then interviews were conducted with physicians, researchers of medicine, public health, economics, and social justice, employees at the Department of Health Services, employees at the Wisconsin Alliance for Women’s Health, and the chair of the Wisconsin section of the American Congress of Obstetricians and Gynecologists. Results: Relatively few Wisconsin women use LARCs in comparison with other states. Lack of provider skill in inserting and recommending LARCs, inability to perform same-day LARC insertion, and absent hospital protocols for immediate postpartum insertion represent barriers to patients obtaining LARCs. The benefits of greater LARC access include increased patient agency, fewer unplanned pregnancies, fewer high risk births, improved maternal health, fewer abortions, and cost savings for patients, hospital systems, and state entitlement programs. Conclusions: Current efforts to make LARCs accessible have been insufficient to fully remove barriers to their use. Removing these barriers will require cooperative efforts between physicians, hospital systems, patients, public health professionals, and policy makers.
RISK FACTORS FOR PULMONARY VASCULAR DYSFUNCTION IN ADULTS BORN PRETERM

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Support: Shapiro Summer Research Program; Department of Medicine

Background: Preterm birth, or any live birth occurring at less than 37 weeks of gestation, accounts for 10% of all births in the United States, and is associated with increased early and late risk for pulmonary vascular dysfunction (1,2,3). Since a growing number of individuals born preterm are surviving into adulthood, there is an increased need to identify the pulmonary vascular complications of preterm birth throughout the lifespan. In this study, we aim to identify neonatal risk factors for developing pulmonary vascular disease in adulthood, and to evaluate the role of angiogenesis in the development of pulmonary vascular dysfunction. Methods: This research was part of a continuation of studies using the Newborn Lung Project (NLP), a prospective cohort study that enrolled subjects born premature (average gestation 28 weeks) with a very low birthweight (<1500g) from 1988-1991. As adults, subjects were recruited for assessment of pulmonary function (n=23) and pulmonary vascular function (n=11) (4). Neonatal factors were correlated to adult diffusing capacity of the lung for carbon monoxide (DLCO) and mean pulmonary arterial pressure (mPAP). ELISA (enzyme-linked immunosorbent assay) kits were used to measure the levels of pro- and anti-angiogenic biomarkers in serum samples obtained from subjects and matched controls. Results: Increased number of days on ventilatory support in the NICU correlates significantly with higher mPAP values (r=0.83, p<0.01), while increased number of days on supplemental oxygen is associated with lower percent of predicted DLCO values (r=-0.41, p=0.05). Conversely, assisted ventilation did not correlate as well with DLCO and supplemental oxygen did not correlate as well with mPAP. A diagnosis of bronchopulmonary dysplasia also predicts elevated mPAP in adulthood (p=0.02), but not reduced DLCO. Serum pro- and anti-angiogenic biomarkers were similar between control and preterm-born adults. Conclusions: Neonatal assisted ventilation and supplemental oxygen in preterm infants may increase adult risk for pulmonary vascular dysfunction, potentially through independent mechanisms. While these two therapies are necessary for survival of preterm infants, prolonged use of either may be useful to identify individuals at high risk for developing pulmonary vascular disease. Angiogenesis may be down-regulated in individuals born preterm, but a larger sample size is necessary for statistical power.

Sources
EMOTION IDENTIFICATION AND VISUAL ATTENTION IN PEDIATRIC PTSD

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Support: Shapiro Summer Research Program; Department of Psychiatry

Background: Post-Traumatic Stress Disorder (PTSD) is a psychiatric condition that follows a traumatic experience, and involves symptoms such as anxiety, intrusive thoughts, and reactive symptoms. Individuals with PTSD often try to avoid reminders of their experience. A recent study demonstrated that youth with PTSD symptoms were not as accurate at identifying angry faces compared to sad and fearful faces. Another study showed youth who have experienced trauma in their past were more likely to demonstrate an attentional bias away from faces that were threatening. But, no studies have examined emotion recognition in youth with PTSD in tandem with eye tracking to ascertain emotion identification abnormalities in pediatric PTSD. Methods: Non-traumatized typically developing (TD) youth and youth with PTSD aged 10-19 viewed a series of emotional faces on a computer screen and were instructed to identify which emotion the faces were displaying. Eye tracking technology monitored the participants’ eye movements and fixations when viewing the faces. Results: There was no significant difference in overall emotion recognition accuracy between children with PTSD and TD youth (t=-1.66, p=0.098). However, youth with PTSD were less accurate than NT youth at identifying angry faces (t=1.96, p=0.056). Furthermore, our model showed a significant group by emotion by age interaction for identification of anger (t=-2.23, p=0.026). As age increased, children with PTSD had a greater difficulty identifying anger relative to neutral than non-trauma exposed children did. Despite the differences in emotion recognition accuracy, there was no difference in proportion of fixation time to the eyes (t=-0.59, p=0.559), mouth (t=0.53, p=0.595) or face (t=0.513, p=0.609) between children with PTSD and TD children. Furthermore, PTSD diagnosis had no overall effect on the time participants took in identifying which emotion they believed the image was representing (t=1.40, p=0.160). Conclusion: Our results show that youth with PTSD have a greater difficulty identifying angry faces than TD children, an effect that increases with age. This difference occurred despite the absence of any eye fixation differences as well as a lack of reaction time differences when viewing angry faces. This may suggest the differences in emotion recognition in children with PTSD could be due to an underlying neurodevelopmental pathology and are not due to simple avoidance.

Citations
COMPETENCY-BASED SKILLS ASSESSMENT IN GRADUATING MEDICAL STUDENTS: A MASTERY LEARNING MODULE FOR STERILE TECHNIQUE

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Support: Shapiro Summer Research Program; Department of Surgery

Background: Internship Preparatory Courses (IPCs) for graduating medical students are a national trend in medical education. Mastery Learning is an educational method that prioritizes all learners achieving a pre-determined Mastery Standard. Achievement of this Mastery Standard in an IPC may allow for competency certification. We examined the use of a Mastery Learning Sterile Technique Module in an IPC to assess medical student competency in sterile technique, a required skill for most interns. We hypothesized that this module would decrease learner anxiety and increase learner confidence while increasing skill competence. Methods: Data was drawn from 41 graduating medical students entering general surgery, orthopedic surgery, emergency medicine, and OB/GYN internships who completed a Mastery Learning Sterile Technique Module during a two-week IPC. The module consisted of gowning, gloving, prepping, and draping a sterile field on a low fidelity model. The learners were given a baseline skills assessment (Pretest). They then watched a didactic video and participated in a supervised deliberate practice session. Three to five days after the Pretest they completed a Posttest. Test performance was evaluated by faculty using a nine item Mastery Checklist. If mastery was not achieved on the Posttest, learners received remediation and retested until achieving mastery. Learner anxiety was assessed immediately before and after the Pretest and Posttest with the short-form State portion of the State Trait Anxiety Inventory. Learner confidence was assessed immediately after both tests with the Cato Confidence Scale. Paired t-tests were used to analyze differences in learner confidence and anxiety from the Pretest to the Posttest. Results: No learners achieved mastery on the Pretest. After didactics and deliberate practice, 27 of the learners achieved mastery on their first Posttest attempt. The 14 remaining learners achieved mastery with one remediation session. From Pretest to Posttest, learner confidence increased (Mean+SD; 2.96+.71 vs 3.32+.78; p<.001). From Pretest to Posttest, the State anxiety score of the learners before the test did not change (10.1+4.2 vs 9.8+2.67; p=.602), but the State anxiety score of the learners after the test decreased (9.63+4.33 vs 8.63+3.7; p=.084). Conclusion: Graduating medical students were able to demonstrate competence in sterile technique skills using a Mastery Learning Module. The module increased learner confidence and did not cause extensive learner anxiety.
IMPROVEMENT IN HYPERPHOSPHATEMIA USING PHOSPHATE EDUCATION AND PLANNING (PEP) TALKS

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Support: Shapiro Summer Research Program, Department of Medicine

Introduction: Hyperphosphatemia is a common complication in patients with end stage renal disease on hemodialysis. The mainstay of phosphorus management involves a low phosphorus diet and use of phosphate binders, yet these alone are often insufficient. This study was the first to encourage the use of phosphate binders and dietary modifications through a series of Phosphate Education and Planning (PEP) talks using behavioral change techniques. Methods: A total of 46 hemodialysis patients with hyperphosphatemia were enrolled. All patients were eligible to receive a series of four talks, each with defined goals relative to the long-term management of serum phosphate levels. Qualitative data from the talks was gathered during each intervention while serum phosphorus was selected as an outcome measure. Results: There was a modest improvement (-0.31mg/dL) in the serum phosphate levels of the patients who received the entire PEP talk series. Furthermore, the most common self-identified barriers were phosphate binder prescriptions not tailored to eating routines and lack of resources for suitable dietary changes. Conclusion: The PEP talk series model is appropriate to manage hyperphosphatemia by identifying patient-specific barriers and providing resources that can mitigate them. The strength of this model lies in using a multifaceted approach applying both pharmacotherapy and dietary changes, along with behavioral change, to achieve lasting improvements in serum phosphorus levels in hemodialysis patients with persistently elevated serum phosphorus levels.
RACE, ETHNICITY, AND INSURANCE STATUS INFLUENCES ON THE TREATMENT AND OUTCOMES IN PATIENTS PRESENTING WITH TRAUMATIC FLAIL CHEST

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Support: Shapiro Summer Research Program, Department of Surgery

Background: Health disparities in trauma have long been identified and literature reviewing disparities in thoracic traumas is lacking. Flail chest injuries are a severe form of thoracic trauma and treatment modalities are continuously changing. Many factors have been previously identified, but it is unknown if race, ethnicity, or insurance status influences physician decision-making, morbidity, or mortality in this trauma population. Our study attempts to identify if these disparities exist and the implications.

Methods: A retrospective cohort analysis was performed using patients identified with International Disease Classification 9 codes corresponding with flail chest injuries from the National Trauma Data Bank (2013-2015). Patients analyzed were aged 16-89 with known race/ethnicity, insurance status, injury characteristics, management adjuncts, and outcomes. These variables were included in multivariate regression models.

Results: The analysis included 12,726 flail chest patients. The sample was 75% male with 80% white, 8% black, 8% Hispanic, and 4% other. The sample’s insurance status was 39% private, 23% Medicare, 9% Medicaid, 10% uninsured and 19% other. After multivariate logistic regressions, race or ethnicity was not a statistically significant predictor of mortality. Compared with private insurance holders, uninsured patients were more likely to die in the hospital (OR=1.66, P<0.001).

Conclusion: Uninsured status, but not other insurance groups, race or ethnicity, predicts increased mortality risk. Insurance status is a higher predictor of hospital outcomes compared to race or ethnicity after controlling for demographic, comorbid, complication, and injury characteristics in the flail chest injury cohort.
AN ASSESSMENT OF SURGICAL DISPARITIES IN CLEFT LIP AND PALATE TREATMENT IN MYANMAR

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Support: Shapiro Summer Research Program; Department of Surgery

Background: Cleft lip and/or palate (CLP) prevalence is known to be highest in Asian countries, however few sources have surveyed the prevalence and disparate care of patients in Myanmar (Burma). The purposes of this study are to (a) increase current understanding of the demographics and socioeconomic status of the patient population to identify disparities of care; (b) evaluate how patients with CLP seek out surgical care; (c) estimate a prevalence of the CLP population; and (d) provide awareness of the needs Myanmar has in managing patients with CLP. Methods: A single-center observational 3 month preliminary survey study on first-time patients with CLP was conducted from May – July 2017 in the New Look New Life Clinic (NLNL), a clinic under the umbrella organization SmileTrain in Yangon, Myanmar. All 30 patients were provided with a survey and responses were self-reported; either completed by guardians or themselves. Additionally, all surgeries conducted in NLNL were recorded to determine the variety of surgical interventions performed and volume of patients treated. Results: During the enrollment period, 146 patients received surgical intervention and 30 patients enrolled and completed the study. The average age of the new patient was 5.8 years old, 63% were male, 67% had cleft lip and palate, 23% had isolated cleft lip, 10% had isolated cleft palate and 53% were first born. In the sample, 23% of patients had family members with history of CLP. The income of the majority of families was less than 120,000 kyats per month and the average travel costs to NLNL was 83,176 kyats excluding the cost of lodging, food, and loss of income. All patients used a car to travel to NLNL and 20% of patients and their families traveled from the northernmost regions: Kachin, Sagaing, and Chin states. During pregnancy with the patients, 60% of mothers took a multivitamin with folic acid. The majority of patients and their families learned about NLNL services either through the internet (40%) or word of mouth from their social community (40%). Conclusion: The results of this study indicate significant delays to care occur because the average age of treatment is 5.8 years old, noting the ideal age for lip repair is at 3 months and palate repair is less than a year. Future studies must continue to identify barriers to care and prevalence of CLP patients in Myanmar to create resources that will better serve patients with CLP and the healthcare providers treating them.
THE EFFECT OF RACE AND INSURANCE STATUS ON BICYCLE TRAUMA OUTCOMES IN ADULTS

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Support: Shapiro Summer Research Program, Department of Surgery

Introduction: Race and insurance status have been shown to predict outcomes in pediatric bicycle traumas. It is unknown how these factors influence outcomes in adult bicycle traumas. This study aims to evaluate the association, if any, between race and insurance status with mortality in adults. Methods: This retrospective cohort study used the National Trauma Data Bank (NTDB) Research Data Set for the years 2013-2015. Multivariate logistic regression models were used to determine the independent association between patient race and insurance status on helmet use and on outcomes after hospitalization for bicycle-related injury. These models adjusted for demographic factors and comorbid variables. When examining the association between race and insurance status with outcomes after hospitalization, injury characteristics were also included. Results: A study population of 45,063 met the inclusion and exclusion criteria. Multivariate regression demonstrated that black adults and Hispanic adults were significantly less likely to be helmeted at the time of injury than white adults [adjusted odds ratio of helmet use for blacks 0.25 (95% CI 0.22-0.28) and for Hispanics 0.33 (95% CI 0.30-0.36) versus whites]. Helmet usage was also independently associated with insurance status, with Medicare-insured patients [AOR 0.51 (95% CI 0.47-0.56) versus Private-insured patients], Medicaid-insured patients [AOR 0.18 (95% CI 0.17-0.20)], and Uninsured patients [AOR 0.29 (95% CI 0.27-0.32)] being significantly less likely to be wearing a helmet at the time of injury compared to Private-insured patients. Although patient race was not independently associated with hospital mortality among adult bicyclists, we found that Uninsured patients had significantly higher odds of mortality [AOR 2.02 (AOR 1.31-3.12)] compared to Private-insured patients. Conclusions: Minorities and under-insured patients are significantly less likely to be helmeted at the time of bicycle-related trauma when compared to white patients and those with private insurance. Public health efforts to improve the utilization of helmets during bicycling should target these subpopulations.
TIME IMPACT OF RADIATION ON OPTICAL METABOLIC IMAGING IN HEAD AND NECK SQUAMOUS CANCER CELLS

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Support: Shapiro Summer Research Program; Harari Lab Department of Human Oncology

Introduction: Head and neck squamous cell carcinoma (HNSCC) is the 6th most prevalent cancer in the world. Optical metabolic imaging (OMI), which measures nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FAD) fluorescence intensities, offers potential as a cost-effective, noninvasive tool for assessment of HNSCC tumor response to treatment. This study examined the effect of radiation on HNSCC at 0.5h, 1h, 2.5h, 24.5h, 25h, and 49h post-radiation by determining the optical redox ratio (ORR), which is a ratio of the NADH fluorescence intensity divided by the FAD fluorescence intensity. Because cancer cells tend to favor the glycolytic pathway for energy production, they produce a greater amount of NADH relative to FAD, resulting in an increased ORR. We hypothesized that the redox ratio would decrease in response to radiation with the greatest decrease at 24 hours after radiation.

Methods: HNSCC cell lines UM-SCC1 and UM-SCC6 were seeded on glass-bottomed cell culture plates and maintained in the appropriate growth media. Prior to imaging, cells were irradiated in vitro using a X-RAD 320 irradiator. Experiments included two irradiated and two control plates. A multiphoton microscope was used for fluorescence microscopy. Imaging was completed using a 40X water objective to collect NADH and FAD images in the same field of view (FOV). Three FOV were collected from each plate. Analysis was completed using SPCImage. Statistical significance was tested using Kruskal-Wallis tests with an α of 0.05. Data was normalized to control plates that received no radiation.

Results: The average redox ratios in UM-SCC6 cells did not show statistically significant trends at 0.5h, 1h, 2.5h, 24.5h, 25h, and 49h post-radiation compared to controls. We did observe that the average redox ratios of UM-SCC1 cells at variable seeding densities showed an increasing trend from 0.1 mil cells/plate, 0.15 mil cells/plate, to 0.2 mil cells/plate and then decreased as the density was increased to 0.3 mil cells/plate. The maximum average redox ratio was observed at 0.2 mil cells/plate. A statistically significant result for this experiment was observed between 0.1 mil cells/plate and 0.15 mil cells/plate and between 0.1 mil cells/plate and 0.2 mil cells/plate. Conclusion: We did not identify statistically significant differences between the irradiated HNSCC cells and the controls at various time points between 0.5h and 49h post-radiation. Because the results from the seeding density experiment suggest a dependence of the ORR on seeding density, the experimental design of future studies can be strengthened by evaluating this dependence in more depth. Using a programmatic approach to cellular analysis and segmentation for data analysis is an additional way in which the experimental design can be further enhanced. The primary next steps will be to establish a seeding density at which confluency is 80% at the 24h time-point and then repeat the experiment with a multiphoton microscope at the Wisconsin Institute for Discovery to further validate results obtained at the Wisconsin Institutes for Medical Research. Additional investigation will focus on the time-dependent and dose-dependent effects of radiation on OMI. These experiments will be conducted across a series of HNSCC cell lines.
HEALTH PROFESSIONALS’ PERCEIVED BARRIERS AND PRACTICES REGARDING IMPLEMENTATION OF PRECONCEPTION CARE.

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Support: Shapiro Summer Research Program; UW Department of OB/GYN

Background: Preconception care (PCC) aims to improve the health outcomes of women and infants through the improvement of the knowledge and health of women “before planning and conceiving a pregnancy”.

Depression screening, intimate partner violence screening, and contraception counseling represent some of the standards of care indicated by current evidence. However, the CDC’s Pregnancy Risk Assessment Monitoring System (PRAMS) data indicates that the implementation of these practices is far from consistent. Physicians’ attitudes toward this issue have been documented and analyzed in Europe, but to date limited work has been done to explore the attitudes and barriers behind the lack of implementation in US health care settings. Most study thus far has focused on the clinician perspective. The purpose of this study was to elucidate further the barriers to implementing guidelines for PCC services from the perspective of service providers.

Methods: Fifty-four semi-structured interviews were conducted at fourteen health centers serving women of reproductive age across four Wisconsin counties to discuss attitudes and ideas about preconception care and barriers to implementing these evidence-based practices. Interviewees were managers (n = 16), providers (n = 19) and support staff (n = 18) in community health centers, OB-GYN practices, family medicine, and family planning clinics. This study was approved by the UW IRB.

Results: Implementation of PCC varied greatly across different healthcare settings. Awareness of published PCC guidelines was low among people in all roles at all sites (19%, n = 54); provider awareness of published guidelines was 37%. Only 6 out of 14 sites (43%) reported having a standardized protocol for universal depression screening for women of reproductive age. Common reported barriers to PCC implementation included patients’ barriers (n = 20), time and competing priorities during clinical encounters (n = 15), insurance reimbursement (n = 10), and appointment access (n = 7).

Conclusion: This study elucidates the need for further provider education regarding preconception care guidelines and implementation of broader evidence-based practices such as universal depression screening.

References


VALIDATION STUDY FOR PEEK ACUITY IN PEDIATRIC SCREENING PROGRAMS IN PARAGUAY

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Support: Shapiro Summer Research Program, Dan and Ellie Albert Student Vision Research Award

Background: Refractive errors constitute most visual impairments in 19 million children worldwide. The highest density of untreated refractive errors occurs in children of low income settings; therefore, a vision screening program is necessary in these settings. Mobile phone apps show promise in their technology as screening devices. Peek Acuity, a free app, has been validated in adult populations in Kenya, and may have utility in pediatric vision screening programs. Methods: The cohort consisted of 393 subjects aged 5-16 years from Fernando de la Mora, Paraguay. Subjects were randomly assigned a sequence of each vision screening modality from Peek Acuity, a single line of tumbling E optotypes set at 20/40, and Spot Vision Screener. All three screening techniques were performed. Referral criteria were used based on the current American Association of Pediatric Ophthalmology and Strabismus recommendations: 20/40 for Peek Acuity and tumbling E, and refractive error detection for Spot Vision Screener. If subjects failed to achieve the cut-off of any of the three screening techniques or if the subject passed the screening and was randomly selected to calculate false negative rate, the subject was seen by a pediatric ophthalmologist for confirmatory exams. Pediatric ophthalmology evaluation was the gold standard, and consisted of visual acuity (VA) assessment by a Snellen chart, strabismus evaluation, cycloplegic refraction, and dilated fundus exam. The results obtained from the screening modalities were compared to the gold standard for referral and VA agreement. Results: The referral agreement (set at ≥20/40) between Peek Acuity and the Ophthalmic Evaluation resulted in: sensitivity 43.2%, specificity 85.6% and 76% exact agreement. When the VA obtained from Peek Acuity was compared with the VA from Ophthalmic Evaluation, the exact agreement was 31%. Exact agreement of the referral agreement between the other screening modalities, Tumbling E and Spot Vision Screener, and Ophthalmic Evaluation were 77% and 78% respectively. Conclusion: Peek Acuity was not able to reliably predict indication for referral nor accurately predict the VA as determined by ophthalmic evaluation. Peek Acuity trended towards under-referring, indicating a higher VA status than was determined by gold standard. Comparing the app against the other screening modalities used, there was not consistent agreement among the modalities nor between the modalities and the gold standard.
IMPACT OF LIPOSOMAL BUPIVACAINE INJECTED FOR ADDUCTOR CANAL BLOCK ON PAIN AND RECOVERY PROFILE FOLLOWING TOTAL KNEE ARTHROPLASTY

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Mentor: Hubert Cios, MD

Support: Shapiro Summer Research Program; Department of Anesthesiology

Background: With such large rises in the demand for the Total Knee Arthroplasty (TKA) procedure, there are ongoing efforts to increase safety and to improve pain relief, with the intent of achieving fewer complications as well as reducing costs, hospital stays, and opioid consumption. Adequate pain control after TKA is essential for patients to begin their early rehabilitation which serves to decrease swelling, enhance muscle control/strength, and increase range of motion. Regional anesthesia via peripheral nerve blocks such as the adductor canal nerve block (ACB) have become standard for managing postoperative pain but are currently limited by the short duration of analgesics. Attempts to prolong the duration of local anesthetic action has led to the development of liposomal bupivacaine (LBP), which is an extended release drug delivery method. Using the properties of this medication to achieve a longer duration of pain relief in adductor canal nerve blocks could be a potential alternative to continuous infusion techniques while also allowing for quicker rehabilitation. This study aims to evaluate the impact of the use of LBP in ACB on postoperative pain and recovery time profiles compared to a standard bupivacaine formulation.

Methods: This study was conducted as a prospective, single-center, double-blind, randomized trial in which 60 subjects were to be enrolled through UW Health at The American Center. Prior to nerve blockade, subjects were assessed for baseline pain at rest and with activity. Subjects then underwent adductor canal block with either 20ml 1.33% LBP or 20ml 0.5% bupivacaine. Follow-up at time points: 0, 24, 48, 72 hours post operatively assessed satisfaction with regional anesthesia, level of pain, location of most severe pain, opioid consumption, nausea, and duration of stay.

Results: At this time, recruitment is ongoing but as of October, 47 subjects have been recruited and evaluated.

Conclusion: After recruitment of the remaining necessary subjects has been completed, the compiled data will be available for the relevant statistical analyses to evaluate the impact of LBP on post-operative pain and recovery parameters in comparison to standard bupivacaine. This will aid in the determination of the effectiveness of LBP in reducing pain scores, opioid consumption, and hospital stays in patients undergoing TKA.
USE OF E-LEARNING APPLICATIONS TO IMPROVE QUALITY OF LIFE IN PATIENTS WITH CATARACTS IN IMO STATE, NIGERIA.

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Background: Cataracts is a leading cause of visual impairment globally. A community health assessment performed in rural Imo State, Nigeria by Mezu International Foundation (MIF), a non-profit organization, in collaboration with University of Wisconsin Shapiro medical students, found a high prevalence of cataracts in the population. Follow-up studies determined that poor preventative health culture, poor knowledge of personal health conditions, and lack of finances to afford surgery were contributory risk factors to cataracts formation. MIF initiated a vision educational program, and partnered with Combat Blindness Inc. to provide free cataract surgeries to the community. Out of 100 cataract patients screened, 90 were deemed too high risk for same day surgery due to uncontrolled hypertension, diabetes, severe anemia, and advanced glaucoma. This study seeks to investigate the feasibility of using an Electronic based (E) educational program for management of chronic medical conditions aimed at reducing co-morbidities in order to reduce the cataract burden in this community. Methods: A cross-sectional study was done on 83 patients aged 45 to 80 years with mature cataracts. A questionnaire was used to determine Socio-economic status (SES), quality of life (QOL) scores, and E-learning readiness. All subjects underwent detailed medical and ocular exam to identify co-morbidities. Institutional Review Board (IRB) was obtained from a collaborating local institution, Federal University of Technology, Owerri. Results: Out of 83 cataract patients surveyed, 48% were male (n=40) and 51% were female (n=43). Only 2% (n=2) were E-learning ready, while 97% (n=81) were not E-learning ready. 12% of patients had a low QOL score, 55% had moderate, and 33% had high QOL scores. There was a significant association between lower SES scores and lower QOL scores (P=0.0210), as well as lower SES scores and lower E-learning readiness scores (P =0.0400). People with lower QOL scores were not more likely to have anemia (P=0.5172), hypertension (P=0.3298), diabetes (P=0.8242), or glaucoma (P=0.1737). Conclusion: 97% of patients were not E-learning ready. People with lower SES scores had a lower QOL and were less E-learning ready. Interventions aimed at improving E-learning readiness in the community would be critical to the successful implementation of a visual education program in this rural population to reduce cataract surgery screening failure.
EFFECT OF SOCCER HEADGEAR ON LIKELIHOOD AND SEVERITY OF NON-CONCUSSIVE INJURIES IN HIGH SCHOOL ATHLETES

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Mentor: Tim McGuine, PhD

Support: Shapiro Summer Research Program, National Operating Committee on Standards for Athletic Equipment

Background: In response to the rising awareness and concern over sports related concussions (SRCs) in high school soccer players, some athletes are choosing to wear protective headgear (HG) as a form of defense. One criticism of HG use is that it encourages more aggressive play, potentially increasing the incidence or severity of non-concussive injuries. The purpose of this study was to assess associations between use of HG and non-concussive injury in high school athletes. Methods: In a randomized control study of n=1577 Wisconsin high school soccer players, athletes were assigned to a HG group (n=925), or a control group, without the use of HG (n=652) for the 2016-2017 interscholastic seasons. Each athlete provided an SRC history and baseline survey of their concussion symptoms. Athletic trainers at each school recorded the SRCs and non-concussive injuries weekly, as well as additional information about the injuries such as days lost to play. Chi-square tests and logistic regression methods were used to assess for potential associations using intention to treat analyses. Results: 440 non-concussive injuries were reported, affecting 352 (22%) unique athletes. No difference in the likelihood of obtaining at least one non-concussive injury between the control group (21.9%) and the HG group (22.8%) was detected (p=0.157). Further, no difference was detected in the number of days lost between the control group (mean=11.46 days) and the HG group (14.83 days) (p=0.234). While girls were 2.53 (95% CI: 1.80, 3.55) times more likely to sustain a non-concussive injury than boys (p=0.001), after adjusting for HG use there was no significant interaction between the sex of the player and use of headgear on sustaining a non-concussive injury (p=0.21). Conclusion: Wearing HG designed to prevent SRCs does not influence the likelihood of obtaining a non-concussive injury, or the severity of that injury as defined by number of days lost, both of which would be expected if players with HG were competing more aggressively.
ADDRESSING THE HEPATITIS C EPIDEMIC IN CRIMINAL JUSTICE SETTINGS THROUGH
ACADEMIC-PUBLIC HEALTH PARTNERSHIPS

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Support: Shapiro Summer Research Program, This work was supported by NIH/NIDA grants K23DA032306, R01DA030770, and R01DA030770-06S1.

Background: Criminal justice-involved adults tend to be inconsistently engaged in health care. Lack of a national infrastructure for health informatics makes monitoring trends in hepatitis C virus (HCV) screening, linkage to care and treatment difficult for this population. Collaboration across multiple agencies is therefore necessary to fill the data gaps required for epidemiologic descriptions. Through partnerships between the University of Wisconsin and various public health entities, a dataset was created, which was able to describe the continuum of HCV care of incarcerated individuals in Wisconsin between the years 2011-2015. Methods: Since 2011, quarterly meetings have been convened, involving the leadership of 4 entities; The Wisconsin Department of Corrections (DOC), The WI Department of Public Health AIDS/HIV and Viral Hepatitis Program (DHS), The WI State Laboratory of Hygiene (WSLH) and The Division of Infectious Diseases at the University of Wisconsin (UW). The Wisconsin DOC provided name, date of birth and admission/release data for incarcerated individuals from the years 1990-2015 as well as a list of individuals who were prescribed HCV drugs by the DOC pharmacy during incarceration. The WSLH contributed HCV PCR data taken upon intake corresponding to inmates from the years 2000-2015. EMR data was provided by UW Health, including treatment and SVR status for all individuals seen by UW Gastroenterology or Hepatology and evaluated for HCV treatment between 2007 and 2015. In order to assess HCV treatment for those individuals released from prison the Wisconsin DHS contributed data on All HCV RNA and genotype test dates and results which took place in the community within the study period. Results: We identified 3,126 individuals with chronic HCV infection who were incarcerated in the WI DOC between 2011-2015 for at least 30 days. 570 individuals (18%) engaged in HCV care while incarcerated during the study period, while 328 individuals (10%) were treated for HCV and 170 individuals (5%) are known to have achieved SVR (Sustained Virologic Response) 2,556 individuals (82%) were not engaged in HCV care at UW Health during incarceration. Of these, 1,605 individuals (63%) were released from prison for at least 6 months. Laboratory data were available in WEDSS for 1,594 (99%). Evidence of a PCR or genotype test within 6 months of release were identified for 138 individuals (9%), indicating they were likely engaged in medical care in the community. Conclusion: Building partnerships and accessing data from a variety of sources allows for the construction of a complete cohort likely to capture all HCV infected individuals incarcerated across the state of Wisconsin. As efforts to scale up HCV treatment proceed, this cohort will provide a useful framework for studying state-wide HCV control efforts. Public health partnerships have the synergistic potential to not only better understand the HCV epidemic in correctional settings but also inform policy and improve entity-specific outcomes, allowing for mutually beneficial discovery.
IMPLEMENTATION OF NUTRITION AND PHYSICAL ACTIVITY PROGRAMS BY WISCONSIN COUNTY HEALTH DEPARTMENTS

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Support: Shapiro Summer Research Program; Health Resources and Services Administration-Prevention Innovations in Medical Education (PRIME)

Background: Obesity rates in Wisconsin have risen over 50% in the last 15 years, and the current adult rate is over 30%. In 2016, Wisconsin had the 19th highest obesity rate among US states. In Wisconsin, local health departments (LHDs) are primarily county-based and are on the ground implementing evidence-based and evidence-informed programs to address the obesity epidemic. Therefore, we sought to understand the experiences of Wisconsin LHDs implementing nutrition and physical activity (NPA) programs aimed to curb the rising obesity rate. Methods: We conducted semi-structured interviews with key informants working at Wisconsin LHDs and representing different counties. We focused on identifying counties where there had been a decrease in adult obesity rates during the 10-year period from 2004-2013, as characterized by the County Health Rankings. During interviews, we inquired about existing programs to promote NPA, partnerships formed with community organizations, and any program evaluation. Additionally, key informants were asked about program sustainability, barrier, and factors contributing to program success. Results: We conducted 17 semi-structured interviews with key informants from 17 counties. Among the counties represented, adult obesity rates showed 1.8-13% increase. County populations ranged from 7000-500,000; median household income $41,000-$69,500; and percent rural 15.5-100%. Informants reported implementing a broad spectrum of programs that range from nationally-supported evidence-based to grassroots. One partnership to highlight is the collaboration of LHDs with higher education institutions which provide capacities for research, data collection, analysis, and program evaluation. Three main barriers to the success of NPA programs were commonly reported: 1) inadequate built environment, 2) low community buy-in, and 3) policy inaction. Regardless of county characteristics, key informants highlighted the need for community champions, engaging partners during planning stages to align goals, and capability to track outcomes to facilitate program implementation and sustainability. Conclusions: Our conversations with LHDs shed light on the challenges they faced adapting evidence-based programs into each community. The strategies and solutions that the LHDs provided can be helpful for other counties across the US that are also experiencing the same barriers of low buy-in, funding limitations, staff turnovers, and non-ideal built environment.
STANDARDIZED TRAIN-OF-FOUR MONITORING WITH THE USE OF NEUROMUSCULAR BLOCKADE AGENTS TO REDUCE ADVERSE POST-ANESTHESIA OUTCOMES

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Support: Shapiro Summer Research Program

Background: Neuromuscular blocking agents (NMBA) can leave multiple lasting effects on a patient’s post-anesthesia outcomes. Residual block can lead to respiratory muscle weakness that may lead to aspiration, pneumonia, and even reintubation. One method of monitoring this muscle weakness is train-of-four (TOF) monitoring, which can be utilized multiple times throughout the neuromuscular block to provide important information regarding the depth of the block. Additional information can be obtained from a TOF ratio, the ratio of twitch four (T4) to twitch one (T1) height using acceleromyography (EMG). A TOF ratio greater than 0.9 is associated with an acceptable level of recovery to reduce adverse post-anesthesia muscle weakness (1,2). A quality improvement initiative was started at this quaternary care center involving charting TOF, charting reversal of blockade, and reviewing post-anesthesia reintubation rates. Beginning the Plan-Do-Check-Act cycle, it is intended to decrease the rates of post-anesthesia reintubation, improve TOF charting compliance, improve TOF ratio use, and improve appropriate blockade reversal. Methods: Eligibility included adults eighteen years and older that had received general anesthesia with endotracheal tube placement and received either vecuronium, rocuronium, cisatracurium, or atracurium in the inpatient operating room from March 1st, 2017-March 28th, 2017. Exclusion criteria included all cardiac surgery, pediatric patients, patients left intubated, and ASA class 5 or 6. Parameters evaluated included: 1. TOF charted prior to reversal, 2. TOF ratio charted, 3. if no reversal then was TOF ratio > 0.9, 4. if no reversal or TOF ratio > 0.9 then was it more than 3 hours since last NMBA dose, and 5. reintubation within two hours postoperatively. We then worked in an interdisciplinary team with pharmacy, information technology, and multiple anesthesia providers (faculty, resident, CRNA, AA, medical students) to design updates in the EPIC electronic health record (EHR). Pop-up reminders were implemented to prompt providers to monitor TOF during the case after any non-depolarizing blockade agent was given, and then to chart reversal given. Results: The initial four-week data collection showed a few notable behaviors in this department regarding neuromuscular blockade. Charting TOF compliance was lower than expected at 81.78% and TOF ratio use was 21.38%. Failure to give patients reversal without charting return of neuromuscular function was 3.90%. Data was again collected between June 26th, 2017 and July 23rd, 2017. Comparison between groups in the parameters listed above revealed TOF charting compliance increase from 81.78% to 87.08%. There was also a decrease in reintubations due to respiratory muscle weakness from residual neuromuscular blockade from one to zero between groups. TOF ratio use continued to be poor, however this was likely due to engineering issues with monitor compatibility issues that are being investigated. Conclusion: Due to the brief period of data collected pre- and post-intervention, it is worthwhile for additional data collection over a longer period to assess any statistical significance to our findings, but the trend is encouraging. It is intended to continue these “pop-up reminders” in the EHR. Future iterations of the PDCA cycle could include developing additional reminders in EPIC to providers to give appropriate doses of neostigmine and sugammadex (reversals) based on TOF and TOF ratio based on current literature. As this first cycle of PDCA completes, we will need to finish assessing our effectiveness and plan for the future, all in an effort to reduce adverse patient outcomes.

References
SINGLE SCREW ANTERIOR HEMI-EPIPHYSIODESIS FOR THE TREATMENT OF FIXED KNEE FLEXION DEFORMITIES

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Support: Shapiro Summer Research Program

Background: A normal active range of motion (AROM) of the knee is 0° extension and 140° flexion. A fixed knee flexion deformity (FKFD) is defined as a reduced active range of motion of one or both knees. This is most often seen in patients with cerebral palsy, spina bifida, or arthrogryposes, but can arise in other neuromuscular conditions as well. Due to the varying degrees of severity there are several different treatment approaches, ranging from physical therapy to supracondylar osteotomy or even amputation. A new concept is to utilize guided growth (anterior hemi-epiphysiodesis) of the anterior distal femur to achieve safe and gradual correction of the crouch pattern. The most common modes of guided growth have been accomplished via staples or 8-plates. UW Health is the only hospital that utilizes a single screw technique to promote guided growth. Knee pain, progressive crouch gait, and muscle weakness are just a few of the complications that can result from lack of, or improper treatment, of a FKFD. The 8-plate technique is the most documented of the guided growth techniques and has seen complications due to the hardware being inside of the knee joint itself. A single screw approach may have fewer complications and higher patient satisfaction compared to other FKFD treatments.

Methods: There were four main areas of data collection. Patient identification: after figuring out the billing codes we created a comprehensive list of patients who have undergone single screw guided growth dating back to September 2009. Preoperative data: such as the diagnoses creating the necessity of the surgery, comorbidities, previous surgeries, and age at surgery. Surgical data: ongoing pain, valgus/varus, pre/post-surgery knee extension, AROM, and several measurements to demonstrate the effectiveness of the surgery. Lastly, follow up appointments: we assessed their new AROM and took both lateral and anterior x-rays. The PACs operating software was used for the following measurements for pre, post, and follow up x-rays (images are vital in understanding the measurements). Anterior & posterior (A/P) femoral vs physeal angle, A. femoral vs A. tibial angle, A. femoral vs screw angle, and Koshino index (determines patella height) were all measured. Results: Our results have not been completed at this time, but a lot of progress has been made. We have had 95% of our patients come back in for their follow up appointment and are just waiting on two patients so we can complete our data set. As of now our ongoing pain and complication rates are very low. We are anticipating a correction rate comparable to if not better than traditional methods.

Conclusion: In conclusion, the single screw guided growth technique has only been implemented in one hospital but has shown promising results indicating that more hospitals should look at it as a treatment option for FKFDs and that further studies need to be done to more accurately compare the two procedures in a controlled setting. The next step is to compare our single screw data with the double screw technique practiced at the Children’s Hospital of Los Angeles. We have been working closely with them to make sure we cover the same data points and measurements so we can more accurately compare the two techniques.
TOBACCO USE AND HYPERTENSION CONTROL AMONG YOUNG ADULTS

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Support: Shapiro Summer Research Program; University of Wisconsin School of Medicine & Public Health - Department of Medicine and Division of Cardiovascular Medicine; K23 HL112907-01 National Heart, Lung and Blood Institute (NHLBI) Johnson (PI)

Background: Uncontrolled hypertension (blood pressure ≥140/90 mmHg), the leading preventable cause of death in the United States, is associated with an increased risk of premature cardiovascular disease (CVD), stroke, and chronic kidney disease among young adults (18-39 year olds). A few studies have demonstrated differences in hypertension clinical care delivery between current/former tobacco users compared to those with no prior tobacco use. The purpose of this study is to compare the rates and predictors of achieving hypertension control by tobacco use status (current, never, former) among young adults with incident (new) hypertension. Methods: A 4-year retrospective analysis included 2752 patients ages 18-39 who received primary care at a large academic group practice from 2008 to 2011. Patients met national guideline clinical criteria for a hypertension diagnosis. Kaplan-Meier analysis estimated the probability of achieving control for patients with a current, former, or never smoking status. Cox proportional hazard models, including hazard ratios (HR) and 95% confidence intervals (CI) were fit to identify predictors of hypertension control, adjusting for a patient's type of hypertension (systolic, diastolic, combined systolic/diastolic hypertension), sociodemographics, comorbidities, and provider characteristics. Results: Overall, 31% were current tobacco users and 32% were former tobacco users. Only 14% of young adults achieved control within 24 months of developing incident hypertension. After adjustment, there was not a significant difference in hypertension control rates among current (HR 0.72; 0.52-1.02) or former tobacco users (HR 0.84; 0.60-1.17), compared to never smokers. Factors associated with a slower rate of hypertension control included female sex (HR 0.39; 0.30-0.51), white race (HR 0.69; 0.50-0.94), and non-English primary language (HR 0.33; 0.19-0.59). Factors associated with a faster rate of hypertension control included hyperlipidemia (HR 1.60; 1.07-2.41) and number of primary care (HR 1.06; 1.01-1.12) and specialty care visits (HR 1.15; 1.07-1.24). Conclusion: Tobacco use status is not associated with faster or slower hypertension control rates in young adults. The very low rate of overall hypertension control at 24 months was a surprise to our research group and will be the focus of our next project.
TRENDS IN CANCER INCIDENCE AND MORTALITY RATES IN AMERICAN INDIANS AND WHITES IN WISCONSIN, 1995-2012

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Mentor(s): Tracy Downs, MD, FACS; Rick Strickland, MA; Charles Wiggins, PhD

Support: Shapiro Summer Research Program; Department of Surgery

Introduction: American Indians in Wisconsin like other AI/AN in the Northern Plains region experience significantly higher cancer incidence and mortality rates than Whites. Previous analysis has examined rates for a specific time period but the question is, have they changed over time and if so how? This research is the first to explore trends in disparities in cancer incidence and mortality between American Indians and Whites in Wisconsin which occur over the period 1995-2012. Methods: Incident cancer cases were identified from records of the Wisconsin Cancer Reporting System. Deaths due to cancer were ascertained from the Wisconsin Bureau of Vital Statistics. All rates were calculated with the SEER*Stat software package and are expressed per 100,000 person-years. Time trends in incidence and mortality rates were assessed with joinpoint regression techniques using software from the National Cancer Institute. Results: Cancer disparities persisted for American Indians and Whites in Wisconsin CHSDA counties over the 17-year study period. Trends over this period reveal a mixed picture by cancer site and sex, including some declines in disparity. For AI men, there are some signs of progress, but for AI women, cancer disparity increased or remained constant over the period. For AI women, the disparity in lung cancer mortality also increased, but it declined for men. In the case of colorectal cancer, the disparity rates have remained relatively constant. Conclusions: This trends analysis resulted in an enhanced understanding of Wisconsin AI/AN cancer rates and additional information of value to tribes. The next step in the future is to work with tribal communities to ask why these specific trends are occurring using methods that recognize and integrate indigenous knowledge into a more traditional Western research model.
POSTOPERATIVE COMPLICATIONS OF BACLOFEN PUMPS IN SCOLIOSIS SURGERY FOR CEREBRAL PALSY PATIENTS

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Support: Shapiro Research Program; Department of Orthopedics and Rehabilitation

Background: Patients with cerebral palsy experience significant complications associated with baclofen pump placement before, during or after spinal fusion. Some of the complications include infections, pump- or catheter-related complications or malfunctions as well as the risk of scoliosis progression. Methods: A retrospective review was completed comparing CP patients undergoing posterior spine fusion (PSF) to those who had a PSF after an intrathecal baclofen pump (ITB) placement over a 15-year period at a single center. Aspiration pneumonia, swallow studies, percentile weight change and hospital admissions for constipation were compared two years preoperative and postoperative PSF. Intraoperative measures during the 10-day hospital admission included weight based morphine equivalents administered, baclofen administration, need for further surgery and infections during surgery were also compared. Results: 16 patients with ITBP and 23 patients without ITBP met inclusion criteria. Age, co-morbidities, number of levels fused and fixation techniques during PSF were not significantly different between cohorts. Children without an ITB received more weight based morphine equivalents 4.96 compared to 3.90 with an ITB (p=0.288). Additionally, children without an ITB received significantly more baclofen during their 10 days of admission (p=0.038). Constipation visits increased for both cohorts (1.83 versus 0.938; p=0.347) two years post PSF. ITB patients also had a 3.9 fold increase in percentile weight gain (p=0.154) compared to those without an ITB. Children without an ITB received a greater amount of weight based morphine equivalents (4.96 versus 3.90; p=0.288). Lastly, there was an 11-fold increase in aspiration pneumonia for patients with an ITB (0.44 versus 0.04; p=0.341) two years post PSF. Conclusion: Children with ITB did not experience significantly higher complication rates with regards to constipation, percentile weight change, weight based morphine equivalents and baclofen dose. Conversely, ITB patients had a much greater rate of aspiration pneumonia following their PSF surgery. This is the first investigation to report higher rates of aspiration pneumonia in children with ITB following PSF surgery. Additionally, this study shows patients with ITB had greater increases in percentile weight gain and received less weight based morphine equivalents than their non-ITB counterparts.
4D-DIGITAL SUBTRACTION ANGIOGRAPHY: A NOVEL TECHNIQUE FOR QUANTIFYING CHANGES IN HEPATIC ARTERIAL FLOW DURING TRANSARTERIAL EMBOLIZATION

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Support: Shapiro Summer Research Program; Department of Radiology

Purpose: Degree of stasis affects response to and survival after transarterial embolization (TAE). Despite this, angiographic endpoints during TAE are subjective and highly variable. Time-resolved 3D- Digital Subtraction Angiography (4D-DSA) is a recently developed technique that permits quantification of blood flow and velocity. We aimed to validate the accuracy of 4D-DSA for quantifying hepatic arterial blood flow/velocity along with its ability to show changes in flow during TAE. Materials: Hepatic arteriography and TAE of two of the four liver lobes were performed in five female domestic swine using 100-300μm and 300-500μm Embosphere Microspheres. Conventional 2D- and 4D-DSAs were performed before, during, and after each embolization. From the 4D-DSA reconstructions, blood flow and velocity values were calculated for the common, right, left and lobar hepatic arteries using a pulsatility based algorithm. 4D-DSA flow and velocity values were compared to those measured using an intravascular Doppler wire with a linear regression analysis. Paired t-tests were used to compare data before and after embolization.

Results: There was a statistically significant but suboptimal correlation between the two methods (r=0.36, N=42, p.05). The Doppler measurements were positively biased in vessels with high pulsatility (χ2(1, N=11)=13.3, m=.55, b=4.5, p>.05). This might be related to the difference in data acquisition (average peak in Doppler vs spatially averaged velocity in 4D-DSA) or the flow dynamics of blood and contrast. 4D-DSA performed mid-embolization showed a global reduction in hepatic blood flow and velocity in the embolized liver when compared to pre-embolization (10.9±1.9 vs 4.5±0.7 cm/s, p=0.008). Complete stasis was achieved in all cases, at which point reliable measurements could not be made using 4D-DSA due to low signal. Conclusions: 4D-DSA can accurately reflect changes in hepatic arterial blood flow during TAE and it is a promising method for quantifying blood flow and velocity during angiography. While further work is needed to optimize the injection protocol and acquisition parameters, 4D-DSA may provide an objective, C-arm based means of determining angiographic endpoints during embolization.
EVALUATION OF CLINIC-COMMUNITY PARTNERSHIPS IN RESIDENT CLINICS IN UW MEDICINE CLINICS

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Support: Summer Research & Clinical Assistantship, Department of Family Medicine and Community Health

Background: Residents, faculty, and staff participate in community health projects at each of the four Madison-area residency clinics: Belleville, Northeast, Verona, and Wingra. No central report exists for faculty, staff, and community members to learn about these community health projects. The aim of this study is to gather the perspectives of clinic informants and community partners and to start creating a database of current projects. Methods: Clinic informants, clinic members conducting community health projects, from the four Madison-area residency clinics were surveyed by email and interviewed in person. The multiple-choice survey for clinic informants focuses on identifying current and top most important collaborations. Community partners, individuals that collaborate with these clinics on community health projects, were surveyed by email. The multiple-choice survey for community partners identified collaborations of most interest and facilitator and barriers to the partnerships. Results: Clinic informants identified partnership to influence policies impacting upstream determinates of health was identified as a top important collaboration. Community partners identified partnership to provide health education to individuals and families as a top collaboration of interest. Shared understanding of community needs and mutual trust were identified mainly as major facilitators to clinic-community partnerships, engaged clinic leadership as a facilitator, adequate clinic staff availability and shared funding as barriers. Six clinic member interviews have been conducted to date. Based on interviews, improving patients’ lives and increasing staff morale are top motivators to continuing community health projects. Conclusion: Community partners’ responses can inform the clinics of potential improvements in community health projects. While the clinic’s and community’s goals generally align, clinics will be able to address differences in community partners’ expectations revealed by the surveys. Furthering partnerships will require follow-up interviews with community partners, engaged staff and dedicated time. Surveys could be used to evaluate future clinic-community partnerships at other Family Medicine clinics.
FUNCTIONAL RECOVERY IN TOTAL KNEE ARTHROPLASTY USING LIPOSOMAL BUPIVACAINE FOR ADDUCTOR CANAL BLOCK

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Mentor(s): Hubert Cios, MD

Support: Shapiro Summer Research Program; Department of Anesthesiology

Background: Effective postoperative pain control is critical to improve functional outcomes and facilitate faster recovery after total knee arthroplasty (TKA). Adductor Canal Blockade (ACB) provides effective analgesia and preserves quadricep motor strength by selectively blocking sensory nerves, which may improve postoperative mobility and reduce time to discharge. Liposomal bupivacaine (LBP) is an attractive candidate for ACB due to its potential for longer-lasting analgesia combined with reduced motor weakness, but its use in ACB has not been evaluated. This study compares functional recovery and motor strength in TKA between adductor canal blocks using LBP or bupivacaine. Methods: This was a prospective, double-blind randomized trial with recruitment goals of 30 patients receiving LBP and 30 patients receiving bupivacaine HCl for ACB in elective TKA. Gait velocity, duration of Post-Anesthesia Care Unit (PACU) stay, duration of hospital stay, range of motion, pain at rest, and pain with activity were evaluated to assess functional recovery. Quadriceps strength was assessed preoperatively and postoperatively using the Kilo FLEX System Isokinetic Dynamometer. Results: As of October, 47 subjects have been recruited and evaluated. Recruitment is ongoing. Conclusion: After recruitment and data collection are complete and data can be unblinded, measures of functional recovery, pain control and length of hospitalization will be compared between groups receiving LBP and bupivacaine HCl to determine if the use of liposomal bupivacaine in ACB improves outcomes or shortens hospital stays.
IDENTIFYING FACTORS IMPACTING TIME TO MRI FOR EMERGENCY DEPARTMENT PATIENTS

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Mentors: Michael Repplinger, MD, PhD; Becky Bracken, BS

Support: Shapiro Summer Research Program, Department of Emergency Medicine

Introduction: As of 2014, there were over 80 million computed tomography (CT) scans performed each year, and an estimated 1.5-2% of all current cancers are hypothesized to be related to patients’ exposure to radiation from these scans. Magnetic resonance (MR) imaging, however, does not expose patients to ionizing radiation and is equally effective or superior to CT in the workup of multiple conditions, though its adoption into routine clinical practice has been generally slow and highly variable. Several factors have been suggested as barriers to its widespread adoption, including long image acquisition time, high cost, and limited access to MR scanners. At the University of Wisconsin (UW) emergency department (ED), access to MR scanners has been less of an issue since the implementation of 24/7 in-house MR technologists in 2014 (previously on call after normal business hours). This study aimed to determine if this increase in MR technologist hours shortened time from order to preliminary interpretation of MR images for UW ED patients. Additionally, we performed a prospective, qualitative study of the MR image acquisition process to identify factors that slow this process for ED patients.

Methods: We performed a retrospective, observational study of every patient who underwent CT or MR imaging during a UW ED visit from April 2012 to May 2017. Patients were identified by searching the hospital’s billing database for CPT codes corresponding to CT or MR studies, and time stamps of image order and preliminary read for these studies were abstracted using an automated process. 5,948 MR studies and 44,011 CT studies were included in analyses. A linear regression was used to compare the time interval before and after May 2014, adjusting for age, sex, and body region scanned. For the qualitative portion of the study, a convenience sample of 50 patients for whom MR was ordered in the ED was prospectively selected and followed from study order through the image acquisition process. Study staff interviewed ED nurses and MR technologist caring for that patient to identify barriers or delays in the MR imaging process.

Results: Of the retrospective study cohort, 60.3% of the MR group and 54.7% of the CT group were female. The mean age of subjects was 44.3 years and 50.8 years for MR and CT, respectively. For MR, the time interval for studies conducted after May 2014 was on average 0.094 hours shorter (p=0.463, 95% CI: -0.345, 0.157) than for those before May 2014. When studies with time intervals over 24 hours were excluded, the average time interval was 0.125 hours shorter (p=0.02, 95% CI: -0.231, -0.0192), but when scans with time intervals over 13 hours were excluded, the average time interval was 0.089 hours longer (p=0.038, 95% CI: 0.005, 0.173). For CT, the time interval for studies conducted after May 2014 was about 1.5 hours shorter, regardless of exclusion criteria (p<0.001 in each case). Of the prospective study cohort, consistent factors causing delays in the MR process were found to be poor communication and unclear responsibilities of ED vs MR staff. An example of a common breakdown in communication was ED staff not knowing when MR had availability, sometimes resulting in the MR scanner sitting vacant while the patient to be scanned was merely idle in the ED. Also, there was confusion as to who should perform the screening of patients to determine if they had any implants disqualifying them from being imaged by MR.

Conclusion: Time from study order to preliminary read increased after May 2014 for MR but decreased for CT. As it is unlikely that adding personnel would cause longer times, it is likely that factors unaccounted for in this study caused the longer times for MR. One such factor could be recent hospital construction, which would affect MR more than CT due to the distance of the MR suite from the ED. Additionally, while we discovered significant factors slowing the MR process, further work could be done to quantify the impact of these factors and rectify them.
SIMULATION-BASED MEDICAL EDUCATION: DEVELOPMENT OF AN ASSESSMENT TOOL FOR NOVICE USE

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Support: Shapiro Summer Research Program, Department of Surgery

Introduction: Implementation of Simulation-Based Medical Education (SBME) has been shown to improve student’s clinical skills. Assessment and feedback of students’ performance is necessary for learning and improvement. However, assessing students typically requires prior training, and, therefore an experienced clinician. The efficiency and frequency of SBME could be improved if assessment could be completed without the need for prior training in medicine. Using a group of non-clinically experienced persons, or crowdsourcing from clinical-novices, to assess student performance in simulation has been shown to be efficient and has the potential to provide the same quality of assessment as a clinical expert. The purpose of this study was to develop a performance assessment for clinical simulations that would allow clinical novices to assess students and provide scores comparable to that of an experienced clinician. Methods: An internship preparatory curriculum implemented SBME by conducting simulations of common on call scenarios utilizing a high-fidelity mannequin. Twenty-three fourth-year medical students participated in three simulations. Faculty and resident surgeons used an adapted Oxford Non-Technical Skill (a-NOTECHS) scale to assess student performance. Two faculty surgeons and two clinical novices collaborated to produce a checkbox-based assessment specific to each scenario, the modified NOTECHS (m-NOTECHS). The two clinical novices and one non-clinical researcher then used the m-NOTECHS to assess student performance in the course simulations. Interrater reliability will be calculated among the three novices and compared to the faculty scores provided during the course.

Results: Currently, the simulations are still being scored by the third novice. Preliminary data on the third simulation shows an intraclass correlation of 0.84 < ICC < 0.928 at 95% confidence between the two clinical novices that developed the assessment. This data suggests good correlation in scoring, however, current box plot comparison of the novice scores to the faculty scores shows the novices tended to rate student performance lower than the faculty. Conclusion: Our preliminary results suggest good reliability between the novice raters using the m-NOTECHS for simulation 3. However, descriptive data show that students receive lower scores when assessed by clinical novices using the m-NOTECHS compared to faculty surgeon scores using the a-NOTECHS. This could mean the newly developed assessment is at a higher level than the skill of the students, or perhaps faculty raters were more lenient because they knew they were scoring medical students and the a-NOTECHS scoring choices were more subjective. The main weakness of this study is that there were multiple faculty assessors and the faculty scores were obtained using the a-NOTECHS, whereas the novices used the m-NOTECHS. More statistical comparisons will be done once the additional novice data set is available. Future work will compare scores from an experienced physician using the m-NOTECHS to the clinical novices’ ratings.
DIALYSIS DECISION-MAKING CONVERSATIONS BETWEEN NEPHROLOGISTS AND OLDER ADULTS WITH LATE-STAGE RENAL DISEASE

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Support: Shapiro Summer Research Program; Department of Surgery NIH T35DK062709

Background: Each year, nearly 30,000 adults age 75 and older will initiate dialysis for end-stage renal disease. The survival advantage of dialysis for older patients can be limited, especially for those with serious comorbidities whose 1-year mortality is upwards of 40%. Furthermore, the burdens of treatment are significant, including frequent hospitalizations, chronic pain, fatigue and functional decline. The objective of this study is to characterize dialysis decision-making conversations between nephrologists and older adults with late-stage renal disease to identify opportunities to support access to palliative care.

Methods: We audio-recorded 12 conversations between nephrologists (N=6) and patients age 70 and older with eGFR of less than 20. We used OPTION 5, a validated observer measure of patient engagement in decision making, and qualitative analysis to characterize the decision about dialysis initiation.

Results: Out of a total of 100, the median OPTION 5 score was 17.5 (IQR=15-32.5). The median scores of the five domains within the OPTION 5 instrument ranged from 2.5 to 5 (out of 20), suggesting global opportunities for improvement in shared decision making regarding dialysis initiation. Nephrologists typically focused these conversations on causes of kidney disease, review of lab values, lab scheduling, medication adjustment, and strategies to prepare the patient for dialysis, such as surgical consultation for dialysis access. Many conversations did not include information about prognosis, illness trajectory or expected changes in quality of life. A few proposed consideration of “no dialysis,” but this option was not described in detail. While nephrologists carefully sought out patient preferences for mode of dialysis, there was limited discussion about how this treatment might support patients’ values and goals.

Conclusion: Currently, conversations between nephrologists and patients emphasize routine kidney disease management and preparation for dialysis. They do not provide information patients need to decide between dialysis and no dialysis, or recognize the value of palliative care concurrent with either route. Our OPTION 5 scores are consistent with scores from other settings, where clinicians typically score <25 at baseline and can improve to ≥50 with interventions to improve shared decision making. As such, interventions to support patient engagement in treatment decisions may help patients with late-stage kidney disease better understand their illness, anticipate poor outcomes, and make shared treatment decisions aligned with their goals.
QUANTITATIVE MRI AND EM ANALYSIS OF MYELIN CONTENT IN CATS

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Support: Shapiro Summer Research Program, Department of Radiology, Department of Medical Physics, University of Wisconsin School of Veterinary Medicine - Department of Medical Sciences, National Multiple Sclerosis Society Grant RG-1501-02876

Background: Development of novel myelination-promoting therapies for myelin diseases (e.g. multiple sclerosis) requires in vivo imaging-based measures of myelin content. Magnetization transfer (MT) MRI imaging of cats affected by extensive, reversible demyelination of the central neural system (CNS) have revealed tissue changes during disease progression1. However, standard MT parameters such as MT Ratio (MTR) have low specificity for myelin. This project aims to create more accurate tools for evaluating changes in myelination based on noninvasive (MRI) and ex-vivo electron microscopic (EM) imaging.

Methods: Our approach was based on quantitative modeling of MT imaging, which yields an estimate of the Macromolecular Proton Fraction (MPF) in tissue. MPF previously demonstrated greater sensitivity and specificity to myelin than existing metrics. To evaluate CNS myelination, supervised automated software for MPF mapping was developed in MatLab. The processing pipeline was validated using MR images obtained in cats (n=10) before disease manifestation. Additionally, EM images were used to create an automated software tool for calculating the myelin G-ratio (measure of myelin thickness relative to axon diameter) and myelin density. Results: The newly developed programs were able to produce MPF maps from raw MT MRI scan sequences and myelin densities from EM of the spinal cord. The developed MPF calculation software produced MPF maps of diagnostic quality with high contrast for myelinated areas of the feline brain and spinal cord. Automated EM processing calculated myelin G-ratios, a measure of myelination, comparable to manual image processing and produced myelin density maps. Both programs improved efficiency of image analysis by significantly reducing user input and accelerating processing (>30 minutes to <10 minutes per EM image). Conclusion: The developed tools will facilitate ongoing and future studies of myelination in animals and humans. In the near term, the MPF processing will be utilized for analysis of MR images of cats as they progress through demyelinating disease and during recovery. These results will be compared to EM measurements of myelin density throughout the spinal cord to determine the sensitivity of MPF to disease- and treatment-related changes in myelin.

Citations:
LYMPHANGITIC CARCINOMATOSIS AND PULMONARY TUMOR EMBOLISM IN A BREAST CANCER PATIENT: DIAGNOSTIC CHALLENGES AND LESSONS

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Support: n/a

Introduction: Screening, diagnosis, and treatment of breast cancer in the United States has been the target of robust research, medical, and public health efforts. Consequently, mortality from breast cancer in the United States has been decreasing at the rate of approximately 2.2% annually since 1990. However, breast cancer remains the second most common cause of cancer deaths among women in the United States, and is the focus of significant effort at the level of basic research, clinical study, and policy. In this case report, we will review the presentation of a female patient with clinically occult breast cancer who died as a result of respiratory failure attributed to lymphangitic carcinomatosis and pulmonary tumor embolism. We present this case report as an example of the limitations of current screening and diagnostic protocols.

Methods: A retrospective chart review of a single patient was performed, including clinical history and findings on autopsy performed at the University of Wisconsin School of Medicine and Public Health Department of Pathology and Laboratory Medicine.

Results: Study of the clinical history of the case revealed a rapidly progressive course of dyspnea that developed over a two-month period, resulting in patient demise due to respiratory failure. Clinical evaluation of the patient included a differential diagnosis of pneumonia, obstructive lung disease, and unknown pulmonary lymphangitic process. Ultimately a bone marrow biopsy revealed metastasis from a solid organ malignancy of unidentified origin most consistent with a breast cancer primary. Findings on autopsy demonstrated extensive tumor cell invasion of pulmonary lymphatics and arterioles, in addition to small vessels in the right ureter, liver, and dura. Thorough review of breast specimens collected at autopsy yielded a small focus of ductal carcinoma with lobular features against a background of extremely dense breast tissue. Review of the patient’s medical record indicated that the breast density had been documented by her medical providers at regular screening mammograms, and that recommended additional imaging via MRI and/or ultrasound had not been pursued. No breast masses or other abnormalities were noted throughout the sixteen-year period of screening mammograms available for review.

Conclusion: Significant progress in breast cancer morbidity and mortality has been achieved via improved screening and diagnostic modalities and criteria, including the development of evidence-based guidelines stratifying breast cancer risk and prognosis by clinical factors such as breast density. Current barriers to effective screening and diagnosis of breast cancer, especially in patients with highly dense breasts, include limitations in imaging technology, paucity of biomarkers for breast cancer, and challenges in adherence to guidelines for advanced evaluation of high risk patients. Future directions include an upcoming retrospective chart review of a larger cohort of cases of lymphangitic carcinomatosis and pulmonary tumor embolism among breast cancer patients evaluated and treated at the University and Wisconsin Hospital and Clinics, to elucidate modifiable factors in the diagnosis and clinical management of these patients.
BARRIERS TO CONTROL OF HOSPITAL ACQUIRED INFECTIONS IN JIMMA, ETHIOPIA

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Mentors: Dawd Siraj, MD, MPH; Nasia Safdar, MD, PhD

Support: Shapiro Summer Research Program; Department of Medicine

Background: Hospital-acquired infections (HAIs) are responsible for high rates of patient morbidity and mortality, particularly in low income countries. This burden can be decreased when a systems approach is taken to improve infection control within a hospital. The Systems Engineering Initiative for Patient Safety (SEIPS) model provides a framework that can be used to identify barriers and facilitators of infection control practices and evaluate interactions between structures, processes, and outcomes to identify areas of potential improvement in the complex environment of a hospital. Methods: A qualitative study was done to evaluate the potential barriers and facilitators to implementation of effective infection control practices at Jimma University Specialty Hospital in Jimma, Ethiopia. Twenty-two semi-structured interviews of physicians, nurses, pharmacists, and environmental services employees, selected by convenience sampling, were conducted in English or with a translator using an interview guide based on the SEIPS framework. The interviews were subsequently transcribed, coded for themes, and analyzed using the software Dedoose. Results: The primary facilitators to effective infection control were identified at the task, organization, and person level. Prominent themes included having a manageable workload, a management system supportive of institutional feedback, sufficient available budget, and positive individual motivation and attitude towards improving infection control. The primary barriers to effective infection control were found to be at the technology and tools, person, and organization levels. The major themes within these levels include poor supply chain management leading to personal protective equipment shortages, an inconsistent and incomplete training program for employees, a lack of infection control policies, a lack of involvement of environmental services, and a nurse rotation program that increases unit staff turnover. Conclusion: To address the identified gaps we recommend that Jimma University Specialty Hospital prioritize the establishment of a functioning infection control department. The aims for this department should include development of infection control policies and protocols based on WHO guidelines, expanding the training program for new employees and including a yearly review for existing employees, incorporation of environmental services to the healthcare team, oversight of quantification and management of personal protective equipment supply chain, and establishing an HAI surveillance program to better identify current risk areas as well as track progress.

References:
IMPROVING RECRUITMENT FOR COMMUNITY WELLNESS WORKER-LED POSTPARTUM SUPPORT GROUP

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Mentor: Sarah Webber, MD

Support: Shapiro Summer Research Program; Wisconsin Partnership Program

Background: In Dane County, the health indicators of postpartum Latina mothers and their young children lag behind corresponding indicators among Caucasians.1-3 To address these disparities, Centro Hispano of Dane County partnered with UW Health Department of Pediatrics to offer a monthly support group program to postpartum Latina mothers, to be led by Spanish-speaking Community Wellness Workers (CWWs). The program began in April 2017 with a plan for ongoing evaluation using the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework.4 One of the early focuses was on the Reach component of the evaluation framework. While on average 539 Latino infants are born in Dane county each year, the average number of participants in the support group during the early months was only two.5-7 In order to improve the reach of the program, we sought to develop a comprehensive plan to enhance recruitment. Methods: We began our intervention in June 2017, two months after the program was started. We used multiple methods to address marketing and barriers to attendance. We held a focus group in which CHWs identified factors that could impact attendance, including household responsibilities, child care obligations, health insurance status, citizenship status, discomfort with session topics listed on the pamphlet, family dynamics, travel difficulties, perception of self-care, and unfamiliarity with the local organization. In addition, we held meetings with Centro Hispano’s administration and staff, and we instituted recruitment at a local clinic through a research nurse. Finally, we discussed marketing ideas with peers. On our program handouts, we clarified that insurance is not necessary for attendance and that childcare is offered for free, and we removed mention of mental health and obesity. In the handouts we also explained how Latina mothers and their infants can benefit from meeting with CHWs and fellow mothers in Dane County once a month, and described the sessions as a safe space where mothers can ask questions. Centro administration emphasized the importance of partnering with Access Community Health Centers, the Women, Infants, and Children (WIC) office, Planned Parenthood, and other Madison-area UW Healthcare organizations to provide our handouts to service and healthcare providers, and to encourage them to recommend Centro’s program to qualifying patients. Centro administration and staff suggested we provide our handouts at places in Madison where new Latina mothers may frequent, such as laundromats, grocery stores, health centers, libraries, hair salons, and restaurants. Results: Monthly attendance has increased on average since the early months of the program. Mean attendance between August-October 2017 is five mothers, compared to the mean of two during the first three months. Conclusion: Because mothers that attend during monthly sessions are not yet asked how they heard of the program, it is not clear to what extent our summer marketing efforts contributed to the increase in attendance over time. Although more than 500 newborns are born to Latina mothers in Dane County each year, challenges to recruit Latina mothers in the community are numerous. Word of mouth advertising by CWWs to potential attendees is less effective when there are only six CWWs available to advertise regularly in the community. Given that members of the Latina community may be more likely to have phone numbers than email addresses, it is not possible to send out mass informational emails to potential attendees. Therefore, one of the few ways that Centro can reach mothers directly is if mothers visit Centro in person. However, recent politics around immigration may influence Latino community members’ perception of safety in a way that impacts participation. Lack of convenient transportation may also prevent mothers from reaching Centro. Next steps will include both training CWWs to track recruitment in greater detail, and holding a focus group with Latina mothers that regularly attend the monthly sessions. These actions will enable us to identify and implement ways to improve marketing and recruitment.

References
COMPARTMENT SYNDROME IN PEDIATRIC MONTEGGIA FRACTURES AND EQUIVALENTS

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Mentors: Kenneth Noonan, MD; Paul Whiting, MD

Support: Shapiro Summer Research Program; Department of Orthopedics and Rehabilitation

Background: Compartment syndrome (CS) is an orthopedic emergency that requires a timely diagnosis to prevent irreversible muscle and nerve damage. Diagnosing CS can be especially difficult in children, thus requiring well-informed providers with appropriate clinical suspicion. Current literature has little to no association of CS with Monteggia fractures, a well-defined pediatric elbow fracture-dislocation injury. The aim of this study was three-fold: (1) to determine the incidence of CS in pediatric Monteggia fractures and equivalents (2) to characterize the cases of pediatric Monteggia fractures, looking for significant variables in those that developed CS, and (3) to compare the incidence of CS in Monteggia fractures to the incidence of CS in supracondylar humerus (SCH) fractures (a fracture pattern classically associated with CS).

Methods: A retrospective chart and radiographic review was performed of children ages 2-12 with Monteggia fractures and equivalents requiring operative management at a single institution over a 14-year period (1/1/03 – 5/29/17). All cases of Monteggia fractures were further reviewed, with special focus to identify key variables in those cases that developed CS. The incidence of CS in Monteggia fractures was then compared to the incidence of CS in surgically treated Type 3 SCH fractures in the same population at the same institution over the same time. Results: For the first objective, 9 of the 61 operatively managed Monteggia fractures developed CS (14.75%). Analysis of collected data specific to Monteggia fractures is currently underway, attempting to better predict cases likely to develop CS. Points of analysis include fracture pattern, age, ER/OR timing, other ipsilateral injuries, surgical techniques, and follow up data. The incidence of CS in Monteggia fractures was significantly greater than the incidence of CS in surgically treated Type 3 SCH fractures (2/230, 0.87%, p <0.00001). Demographic comparisons between SCH and Monteggia fractures are currently underway. Conclusion: The result of objective three is alarming and will surprise many in the pediatric orthopedics community when it comes to acute care management of Monteggia fractures. Going forward, our second objective, analyzing the Monteggia fractures, will provide direction for further study. Questions to be addressed: Are certain fracture patterns more susceptible? Are certain pre-op exam findings critical? Are we using too low of a diagnostic compartment pressure threshold and thus proceeding to fasciotomies too aggressively? Because of the relatively small sample size, it will be difficult to prove any significant variables predisposing for CS. However, trends may be seen that will be important for further research into not only characterizing, but preventing, compartment syndrome in pediatric Monteggia fractures and equivalents.
SEPARATE AND SICK: RESIDENTIAL SEGREGATION AND CHILD HEALTH IN LARGE METROPOLITAN AREAS

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Support: Shapiro Summer Research Program, Department of Population Health Sciences

Background: Residential segregation has often been investigated as a potentially important community-level influence on health outcomes for black and white infants and adults. However, there is a dearth of investigation on segregation’s effects on child health. Therefore, this study examined the relationship between measures of black-white residential segregation, defined in this study as the Index of Dissimilarity, and a suite of child health measures in U.S. Metropolitan Statistical Areas (MSAs).

Methods: Child health measures included disconnected youth, child mortality, teen births and children in poverty. Simple linear regression and two-level hierarchical linear regression models, controlling for MSA median income, MSA total population, percent of MSA population that is black and MSA Census Region, were used to examine the association between black-white residential segregation and white outcomes, black outcomes and the black-white disparity in outcomes. Effect modification by MSA population size was explored. Results: Black children appeared to have worse health across all measures, both overall and in large and small MSAs. As segregation increased, black children had significantly worse health outcomes across all four measures, regardless of the MSA population size. However, in white children, the association between segregation and health was dependent on MSA population size, where those in smaller MSAs had significantly worse levels of disconnected youth, teen births and children in poverty with increasing segregation, but no statistically significant associations were found for white children in large MSAs. Segregation significantly worsened black-white health disparities across all four outcomes, regardless of MSA population size. Conclusion: This study found segregation adversely affects the health of black children in all MSAs and white children in smaller MSAs, and these effects are seen in measures that span all of childhood. Further research should investigate the causal pathways by which segregation may negatively affect children’s health, and test interventions that aim to mitigate them.
GAUGING KNOWLEDGE & ATTITUDES ABOUT HEALTH REFORM AMONG CURRENT AND FUTURE PHYSICIANS

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Mentors: Patrick Remington, MD

Support: Shapiro Summer Research Program; Population Health Institute

Background: Physicians are as diverse in their political beliefs as any other groups. On divisive issues in health reform, previous research has indicated that physicians stratify by political beliefs and medical specialty. Even so, physicians are united in efforts to augment both patient and public health. With debates about the US healthcare system as heated as they have ever been, understanding what providers and medical trainees know and believe about health reform is vital.

Methods: We surveyed via email 813 respondents (111 undergraduates, 390 medical students, 102 residents & fellows, and 210 physicians, with response rates of 2.9%, 24.7%, 37.4%, and 5.4%, respectively). This pilot study aimed to understand the self-assessed knowledge and attitudes about health professional students and physicians. In June and July 2017, an anonymous survey was distributed to undergraduates, medical students, residents, and physicians in the state of Wisconsin. Some survey items addressed specific policies within the Patient Protection and Affordable Care Act (ACA). Self-assessed knowledge was examined through questions across four domains of health policy: access, cost, quality, and population health. Attitudes about health reform, beliefs about individual physician and health system responsibilities spanned the same four domains.

Results: Compared with students and residents, physicians were more likely to support the ACA (87.5% vs. 93.3%, respectively). Support for the ACA stratified according to political identification. In general, support for individual physician and health system advocacy was strong across most surveyed groups. Respondents felt greater responsibility to advocate for patients’ best interests than their profession’s. Self-described liberals were more likely than all other subgroups to support such reforms. Despite showing less support than other politically-described subgroups, conservatives still displayed overall agreement with government-based health reforms. Experience in patient care was the strongest predictor of knowledge about the healthcare system.

Conclusions: Despite strong support for both types of advocacy, respondents consistently held the opinion that health systems have a greater responsibility for advocacy than individual providers. This may signal an overall favorability toward top-down advocacy in medicine. Self-reported knowledge was nearly identical among the three earliest levels of medical training, but licensed physicians displayed more knowledge. This suggests that experience in patient care and the healthcare system is the most reliable “exposure” that leads to knowledge of US healthcare. Physicians supported single-payer, or nationalized healthcare more than any other level of training in our survey. Compared to past surveys of physicians, our results suggest a slowly rising tide of support for a single-payer health system. Physicians and medical trainees strongly supported health reforms to achieve universal coverage, and hear the calling for physicians to be active participants in conversations regarding health reform.
MATRIX-DERIVED REGULATORS OF ANTI-TUMOR IMMUNITY

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Mentor: Fotis Asimakopoulos, MD, PhD

Support: Shapiro Research Program

Background: Modulation of the tumor matrisome, has been proposed to contribute to disease progression from the myeloma precursor state, monoclonal gammopathy of undetermined significance (MGUS) to symptomatic myeloma, a tumor of antibody-producing plasma cells. Further elucidation of the agents that modulate this transition is necessary to provide targeted immunotherapies. Of particular interest is the matrix proteoglycan, versican (VCAN), and its role in regulation between an immunogenic versus a tolerogenic microenvironment upon proteolysis leading to generation of the proteolytic product versikine. The purpose of this study was to further examine the mechanism of versikine in modulation of a pro-inflammatory response, specifically investigating how the hyaluronic acid binding region influences its function.

Methods: We created a mutant versikine molecule that consisted of point mutations at the 6 hyaluronic acid binding regions, which include: 160R>A, 161Y>A, 208Y>A, 219G>A, 230Y>A and 233R>A. We used Gateway Technology BP and LR Recombination Reactions to clone the construct into the expression vector. Standard PCR and Sequencing protocols were used to confirm successful recombination reactions.

Results: We have successfully cloned the mutant construct into the expression vector.

Conclusion: The next step for this project will be to transform B16 melanoma cells with our mutant construct. We will then observe the in vivo responses to various immunotherapy modalities between WT and mutant versikine-expressing cells. These studies will determine if hyaluronic acid binding is essential to the anti-tumor effects of versikine signaling in the tumor matrisome.
INVESTIGATING THE INTERGENERATIONAL LINK BETWEEN MATERNAL STRESSFUL LIFE EVENTS ON CHILD GROWTH IN CHANG MAI PROVINCE, THAILAND

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Mentor: James Conway, MD., Stephanie Koning

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Background: Over 60 years of conflict in Burma has forced hundreds of thousands of people from ethnic minority groups to flee the country, a popular destination being Thailand. The UNHCR estimates that there are currently over 100,000 refugees living in camps along the Thai-Myanmar border. These groups have experienced human rights violations and extreme stressors throughout the conflict and migration process. It is important to understand how these lived experiences of one generation are affecting the next generation of children that are being born in these refugee camps. To properly address issues of child stunting and malnutrition, more research needs to be carried out on the different pathways operating within the framework of child health. More attention needs to be given to understanding the contribution of social influences such as exploitation, fear, and other psychosocial stressors.

Methods: This research project examines stunting prevalence in children sampled from northern Chiang Mai village communities. This project is part of a larger, ongoing research study being conducted in these same areas. Data collection consisted of anthropometry and face-to-face interviews conducted in the native languages by Thai and Shan research assistants. Interviews were recorded on paper questionnaires, including questions on demographics, child health, and human rights violations. Results: The overall prevalence of stunting was 16.08%. Stunting in children whose mothers had experienced a stressful life event rose to 19%. Children born to mothers who experienced 1-5 life events or 6+ life events displayed increased frequencies of stunting with respective adjusted odds ratios of 1.496 and 1.656.

Conclusion: The relationship between stressful life events and childhood stunting in this population suggests that stressful maternal experiences may play a role in child growth and malnutrition. Childhood stunting has lifelong effects and with this knowledge about vulnerable populations, it may indicate the use of more targeted public health interventions to aid in stunting prevention. However, there remains need for more research to strengthen the statistical power and to examine this relationship with more proximate factors to further explore the causal framework.
A QUALITATIVE EVALUATION OF COMMUNITY PARAMEDIC CARE TRANSITIONS INTERVENTION COACH TRAINING

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**Introduction:** The Care Transitions Intervention (CTI) has potential to improve the emergency department (ED)-to-home transition for older adults. Community paramedics may function as the CTI coaches, instead of nurses who traditionally serve in that role. To do so requires that the community paramedics possess the appropriate knowledge, skills, and attitudes, which are not inherently part of traditional EMS education. This study aims to evaluate an expert-panel developed training program for community paramedics serving as CTI coaches who support the ED-to-home transition. **Methods:** This study is a component of an ongoing randomized controlled trial evaluating a community paramedic-实施的CTI to enhance the ED-to-home transition. Community paramedic training covered domains including the CTI program, geriatrics, motivational interviewing, ED discharge, and community paramedicine. One year after starting the study, we conducted audio-recorded semi-structured interviews with community paramedics in both cities (June-July 2017). After transcribing the interviews, team members independently performed preliminary coding. Ensuing group data analysis sessions led to the development of final codes and identifying common themes. Finally, we conducted member checking to confirm our interpretations of the interview data. **Results:** All eight participating community paramedics were interviewed. Of the paramedics, five were women and all were non-Hispanic whites. Their mean age was 43. Participants had extensive backgrounds in healthcare, primarily as EMS providers, but minimal experience with community paramedicine. All reported some prior geriatrics training. Four themes emerged from the interviews: (1) certain characteristics make coaches more likely to succeed in this program; (2) active rather than passive learning may achieve the best results for community paramedic CTI training; (3) training program components require minor refinements; (4) continuing education should more effectively address the paramedic coaches’ evolving needs. **Conclusion:** Paramedics represent an untapped resource for supporting ED-to-home care transitions, such as through the CTI. Participating community paramedics felt that their training program was valuable and thorough, but needed some modifications. They felt that choosing the optimal candidate coaches, delivering training in the most effective manner for the students, and delivering content targeted to student needs would lead to effective implementation of a community paramedic-delivered CTI coaching program.
MITIGATION OF LEARNER ANXIETY AFTER SIMULATION DEATH: IMPORTANCE OF SYSTEMATIC DEBRIEFING

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Support: Shapiro Summer Research Program

Background: Simulator death during simulation-based medical education remains controversial. Exposure increases learner anxiety and their risk for psychological distress during simulation, which may negatively impact learning. Debriefing after simulation can reduce anxiety, which may positively impact learning. Successful debriefing may reduce participant anxiety following simulator death while maximizing learning outcomes.

Methods: Nineteen fourth-year medical students who matched into surgical residencies participated in a simulation of a clinical scenario emphasizing non-technical skills. Immediately after the simulation, the facilitators led a debriefing session based on the Gather-Analyze-Synthesize model. Learners were randomized to facilitator. Each learner completed the State portion of the State-Trait Anxiety Inventory to assess anxiety before simulation and after debriefing. Each learner also completed the Cato Confidence Scale after debriefing. One of the three facilitators concluded the simulation with simulator death regardless of the learners’ actions within the scenario. Learners’ verbal responses to the experience immediately following the simulation but before debriefing were transcribed and underwent sentiment analysis to better understand the feelings of the learners at that moment. The reduction in State anxiety (pre – post) was compared between those who experienced simulator death and those who did not using t-tests.

Results: Six learners experienced simulator death and thirteen learners did not. There was no difference between the average reduction in State anxiety (pre – post) between those who experienced simulator death (M=1.67, SD=2.58) and those who did not (M=2.17, SD=3.07; p=0.723). Equal levels of confidence were reported between those who experienced simulator death (M=2.82, SD=0.906) and those who did not (M=3.10, SD=0.690; p=0.519). Responses to the simulation before debriefing occurred produced 13 sentences of those who experienced simulation death and 44 of those who did not. Of those who experienced simulation death, 7/13 (53.8%) of their sentences contained negative sentiment whereas 14/44 (31.8%) of those who did not experience death contained negative sentiment.

Conclusion: Successful debriefing appears to mitigate the increased anxiety as detected by increased negative sentiment among those who experienced simulator death. Further study is warranted, but ultimately debriefing may allow learners to benefit from experiencing death while reducing their risk of psychological harm.
EVALUATION OF TISSUE BIOMARKERS FOR RENAL CELL CANCER

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Support: Shapiro Summer Research Program; Surgery T35 Summer Research Program; Department of Surgery

Background: Renal cell carcinoma (RCC) is the most common type of renal cancer in adults. RCC is relatively chemo- and radio-resistant, and surgery is the gold-standard treatment for localized RCC. Despite earlier detection and curative surgical treatment, all-cause mortality is increasing. One of the reasons for the increasing mortality is that approximately 25% to 50% of RCC patients treated surgically will develop metastatic RCC. Traditionally, clinical and pathological variables are used to stratify patients for recurrence following surgery. Although recent studies have identified certain proteins in RCC tissue that may predict outcomes, the routine use of biomarkers is not established. The purpose of this study is to evaluate tissue biomarkers for RCC recurrence and cancer mortality following surgery. Methods: Clinical and pathological data were collected and analyzed for all patients in the study cohort. In the previous study, data were obtained for 216 patients with RCC who were treated with partial or radical nephrectomy at the University of Wisconsin Hospital from January 2000 to December 2005. The validation cohort contains approximately 155 new patients. Tissue biomarker data were collected. After quantifying protein expression of each tissue biomarker, univariate and multivariate analyses will be used to evaluate the risk of RCC recurrence and mortality based on the biomarker expressions. These predictions will be compared to the actual RCC recurrence and mortality of patients in the validation cohort. The risk of RCC recurrence and mortality will also be analyzed using the conventional methods described above, and the predictive accuracy of these methods will be compared to that of the automated high-throughput method. Results: Clinical and pathological variables of 155 patients were analyzed. The medium follow-up time is 50 months with an interquartile range of 24 months to 90 months. 17 (10.9%) of these patients had disease recurrence, and 25 (16.1%) died from RCC. Fuhrman nuclear grades (p<0.05), pathologic T stages (p<0.05), and UISS risk groups (p<0.05) are significantly different between those with and those without RCC recurrence. Conclusion: Fuhrman nuclear grades, pathologic T stages, and UISS risk groups are significantly different between those with and those without RCC recurrence. Proportional hazards analysis for disease recurrence and mortality, and biomarker analysis will be done in the future due to a delay in data collection.
COMPARING 1-SURGEON VS 2-SURGEON RESULTS OF POSTERIOR SPINE FUSION IN PATIENTS WITH NEUROMUSCULAR SCOLIOSIS

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Support: Shapiro Summer Research Program; Department of Orthopedic Surgery

Introduction: Corrective posterior spine fusion surgery is considered to be one of the most complicated and high-risk surgeries in pediatric orthopedics\(^1\). As a result, long operative times and extensive blood losses result in higher patient morbidity. We hypothesized that a dual-surgeon approach would result in significantly lower blood losses and operative times. In addition, we also looked at differences in lowest recorded hemoglobin, number of transfusions, length of PICU stay, and total length of hospital stay between our dual-surgeon cohort and control. Methods: This study utilized a retrospective cohort design of individuals <18 years of age at the time of surgery who have been diagnosed with neuromuscular scoliosis (cerebral palsy, skeletal muscle atrophy, or Duchenne muscular dystrophy) and have undergone posterior only instrumentation and fusions utilizing a dual-surgeon technique and compared to a single-surgeon control group using the same inclusion criteria. Results: Twenty-eight patients (24 cerebral palsy, 4 Duchenne muscular dystrophy) were analyzed in the dual-surgeon cohort, whereas twenty-nine patients (28 cerebral palsy, 1 Duchenne muscular dystrophy) were found in the control. We found no significant differences in sex, BMI, or largest pre-op cobb angles between our two cohorts. Although no significant differences in operative time (372 ± 94 minutes versus 329 ± 87 minutes, \(p = 0.081\)) or blood loss (1436 ± 1162 ml versus 1255 ± 969 ml, \(p = 0.216\)) were found, we did notice a significant decrease in the number of blood transfusions needed in our dual-surgeon cohort than our control (1.7 ± 1.5 versus 0.3 ± 0.5, \(p < 0.001\) for intra-op transfusions and 1.1 ± 1.2 versus 0.4 ± 0.7, \(p = 0.008\) for post-op transfusions). We also did sub-analysis of only cerebral palsy patients and found similar results. While there were no differences between operative time or blood loss we did see that our dual-surgeon cohort averaged nearly 30 minutes and 120ml less in operative time and blood loss, respectively. Similar to our first analysis, we found a significant decrease in the number of blood transfusions needed both intra-operatively and post-operatively in our dual-surgeon cohort (1.6 ± 1.4 versus 0.3 ± 0.5, \(p < 0.001\) for intra-op transfusions and 1.1 ± 1.1 versus 0.4 ± 0.7, \(p = 0.011\) for post-op transfusions). Conclusion: Although we did not find a difference in operative time or blood loss between the dual-surgeon cohort and our control, we did see far fewer transfusions in patients that underwent the dual-surgeon approach. Our project remains in progress as we continue to gather more information from our dual-surgeon cohort in order to complete our comparison analysis of lowest recorded hemoglobin, length of PICU stay, and total length of hospital stay. We have also expanded our inclusion criteria to include patients that underwent these surgeries in the past five years so that we have a larger data base and with that, more accurate results.

PROLOTHERAPY FOR SYMPTOMATIC KNEE OSTEOARTHRITIS: IN-PROGRESS QUALITY IMPROVEMENT DATA

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Support: Shapiro Summer Research Program, Department of Family Medicine and Community Health

Purpose: Knee osteoarthritis (KOA) is a debilitating chronic disease with enormous individual and societal impact. Prolotherapy, an injection-based therapy, is efficacious in controlled studies assessing self-reported outcomes including function, but the use of prolotherapy in routine clinical settings has not been assessed. The goals of this quality improvement project are to assess, in the context of routine clinical care, patient care regarding prolotherapy for KOA in our program, and its effect on measures of patient-oriented, self-reported and objectively-assessed outcomes. Methods: Adults with six months of symptomatic KOA and failure of at least two guideline-recommended conservative treatments were invited to participate in this quality improvement project. Patients received up to six monthly prolotherapy treatment sessions. Self-reported outcomes included the Western Ontario McMaster University Osteoarthritis Index (WOMAC) and the EuroQol questionnaires; objectively-assessed measures included three office-based physical performance measures, gait assessment, and activity level using arm accelerometry. Results: Eleven (11) adults were recruited. At this time, five (5) completed the protocol and provided complete six-month follow-up data. Aggregate WOMAC, EuroQol and objectively-assessed outcome scores did not show statistically significant improvements, except for one office-based physical performance test (40m Fast-Paced Walk Test). However, individual patients made marked improvements in WOMAC, EuroQol and objectively-assessed measures. Satisfaction was high. No adverse events were reported. Gait assessment is currently under analysis. Conclusions: 45.5% of patients in this quality improvement project have completed the treatment protocol and provided 6-month follow-up data at this time. On average, aggregate self-reported and objectively-assessed results showed promising improvements, but were not statistically significant. However, compelling individual improvements were seen in self-reported and objectively-assessed outcomes in 60% of patients. These data provide information about the use of prolotherapy in our clinic setting, and suggest feasibility of prolotherapy conduct and use of baseline and follow-up self-reported and functional measures to assess care.
FELLOW SELF-ASSESSMENT OF PROCEDURAL SKILLS NECESSITATES NEED FOR EXPERT FEEDBACK

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Support: Shapiro Summer Research Program

Background: The ability to self-assess one’s performance is a critically valuable tool throughout medical training. It allows trainees to identify strengths and, more importantly, weaknesses in their ability, to take the necessary action to deliberately practice and build upon their previous performance. However, evidence for self-assessment accuracy in medical education is poor. OBJECTIVE: The aim of this study was to examine how accurately fellowship trainees’ self-assess compared with external observations of each person’s competence. Methods: As a proof of concept, one pulmonary critical care and 5 nephrology fellows underwent an assessment of their central venous line (CVL) insertion skills using a CVL simulator. The validated 27-item checklist traditionally used to score CVL insertions examinations was modified to bucket the 27 items into 7 skills categories with descriptions. Participants were asked to identify the skill that needed most and the skill least amount of work using a ‘1’ and ‘7,’ respectively, and then rank the remaining skills in order of comfort level. An expert-examiner assessed participants using the same instrument. Cohen’s kappa, weighted Cohen’s kappa and grouped Cohen’s kappa correlations between each participant’s self-rank and the expert’s rank of skill performance was made using Stata Statistical Software: Release 13. Results: The Cohen’s kappa agreement was 8.14% (expected agreement = 14.29%). The weighted Cohen’s kappa agreement was 25.52% (expected agreement = 31.36%). The grouped Cohen’s kappa agreement was 30.61% (expected agreement = 34.69%). Conclusion: Fellows’ self-assessment of their own performance is poor. These findings necessitate the role of expert feedback in even advanced levels of medical education. A larger validation study is needed to confirm these results.
DEMOGRAPHIC CHARACTERIZATION AND HEALTH NEEDS ASSESSMENT OF MEDIC SOUTHSIDE CLINIC PATIENT POPULATION

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Mentors: Kristi Jones, MPH; Parvathy Pillai, MD, MPH

Support: Shapiro Summer Research Program; PRIME

Background: Immigrant communities represent a medically underserved population with unique health needs and barriers to care. Southside MEDiC Clinic, a student-run free clinic in Madison, WI, anecdotally serves an underserved, largely immigrant population; however, there has been no formal population health assessment. Recognizing the importance of delivering patient-centered care and addressing health inequities, we sought to: characterize the patient population seeking care at Southside, identify medical and social needs of the patient population, and find resources and strategies that address identified patient needs. Methods: A mixed-methods approach was used, combining quantitative analysis of electronic health records (EHR) with qualitative review of semi-structured, key informant interviews. EHR data were reviewed to characterize patient demographics, as well as quantify patients' diagnoses. A total of 10 interviews were conducted with health care and community service professionals. Individuals were recruited based on their experience serving the communities identified in the EHR demographic analysis. The interviews were audio-recorded, transcribed, and coded to identify themes surrounding health needs, barriers to health, resources in the community, and strategies to utilize those resources. Results: The patient population of Southside clinic between May 2016 and May 2017 consisted of 475 unique patients. This population was largely Hispanic/Latino (66%), non-English speaking (76%), uninsured (88%), and without a primary care provider (70%). The most common diagnoses made in clinic were hypertension and diabetes. Based on interviews, primary care, mental health, dental health, and nutrition are significant health needs for the population. The most cited barriers to health were the structure of the healthcare system, lack of insurance, language, and immigration status. Many community resources for patients' individual needs were identified, with major themes of patient navigation, warm handoffs, hub organizations, and patient accommodations emerging as strategies to improve patients' access to identified community resources. Conclusions: Facing enhanced needs and multiple barriers to care, the Southside MEDiC clinic patient population is at unique risk for health disparities. Students and providers should be aware of these needs and barriers, as well as best ways to use and engage with community resources.
CARDIOPROTECTION DUE TO ISCHEMIC PRECONDITIONING: DOES PRECONDITIONING LEAD TO INCREASED SUR2-55A EXPRESSION IN WILD TYPE MICE?

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Support: Shapiro Summer Research Program; Department of Medicine

Background: Ischemic heart disease is the number one cause of death in the US and in the world, making it imperative to delineate the biological pathways that can protect against the effects of ischemic events and reduce mortality. One mechanism that has been shown to reduce cardiac damage after an ischemic event has been ischemic preconditioning (IPC), whereby the heart experiences repetitive brief periods of ischemia (several minutes) that result in reduced infarct sizes after subsequent prolonged ischemic events (30 minutes). The biological pathway for which IPC provides cardioprotection is not well established. However, ATP-sensitive potassium channels (KATP) in the mitochondria (mitoKATP), which sense the metabolic state of the cell, have been thought to play a role in the mechanism of cardioprotection. From previous experiments, it is proposed that the upregulation of a shorter splice variant of a regulatory subunit sulfonylurea receptor (SUR2-55A) is responsible for regulating mitoKATP and the observed cardioprotective effects. This project sought to investigate the ratio of SUR2-55A protein compared to the long form SUR2 in mitoKATP of preconditioned wild type mice to see whether the mechanism of cardioprotection after IPC can be attributed to increase in expression of SUR2-55A. In accordance with the theory, it was hypothesized that SUR2-55A protein concentrations would increase in wild-type mice after ischemic preconditioning while full-length SUR2 levels would stay the same.

Methods: Cos1 cells were transfected with SUR2-55 or SUR2A cDNAs. Western blot was performed on lysates from transfected cells to test recently obtained antibodies BNJ39 and T1, antibodies specifically created to detect SUR2-55A and SUR2, respectively. Once working antibodies were characterized, we tested them on control and SUR2-55A transgenic mice to ensure the antibodies could detect the proteins in mouse tissue. Next we used male mice 8-12 weeks of age and subjected them in vivo to one of four protocols: sham, IPC, ischemia, or ischemia-reperfusion. Hearts were collected at the end of the protocol and used for Western blot to detect SUR2A and SUR2-55A protein levels.

Results: Conditions were optimized for antibodies that permitted detection of SUR2A and SUR2-55A in lysates of transfected cells and mice tissue. Preliminary results for the IPC experiment were inconclusive in demonstrating SUR2-55A upregulation due to insufficient protein concentrations.

Conclusion: Next steps to be taken include purifying mitochondria by protein fractionation and repeating the Western Blot to increase the signal-to-noise, which should increase the sensitivity of the assay. By concentrating the protein in the mitochondrial fraction, we expect to see the distinct SUR2-55A bands and then quantify their level of expression between IPC and control mice.
PREDICTORS OF INTERMEDIATE TO LONG-TERM FUNCTIONAL OUTCOMES FOLLOWING ACL RECONSTRUCTION

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Mentor: Tamara Scerpella, MD

Support: Shapiro Summer Research Program

Introduction: Anterior cruciate ligament (ACL) rupture is a debilitating musculoskeletal injury with an annual incidence of 120,000 in the United States. ACL reconstruction generally provides good outcomes in terms of return to activity and recovery of knee stability, but the patient-specific factors that influence outcomes over the intermediate- to long-term are unknown. Finding significant associations between identifiable factors and functional outcomes would allow sports medicine physicians to provide better informed pre-operative counseling and more thoughtful post-operative management to patients who undergo ACL reconstruction. The purpose of the current study is to explore how functional outcome scores (FOS) at intermediate- and long-term time points following ACL reconstruction are affected by certain factors, and to examine how these scores change over time. Methods: The project was a continuation of an ongoing retrospective review of 491 patients who underwent ACL reconstruction at UW Health. Prospective chart review collected data on surgical characteristics and patient demographics. Subjects completed validated functional outcome surveys at baseline, 3-, 6- and 12-months post-operation. Subjects in the present study completed the same surveys, with the new time point ranging from 2-11 years post-op. Multivariable regression analysis will be performed at the termination of the response period to look for associations between identifiable factors and new FOS, and to see how scores change over time. Results: Survey responses were still being collected at the conclusion of the Shapiro project period. Statistical analysis of the data collected from the first 12 months post operative revealed a negative association between female gender, higher BMI, and older age at time of surgery, with functional outcome scores. Preliminary analysis of the 112 responses received suggested stability of mean FOS from the short-term to the intermediate-term following ACL reconstruction. Conclusion: This is one of very few studies examining the functional outcomes of ACL reconstruction surgery at the intermediate- to long-term follow up. Final analysis completed at the termination of the response period is expected to reveal trends in FOS. Identifying factors that predict functional outcomes at intermediate- to long-term follow up after ACL reconstruction will provide insight into how to better counsel patients before surgery and manage them after.

References:

IDENTIFYING YOUTH AND ADOLESCENT SUICIDE PREVENTION INITIATIVES IN WISCONSIN

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Support: Shapiro Summer Research Program; Prevention Innovations in Medical Education (PRIME) Scholars Program

In Wisconsin over 700 people die by suicide and about 5,500 are hospitalized for self-inflicted injury every year. Notably, suicide is the 2nd leading cause of death among the youth and adolescent (YA) population. A key focus area in Healthy Wisconsin, the state health improvement plan, is addressing suicide, specifically in youth and adolescent (YA) population. To provide evidence-informed guidance for this focus area, we sought to: 1) describe initiatives currently implemented by suicide prevention coalitions throughout Wisconsin that reach the YA population; 2) identify strategies and barriers to implementing initiatives; and 3) describe how Adverse Childhood Experiences (ACEs) and Trauma-Informed Care (TIC) have been incorporated into programming.

We conducted semi-structured interviews with key members of 29 county suicide prevention coalitions across multiple regions of the state. We identified organizations through Prevent Suicide Wisconsin, the state suicide prevention coalition and chose them based on their YA initiatives. The topics we addressed included types of initiatives, key stakeholders, challenges faced in initiative implementation, incorporation of ACEs and TIC, and successful strategies for suicide prevention. Using Dedoose Qualitative Data Analysis software, we coded each interview transcript for overreaching thematic concepts present throughout the state.

Most coalitions addressed suicide prevention in the YA populations through increasing suicide awareness and increasing social connectedness. Barriers to program implementation included mental health stigma and organizational challenges, such as a lack of funding and staff. While most coalitions were aware of the concepts of ACEs and TIC, many found the application of those concepts into programming to be challenging. Key factors in coalitions’ successes included diverse stakeholder engagement and being open to opportunities to advocate against mental health stigma.

Suicide prevention is a key public health priority in Wisconsin, with many initiatives focusing on the YA population. While multiple coalitions are tackling this topic, organizational and stigma-associated barriers, as well as difficulty incorporating ACEs and the TIC framework into programming limit the effectiveness of coalition initiatives. Highlighting effective programs that are applicable across communities could help us identify strategies to overcome these challenges.
INVESTIGATION OF PEDIATRIC-ONSET DISCOID LUPUS ERYTHEMATOSUS

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Support: Shapiro Summer Research Program

Background: Discoid lupus erythematosus (DLE) is a subtype of cutaneous lupus that can lead to permanent scarring in visible, cosmetically sensitive areas including the face and scalp. Untreated disease can lead to disfigurement with emotional stress, occupational disability, and lower health-related quality of life. Some children present with DLE that remains limited to their skin, while others eventually develop SLE with end-organ disease. Small retrospective studies of relatively few patients with pediatric DLE have suggested that 25-30% of children with skin disease at presentation are ultimately diagnosed with SLE over months to years. However, risk factors to identify those at highest risk for SLE are unknown. Because children with SLE follow an aggressive clinical course with two-fold increased mortality relative to adults, determining which children with DLE are at greatest risk for SLE could significantly impact outcomes, with early aggressive initiation of therapy to prevent or delay organ disease. This is a multicenter, retrospective cohort study of pediatric patients with discoid lupus to characterize outcomes in those with skin-limited disease at presentation and to determine risk factors for the progression of DLE to SLE, with an overall goal to establish a consensus treatment plan for optimal management in these patients. Methods: Demographic, clinical data, and laboratory data at each visit will be collected and entered into REDCap. Absolute incidence of SLE will be determined through ACR classification criteria (primary definition) and SLICC classification criteria (secondary definition). SLE severity will be assessed through SLE Disease Activity Index (SLEDAI) scores extracted from visits in the medical record. Data summarized below reflect the University of Wisconsin only. Other sites are beginning data collection, and we hope to begin analysis within the next 6-8 months. Results: 30 charts were identified using the ICD 9/10 diagnosis codes for discoid lupus (605.4, L93, L93.2). After extensive review, 4 patients met the study inclusion. The other 26 patients were deemed to have other cutaneous manifestations of SLE, reflecting the lack of specificity in these diagnosis codes, which also include other subtypes of cutaneous lupus. For demographic information, see Table 1. Incidence was female dominant. Mean age was 13.25 years (range 12-15 years). Two patients (50%) were identified as Black, one was White (25%), and the other patient was Hispanic/Latino (25%). One of four patients (25%) had a positive family history of lupus (systemic or cutaneous), and one had a personal history of other autoimmune disease (25%) associated with Trisomy 21. In total, three out of four patients (75%) were diagnosed with SLE, all of whom met both ACR and SLICC criteria at the baseline visit. Among the remaining patients who were followed for progression, one eventually met SLICC criteria but not ACR criteria, and one remained skin-limited. The mean duration of follow up was 5 years. The ACR criteria met by patients diagnosed with SLE are shown in Table 2a. Two of our four (50%) patients met ACR criteria for SLE at baseline. Both presented with end-organ involvement (biopsy-proven lupus nephritis without proteinuria) in addition to other cutaneous (malar rash, photosensitivity) and immunologic findings (high ANA titer > 1:320, leukopenia, lymphopenia). SLICC criteria met during study follow up are noted in Table 2b. Three patients (75%) ultimately met SLICC classification criteria for SLE, two of whom (67%) were diagnosed at the initial visit. Three out of four patients (75%) were initially evaluated by dermatology, while one patient (25%) was referred first to rheumatology. The patient referred to rheumatology met both ACR and SLICC classification criteria for SLE at the first visit. This patient was not co-managed by dermatology. All other patients were co-managed by rheumatology. Conclusion: Analysis of this small UW dataset within a larger, multi-centered cohort study of pediatric discoid lupus confirms a significant association with SLE, as 75% of patients were ultimately diagnosed with SLE by ACR or SLICC criteria over a short follow up period. The single patient who remained “skin-limited” had multiple autoimmune comorbidities and some laboratory features of SLE, suggesting that longer duration of follow up might have led to subsequent diagnosis of SLE. The study sample was too small to provide statistically meaningful data, but data collection at 18 centers is currently underway. We anticipate beginning analysis on the cumulative dataset in the next 6-8 months.
References:
COMBINED TUMOR TREATING FIELDS AND CABAZITAXEL SHOWED ADDITIVE ANTI-NEOPLASTIC EFFECT IN HUMAN-DERIVED GLIOBLASTOMA STEM-LIKE CELLS

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Backgrounds: The majority of glioblastomas (60%) demonstrates resistance to standard chemotherapy temozolomide (TMZ) via expression of O⁶-methylguanine-DNA-methyltransferase (MGMT) protein; therefore, novel efficacious treatments are needed for these temozolomide-resistant patients. Tumor treatment fields (TTFields) and cabazitaxel are both FDA approved treatments targeting microtubule functions and blocking cell division. We hypothesize that TTFields and cabazitaxel might show synergistic inhibitory effect on tumor growth, independent of MGMT expression level in human-derived glioblastoma stem-like cells (GSCs). Methods: Patient-derived GSCs with different MGMT protein expression (line 22: MGMT expressing/TMZ resistant; line 33: non-MGMT expressing/TMZ sensitive) were used. Dose response curves were constructed to determine the 50% inhibitory concentration (IC50) of cabazitaxel using clonogenic (sphere-forming) assays. TTFields were then applied at 200kHz (the same frequency used clinically) in addition to cabazitaxel. Cell proliferation and clonogenic assays were performed to assess the effect of the treatment combination. Results: Cabazitaxel dose response curves were similar between GSC lines regardless of MGMT expression/TMZ resistance, with both GSC lines exhibiting sub-nanomolar IC50 (22 GSC = 0.039nM; 33 GSC = 0.033nM). TTFields (200 kHz) alone effectively inhibited GSC proliferation for both cells lines: 74% inhibition (p<0.001) for 22 GSC and 80% inhibition (p<0.001) for 33 GSC, compared to untreated controls. In combination, TTFields and CBZ showed an additive anti-neoplastic effect with equal efficacy in both GSCs. Conclusions: Similar inhibition of proliferation were observed in both GSCs exposed to TTFields and cabazitaxel, regardless of MGMT expression level (i.e. TMZ resistance). We observed an additive anti-neoplastic effect when both modalities were used concurrently.
BRACHYTHERAPY DOES NOT PROVIDE WORSE OUTCOMES THAN WHOLE BREAST RADIATION IN PATIENTS WITH DCIS

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Mentor: Bethany Anderson, M.D.

Support: Shapiro Summer Research Program, Department of Radiation Oncology

Background: Ductal carcinoma in situ (DCIS) is the earliest and most common type of non-invasive breast cancer and can increase the risk of developing invasive breast cancer if left untreated. Long-term follow up of DCIS patients receiving breast conserving therapy (BCT), consisting of partial mastectomy followed by adjuvant radiation therapy, has been shown to be as effective as mastectomy in reducing risks of breast cancer development. More recently, the decision to undergo whole breast irradiation therapy (WBI) versus accelerated partial breast irradiation therapy (APBI) has been a topic of interest. The purpose of this study is to explore the characteristics and outcomes of women with DCIS who received WBI with those who received APBI. Methods: A retrospective chart study comparing outcomes of WBI versus APBI in DCIS patients with BCT at the University of Wisconsin Madison Hospital and Clinics (UWHC) was completed. A multivariate analysis using Kaplan-Meier was performed on data from a cohort of 347 patients receiving WBI and 84 patients receiving APBI who received care for DCIS at UWHC between 1/01/1995 and 6/30/2014. Data extracted included patient demographics, previous cancer history, surgical characteristics of partial mastectomies/re-excisions including tumor size, type, and surgical margins, Estrogen/Progesterone/Herceptin-2 Receptor status, radiation therapy characteristics and outcomes, including locoregional recurrence, metastasis, disease free and overall survival. Results: We analyzed a total of 431 women treated for DCIS. Those who only received consultation at UWHC and no actual care were excluded due to lack of follow up. Median follow up time was 71.6 months for WBI and 102.3 months for APBI. There was a 5.5%(+/-1.3%) chance of in-breast cancer recurrence for WBI at 36 months as compared to 4.3%(+/-2.4) for APBI. Patients with tumor size ≥2.5 cm had a 3-year risk recurrence of 9.8%(+/-4.7%), whereas tumor size <2.5 cm in size had a 3.1%(+/-1.0%) risk of recurrence (p=0.039). Axillary lymph node dissection was associated with a 62.5% survival rate after 36 months as compared to 93.5% for sentinel lymph node biopsy (p=0.001) and 95.5% for no biopsy (p=0.001). Sentinel lymph node biopsy yielded lower survival rates than no biopsy (p=0.019). Further result analysis is pending. Conclusion: There were no differences in overall survival time of women who received WBI versus APBI at the UWHC. This suggests that APBI is a good alternative to WBI as a choice for women with DCIS. However, patients in both cohorts with tumors larger than 2.5 cm had significantly higher risk of breast cancer recurrence. Current national guidelines and risk calculators (i.e. Memorial Sloan Kettering) do not take in consideration of tumor size in calculation of risk and survival. These results indicate tumor size is may contribute to outcome. Although no longer common for DCIS patients, interestingly, sentinel lymph node biopsy and axillary lymph node dissection were associated with higher rates of breast cancer recurrence. This is an important when treating patients with recurrent breast cancer.
EVALUATING THE EPIDEMIOLOGY OF FALLS WITHIN THE ELDERLY WISCONSIN POPULATION

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Mentors: Ann O’Rourke, MD, MPH

Support: Shapiro Summer Research Program

Introduction: In the United States, falls are the leading cause of nonfatal injury and injury-related death in the elderly population (those aged 65 and older). 1 It is an important public health issue that causes a substantial amount of morbidity and mortality while also having significant implications on one’s quality of life and ability to live independently. While falls are a problem nationwide, it is an epidemic in Wisconsin. Unintentional falls are the number one cause of injury-related hospital stays, emergency department visits, and death in Wisconsin’s elderly residents. 2 Despite various prevention efforts, Wisconsin has had one of the nation’s highest geriatric fall mortality rates, which is about twice the national average. 3 Therefore, we set out to describe why Wisconsin’s elderly fall, and study the association between falls and alcohol consumption, polypharmacy, and various chronic diseases.

Methods: This was a 5-year retrospective study based on the UW Health’s Trauma Database of elderly patients who received care for an unintentional fall at the University Hospital, the only Level 1 Trauma Center in the region. Data from the trauma database was linked with patient electronic medical records and information regarding patient demographics, fall details, medication use, comorbidities, and outcomes were obtained. Categorical variables were described as percentages of the total study population, while continuous variables were reported as a mean ± standard deviation. Data points underwent both univariate and multivariate analysis to evaluate the presence of any correlations and calculate odds ratios between the factors studied and falls.

Results: The data from the UW Health Trauma Database was recently obtained. Information from the database and respective patient electronic medical records will be extracted and placed in a separate database on RedCap. Data will then undergo statistical analysis as described above.

Conclusions: Although data collection for this pilot project is ongoing, we believe that the results of this study will elucidate the reasons why elderly Wisconsin residents fall at high rates. Ultimately, we hope our study will help better target prevention programs and enable clinicians and public health officials address this issue.

References:
INVESTIGATING THE ROLE OF PADI4 IN RHEUMATOID ARTHRITIS

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Department: Department of Medicine, University of Wisconsin School of Medicine and Public Health

Mentor(s): Miriam Shelef, MD/PhD

Support: Shapiro Summer Research Program

Background: Rheumatoid arthritis (RA) is an autoimmune disease that affects the joints leading to chronic pain and early mortality. It affects 1% of the US population and costs 30 billion dollars in US health related spending annually (1). Although the mechanism behind RA is not well understood, many studies have shown the importance of the peptidylarginine deiminase 4 (PAD4) enzyme in RA. When neutrophils are activated, the PAD4 enzyme moves to the nucleus and citrullinates histones. Citrullination converts arginine in a protein to citrulline, which allows the chromatin to unravel. The unraveled chromatin binds to antimicrobial proteins and forms neutrophil extracellular traps (NETs). NETs are then expelled to trap foreign materials such as bacteria (2). In RA, there is an increase in NETs and anti-citrullinated protein antibodies (ACPAs), which are antibodies against many of the citrullinated proteins including those on NETs. The antibodies are thought to deposit in the joint and cause inflammation that leads to the development of RA (3). Many studies have identified genetic variants in the PADI4 gene that associate with an increased risk of RA, but few have studied how rheumatoid arthritis associated single nucleotide polymorphisms (SNPs) can lead to immune dysfunction. The purpose of this study is then to investigate the mechanisms of two identified SNPs, rs11203366 and rs2240335, of PADI4 and their role in RA (4,5).

We hypothesize that RA patients homozygous for the risk alleles have an increase in anti-citrullinated histone antibodies compared to RA patients homozygous for the non-risk alleles.

Methods: Rheumatoid arthritis subjects were selected and matched based on their genotype, age, sex, and anti-CCP positivity. Anti-CCP is a clinical test to identify ACPAs. We subjected the patients' sera to ELISA to measure antibody levels against native and citrullinated histone H3.1 and H4. We then compared antibody levels among the genotype groups 66- AA 35-GT, 66-AG 35-GG, 66-AA 35-GG, 66-AA 35- TT, and 66-GG 35-GG for both native and citrullinated histone H3.1 and H4 using t-test. We abbreviated the SNPs rs11203366 to 66 and rs2240335 to 35 above for convenience.

Results: Preliminary data showed that in the anti-CCP positive group, there was a trend towards increased antibody levels in 35-TT group compared to 35-GG group for histone H3.1. There was however no significant difference in anti-histone antibody levels between the non-susceptible homozygous and susceptible homozygous alleles for SNPs rs11203366. Conclusions: The results show that allele T in SNP rs2240335 in PADI4 seems to correlate with an increase in anti-citrullinated histone antibodies. A larger sample size is required to show significance. If it is significant, we will do further ELISA to determine which allele G or T in rs2240335 is associated with an increase in NET formation. Overall, the success of the project would demonstrate that genetic variation in PADI4 might contribute to the pathogenesis of RA by increasing histone citrullination leading to an increase in NETs and an increase in anti-citrullinated histone antibodies and potentially other ACPAs that can worsen the inflammatory response in RA.

EFFECT OF ESSENTIAL AMINO ACID RESTRICTION ON THE GROWTH OF TRIPLE NEGATIVE BREAST CANCER CELLS

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Mentor: Vincent L. Cryns, MD

Support: Shapiro Summer Research Program; Department of Medicine

Background: Methionine (Met) restriction has been shown to inhibit cell-cycle progression, induce apoptosis, reduce migration, and enhance the sensitivity of breast cancer cells to chemotherapeutic agents. As such, the dietary approach of using methionine restriction to selectively eliminate tumor cells is an active area of research. Limited data exists, however, examining the effects of the other eight essential amino acids (EAA) on tumor growth and biology. The purpose of the project was to explore the biologic effects of dietary restriction of the other eight EAs on MDA-MB-231 and MDA-MB-468 triple negative breast cancer cells. These EAs include: histidine (His), leucine (Leu), isoleucine (Ile), lysine (Lys), phenylalanine (Phe), threonine (Thr), tryptophan (Trp), and valine (Val). Methods: Ten batches of RPMI media were prepared and used as experimental and control media; nine of which missing a unique EAA and the tenth a control containing all EAAs. MDA-MB-231 cells and MDA-MB-468 cells were allowed to grow for 48 hours in normal growth medium before treatment with different experimental media. Cells were allowed to grow for 24 hours, 48 hours, and 96 hours before staining with crystal violet solution. Cell confluence was measured using the ImageJ software and compared to control.

Results: Crystal violet staining data was acquired from two trials on 468 cells only, and is expressed in the following format: “Medium (% confluence at 24 hours, 48 hours, 96 hours).” Control (69.6%, 70.4%, 71.4%); -Trp (54.4%, 61.4%, 59.4%); -Leu (66.3%, 55.7%, 57.2%); -Val (57.7%, 56.2%, 51.4%); -His (60.8%, 57.7%, 57.2%); -Ile (61.3%, 58.2%, 56.9%); -Met (54.7%, 49.2%, 46.1%); -Thr (56.8%, 57%, 58.3%); -Phe (60.9%, 64.2%, 62.0%); -Lys (60.3%, 64.7%, 59.1%). Discussion: Methionine restriction displayed the greatest negative effect on growth of 468 cells, consistent with prior reports. However, due to low sample size, there is not enough data to form a firm conclusion regarding the effect of EAA restriction on the growth of these cells, though these early experiments show potential with branched chain amino acid (BCAA) restriction, particularly leucine and valine. Further assessment of the impact of EAA restriction on growth, apoptosis, migration, and cancer stem cell activity will provide more detailed insight. Future experimentation should utilize a variable population of triple negative breast cancer cell lines, such as MDA-MB-231 and GILM2 cells, in addition to MDA-MB-468 cells, to increase the external validity of results.
PHENOTYPIC CHARACTERIZATION OF NATURAL KILLER-LIKE B CELLS IN HIV/SIV-INFECTED PRIMATES

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Mentor: Cordelia Manickam, PhD

Support: NIH grant R01 DE026014 (to Roger Keith Reeves)

Background: Human Immunodeficiency Virus (HIV) continues to be a global burden with 36.7 million people infected, of which only 18.7 million people have access to anti-retroviral therapy (ART). Of particular note are elite controllers, who tend to control viremia and delay or completely evade progression to AIDS even in the absence of ART. Currently, the immune correlates of protection in elite controllers and patients with spontaneous HIV clearance are not completely understood. This makes vaccine development and thus, identification of key players in the early immune response against HIV a necessary task. Recently, a novel lymphocyte subset: natural killer-like B (NKB) cells have been shown to respond within 24 hours of microbial infection in mice and prime other innate lymphocytes. The involvement of NKB cells in HIV infection has not been studied. However, IL-12 and IL-18, which are the signature cytokines of NKB cells, have been shown to be elevated in acute HIV infection. Methods: Surface polychromatic flow cytometry was used to identify lymphocyte populations in peripheral blood mononuclear cells (PBMC), spleen, mesenteric lymph nodes (MLN), axillary lymph nodes (ALN), oral lymph nodes (OLN), colon, jejunum and tonsils of naïve and SIV-infected rhesus macaques. Naïve and HIV-infected human PBMC were also analyzed. Results: Based on surface marker expression, we identified NKB cells as CD3−CD20+CD127−NKG2A+IgA+ cells in rhesus macaques. They were found to be distributed in various tissues including PBMC, spleen, MLN, ALN, OLN, colon, jejunum and tonsils – with spleen harboring the highest percentage of these cells. While infection with Simian Immunodeficiency Virus (SIV) did not alter NKB frequencies at day 140 post-infection, we observed significant increases in surface expression of IgA (p=0.0201), CD16 (p<0.0001), IgG (p=0.0132) and CD40 (p=0.0051) in MLN and reduced expression of CD56 (p=0.0058) PBMs of SIV infected animals. In human PBMC, NKB cells were characterized as CD3−CD20−CD127−NKG2A−NKp46−IgA+ cells and, interestingly, IgM levels were significantly elevated in HIV-infected ART-naïve samples compared to uninfected samples (p=0.0083). Conclusion: These preliminary results demonstrate the presence of NKB cells in rhesus macaques and humans and modulation of their surface markers in the context of HIV/SIV infection. Further functional studies are needed to delineate the role of NKB cells in health and infection.
FEEDING PRACTICES FOR PEDIATRIC PATIENTS RECEIVING HIGH FLOW NASAL CANNULA

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Mentor: Kristin Shadman, MD

Support: Shapiro Summer Research Program; Department of Pediatrics

Background: Bronchiolitis is the most common cause of hospitalizations among infants in the first 12 months of life. High flow nasal cannula (HFNC) has been shown to be an effective approach for reducing the need for invasive respiratory support in both intensive care units and general pediatric wards. In spite of the known benefits of HFNC, no literature currently exists to provide guidance regarding best practice for feeding during concomitant high flow nasal cannula in these patients with respiratory distress due to bronchiolitis. The objective of this study is to evaluate the differences in length of stay and aspiration rates in patients who were orally fed while receiving HFNC and those patients who were kept NPO while receiving HFNC. 

Methods: This retrospective cohort study assessed patients admitted for bronchiolitis and treated with High Flow Nasal Cannula for respiratory support in the pediatric intensive care unit, general pediatrics ward, and emergency department of a major university medical center. Cohort included patients diagnosed with bronchiolitis requiring respiratory support using HFNC between January 2015 and March 2017. Patients with pre-existing feeding difficulties, ongoing pre-existing respiratory support requirements, and an admitting diagnosis of aspiration pneumonia were excluded. Two-tailed T test assessed differences in mean length of hospital stay, rates of aspiration pneumonia, and hours of supplemental oxygen following HFNC of patients receiving oral feeds on HFNC (oral) and patients held NPO on HFNC (NPO). 

Results: 94 patients were included (NPO=43 and oral=51). No significant difference was found in the rates of aspiration pneumonia between oral-feeds cohort and the NPO cohort (0/43 NPO vs. 0/51 oral) based on chest X-ray analysis and antibiotic prescriptions. There was no statistically significant difference in hospital length of stay (p>0.20); however, patients fed orally required shorter times on supplemental oxygen following HFNC treatment (27.6 hours NPO vs. 19.5 hours oral, p=0.09). 

Conclusions: Introduction of oral feeds provided benefits of less need for supplemental oxygen following HFNC treatment, at no increased risk of aspiration. Since feeding on HFNC has been shown to be safe, future studies must assess nasogastric and nasojejunal feeds as compared to oral feeds while on HFNC to seek the true most effective feeding guidelines.
KIDNEY TRANSPLANT RECIPIENTS ARE NOT AT INCREASED RISK OF CMV VIREMIA BASED ON CAUSE OF NATIVE KIDNEY DISEASE

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Mentors: Sarah Panzer, MD; Tripti Singh, MD

Support: Shapiro Summer Research Program, Department of Medicine

Background: In the United States, it is estimated that cytomegalovirus (CMV) seropositivity in the general population is 50-60%. In the immunocompetent, a CMV infection often does not result in any symptoms. However, a CMV infection is more problematic in an immunocompromised individual, such as a kidney transplant recipient. Also, these immunocompromised individuals, are at a higher risk of a reactivation of the virus and invasive CMV disease, which can lead to morbidity and mortality. It is well documented that CMV is the most common viral complication in patients after a kidney transplant. However, it is unknown if the cause of end stage renal disease (ESRD), which ultimately results in a kidney transplant, affects the risk of CMV infection posttransplant.

Methods: We conducted a retrospective chart review study of 2,741 kidney transplant patients from January 1993 through December 2014 at University of Wisconsin Hospital and Clinics. The ESRD groups included for analysis were glomerulonephritis (GN), hypertension (HTN), diabetes mellitus (DM), and polycystic kidney disease (PKD). All glomerular diseases were confirmed by a biopsy. We subdivided the GN group into seven specific GN diseases. The primary outcome was the incidence of CMV viremia, as defined by first episode of positive CMV test.

Results: Patients with DM as the cause of ESRD had a higher CMV viremia incidence rate (2.37/100 person years) posttransplantation than those with GN (1.58/100 person years) as the cause of ESRD. On unadjusted hazard ratio, a diagnosis of DM was associated with CMV viremia compared to GN (HR 1.35 (1.02-1.78), p-value 0.038). However, when adjusted for known risk factors for CMV this association was not maintained (aHR 1.02 (0.77-1.37) p-value 0.872).

Conclusion: DM patients have a higher incidence of CMV viremia than GN patients. However, the higher incidence is related to the more advanced age of the DM group. Cause of ESRD was not associated with an increased risk of posttransplant CMV viremia.
DRIVING AFTER CONCUSSION: ASSOCIATION BETWEEN CONCUSSION SYMPTOMS SEVERITY, NEUROCOGNITIVE TESTS, AND A COMPUTER-BASED DRIVING SIMULATOR

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Mentors: Erin Hammer, MD; Alison Brooks, MD, MPH

Support: Shapiro Summer Research Program; Department of Orthopedics

Introduction: Nearly 30% of young adults sustain a concussion by the age of 25.¹ Common concussion symptoms include difficulty concentrating, drowsiness, and feeling mentally slowed down, which may impair driving performance. Young adults are also at high risk for motor vehicle collisions and accounted for 2.5 million crashes in 2014, which was nearly three times higher than individuals over 35 years of age.² Given that driving a motor vehicle can be dangerous, especially in this cohort, it is imperative that health care providers offer adequate counseling regarding the risks of driving after sustaining a concussion. However, there are currently no objective measures to assess a concussed patient’s fitness to drive after concussion. The purpose of this study is to assess the correlation between the subacute effect of concussion on drivers’ simulated driving performance and to establish which concussion symptoms and clinical measures of cognitive function are correlated with poor simulated driving performance. We expect to find a positive correlation between severity of self-reported concussion symptoms, measures of cognitive impairment, and driving performance.

Methods: In this case-control study, participants with a sport-related concussion and control participants with other orthopedic injuries completed the Concussion Symptom Checklist (CSC), a 22-symptom questionnaire; the Trail Making Test Part B (TMT-B), a neuropsychological tool; and STISIM driving simulation, a computer-based simulation. Duration of speed exceedances, number of lane deviations, and crashes were recorded. Basic descriptive statistics were used to compare demographic and clinical characteristics of the two groups. Multivariable ordinal logistic regression will be used to assess associations between CSC and measures of driving performance, CSC and TMT-B scores, and TMT-B scores and measures of driving performance.

Results: Twelve total subjects have undergone testing, 3 cases and 9 controls. In a preliminary analysis, there were no differences between the cohorts on any demographic variable or on the results of the CSC, TMT-B, or measures of driving performance. Conclusion: An insufficient number of subjects have been tested to reveal any conclusive results. Data collection is ongoing. We hope this pilot project will lead to a validation study of a return to driving tool for clinical use.

References:

CHARACTERIZATION OF PORCINE XENOANTIBODY RESPONSE \textit{IN VITRO}

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**Department:** Surgery, Division of Transplantation. University of Wisconsin School of Medicine and Public Health

**Mentor:** Robert R. Redfield III, MD

**Support:** Shapiro Summer Research Program; NIH Surgery T35 Grant

**Background:** One possible solution to the current shortage of donor organs is the use of xenografts. A potential model for viable xenotransplantation has been porcine organs but the associated immune barriers has delayed its transition to clinical practice. A key component to this barrier is the difference in carbohydrate structures expressed on porcine cells, which serve as antigens to humans. Using carbohydrate knock-out pigs in combination with immunosuppression, progress has been made such that the initial hyperacute reaction can be overcome in non-human primates. Yet, even with these advancements, there are still issues with long term graft survival and function in non-human primates. The goal of our experiment is to characterize the initial immune response of porcine xenotransplantation \textit{in vitro}.

**Methods:** Using six samples of naïve rhesus macaque serum, we performed a flow crossmatch assay with porcine peripheral blood mononuclear cells (PBMC). Porcine PBMC’s were incubated with three different groups: R10 (used as a negative control), porcine plasma (self), and rhesus macaque plasma (the experimental group). We analyzed IgG and IgM binding between lymphocytes and macrophages using flow cytometry. Results were reported as median fluorescence intensity (MFI) and unpaired two-tailed T test was used for statistical analysis.

**Results:** It was found that naturally occurring anti-pig IgG binding was significantly increased in the six rhesus macaque plasma samples when incubated with porcine PBMC (P value < 0.01). Anti-pig IgG binding was also found to be most prevalent in cells outside the lymphocyte gate. In terms of IgG binding, MFI did not change for lymphocytes when compared to negative control (self and no plasma). IgG binding to macrophages resulted in an average delta MFI of 100 when compared to negative controls. Interestingly, there appeared to be a heterogeneous response when comparing individual amounts of anti-pig IgG and IgM. Ranges for IgG included MFI values of 737 to 1046. As for IgM, MFI ranged from 291 to 430. **Conclusion:** With this experiment, we confirm previous reports that naturally occurring antibodies do bind to xenoantigens. There appears to be an increased presence of IgG binding, particularly among cells that may be macrophages. This is consistent with previous results that implicated cells which appeared to be macrophages and xenoantibody of the IgG isotype. However, we need to analyze the data to determine whether the cells in this gate, in which most binding occurred, bind CD68 to show they are indeed macrophages. Future considerations will involve a more in-depth investigation of the role of macrophages in this flow crossmatch assay and also if PBMC’s represent a valid model for xenograft failure.
FABRICATION OF AGAR BEADS FOR X-RAY/ULTRASOUND COMPATIBLE PHANTOM CONSTRUCTION AND IMAGING CO-REGISTRATION

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Mentors: Amish Raval, MD; Michael Speidel, PhD

Support: Shapiro Summer Research Program; Division of Cardiovascular Medicine – Department of Medicine

Background: From transcatheter aortic valve replacement to therapeutic stem-cell injections, interventions that occur in the cardiac catheterization lab rely heavily on both X-ray fluoroscopy (XRF) and echocardiography/ultrasound (US). XRF is required for clear visualization of the catheter and echocardiography is required for real-time visualization of cardiac and surrounding tissue. In recent years, there have been many examples of co-registering XRF with invasive ultrasound imaging modalities (trans-esophageal and intra-cardiac US) to provide more accurate spatial representations during structural heart procedures. However, these registration methods have not been adapted to fusing XRF with 3D surface echocardiography (3D-SE), which is a non-invasive, safer form of ultrasound. Our group has developed agar beads that can be visualized under both XRF and US imaging. These agar beads will be used to construct a phantom which can help validate and refine XRF/3D-SE registration algorithms.

Methods: We follow established procedures for 5mm agar bead synthesis developed by the Hall Lab. In our fabrication, we combine powdered agar with deionized water and n-propanol and heated the mixture until boiling. Upon the solution becoming clear we added microscopic glass beads and barium sulfate (US and XRF signal agents, respectively) and allowed the mixture to be stirred in a warm water bath. Once homogenous, we placed the mixture (~400mL) into a cold-water bath and checked the temperature until it was at 55°C. At this point we casted the beads in poly-acrylate molds and allowed them to rotate overnight until solidified. Following this we imaged the beads suspended in water with both XRF and US. This is repeated for various barium sulfate concentrations.

Results: 5mm agar beads were successfully fabricated with varying concentrations of barium sulfate yielding beads that could be visualize both with XRF and US. We found that higher concentrations of barium sulfate (with adequate mixing to reduce granularity) showed promising XRF signal with no compromise to the integrity of the beads or US signature. The consistency of the signal over time was also noted and showed no attenuation which helps to validate the temporal stability of our beads. Conclusions: Our lab successfully synthesized 5mm agar beads with both XRF and US imaging capabilities that persisted over time. Our next steps involve the creation of an agar cube phantom with our agar beads embedded in an array or helical pattern inside a 10cmx10cmx10cm agar cube that can be imaged under XRF and US. This will allow us to test the co-registration algorithms for XRF and 3D-SE without the use of actual patients who would then need to be exposed to XRF unnecessarily. We also hope that the stability of our beads will allow this phantom to be optimized and used as a standard for this type of registration in the future.

References:
UNDERSTANDING INDIVIDUAL AND CONTEXTUAL FACTORS THAT IMPACT NON-HISPANIC BLACK INFANT MORTALITY DISPARITIES IN WISCONSIN

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Department: Department of Obstetrics & Gynecology

Mentor(s): Deborah Ehrenthal, MD, MPH

Support: Shapiro Summer Research Program; Department of Obstetrics & Gynecology

Background: Wisconsin has some of the largest infant disparities in the country. Previous research has focused on understanding drivers in disparities by comparing non-Hispanic Blacks (NHB) to their non-Hispanic White (NHW) counterparts. We examined these disparities by comparing the birth profiles of NHB mothers residing in Wisconsin to NHB mothers in U.S. Public Health Region V in terms of individual and contextual county-level characteristics. Methods: We merged the 2013 National Center for Health Statistics (NCHS) Period Linked Birth/Infant Death Data File and the 2012-2013 HRSA Area Health Resource Files (AHRF), using state and county geocodes, to compare profiles of NHB births in Wisconsin and Region V (WI, MN, IL, MI, IN, OH). We included all births for which there was a reported gestational age at birth of 20 weeks or greater. Maternal race and ethnicity information was obtained from the birth certificate. We conducted descriptive statistics using maternal, infant, obstetric, and county-level variables available in the dataset shown to impact infant mortality. Results: 6,653 Wisconsin and 95,922 Region V births met inclusion criteria for this analysis. The infant mortality rates for NHBs were 10.1 per 1,000 live births and 8.1 per 1,000 live births, respectively. 98.2% of Wisconsin NHB births took place in urban centers, which was not statistically different from Region V at 97.8%. More NHB deliveries in Wisconsin were covered by Medicaid than in Region V (77.9% to 68.7%). 61.1% of Wisconsin NHB mothers reported completing high school or less, a larger proportion than in Region V (53.6%). 49.5% of pregnancies in Wisconsin received adequate prenatal care compared to 51.4% in Region V. Both were found to be lower than the national average (53.6%). Medical and obstetric characteristics, including rate of vaginal deliveries, in-hospital deliveries, and rate of newborn transfers were statistically better in Wisconsin than in Region V. Infant characteristics such as gestational age, birthweight, and in-hospital breastfeeding were not statistically different from Region V births. County-level characteristics surrounding urban NHB mothers in Wisconsin indicated a lower resourced contextual environment than urban counties in Region V, demonstrated by factors including poverty, education, and obstetric healthcare availability. Conclusion: Not only is there a disparity in non-Hispanic Black and non-Hispanic White birth outcomes, but non-Hispanic Black infant mortality in Wisconsin is greater than in Region V. Individual and contextual factors can be used to further understand these disparities and develop targeted interventions for non-Hispanic Black mothers, particularly in Wisconsin.
BARRIERS AND FACILITATORS TO MEDICAL DEVICE REPROCESSING IN AMBULATORY CARE SETTINGS

Authors: Anna Reagan, Nasia Safdar, Laura Anderson

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Mentors: Nasia Safdar, MD, PhD; Laura Anderson, BSN, MPH

Support: Shapiro Summer Research Program; Department of Medicine

Background: Reprocessing of medical devices is a complex process dictated by the type of device and how it is used, and improperly cleaned reusable medical devices has been linked to transmission of healthcare-associated infections. To better understand the barriers and facilitators to proper reprocessing in the ambulatory care setting, we conducted a study to assess reprocessing through direct observations and interviews of clinic staff. We used the Systems Engineering Initiative for Patient Safety (SEIPS) model as a framework to address the issue from a systems level perspective. The core of this model is the work system, and elements within the work system include person, tasks, tools and technologies, environment, and organization. We hypothesized that there were barriers and facilitators to proper reprocessing within each of these elements, as well as the different steps in the reprocessing workflow.

Methods: We conducted direct observations and interviews at 15 of the 150 university-affiliated ambulatory clinics around the Madison, Wisconsin, area during June and July 2017. Sites were chosen to include a variety of clinical settings. All clinics included performed reprocessing of surgical instruments and two performed reprocessing of endoscopes. We conducted direct observations and interviews of ambulatory care staff involved in reprocessing. An observation checklist was created to include all of the Joint Commission (TJC) standards. Interview questions were developed to assess barriers to reprocessing. Interviews were recorded and transcribed and then coded by two members of the study staff. Responses were grouped by reprocessing step, work system element, and barrier versus facilitator.

Results: Observations and interviews were completed at the 15 included clinics. In observations, clinics were least likely to meet TJC standards in correctly mixing cleaning chemicals (0%), having distinct separation between clean and dirty processes (27%), ability to locate reprocessing instructions (27%) and reprocessing or disposal of decontamination brushes (27%). Neither clinic performing endoscope reprocessing met all TJC requirements. 72 of 158 coded interview excerpts were facilitators and 85 were barriers. The most cross-coding was between pre-treatment and organization. Conclusion: Results suggest gaps primarily related to reprocessing education and clinic flow or space. Efforts will be made to prioritize improvements in the efficient and appropriate use of available space and to improve standardization and dissemination of education and training.
LONG-TERM OUTCOMES OF HYBRID TECHNIQUE FOR OPEN REPAIR OF INGUINAL HERNIA

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Mentors: George Fall, MD; Amber Shada, MD

Support: Shapiro Summer Research Program

Background: Approximately 800,000 inguinal hernia repair surgeries are performed annually in the United States. Hernia recurrence for primary closure is up to 15%, while recurrence for tension-free mesh repair is approximately 1-2% (Scott et al., 2001). Since 1993, we have been using an open hernia repair technique which involves approximating the transversus abdominis to the inguinal ligament, reinforcing the closure with an onlay mesh, and making a relaxing incision in the lateral rectus. This technique is a hybrid of other common inguinal hernia repair techniques today, which motivated us to question its efficacy in terms of hernia recurrence, chronic pain, and patient satisfaction. Methods: We performed a single center, single surgeon, retrospective study of patients undergoing inguinal hernia repair between 1996 and 2016. A phone symptom questionnaire was administered to obtain information on hernia recurrence, groin pain, and subsequent hernia repair as well as patient satisfaction. Success was defined as lack of recurrence and patient reported satisfaction. Results: Two hundred seventy-six patients were identified. One hundred eighty-six patients with two hundred five hernia repairs completed the questionnaire (fifty-five lost to follow up, thirty-four deceased, one declined to answer). Respondents had a mean follow-up of 11.4 years. Overall, 196/205 (95.6%) of hernia repairs were reported as being satisfactory. Of the 205 repairs, there were five recurrences reported (2.4%), with a mean time to recurrence of 6.9 years. One patient underwent repair after their recurrent hernia. Twenty-eight (13.7%) of patients reported chronic groin pain, of which only six reported daily or constant pain (2.9%). Conclusions: Long-term results of our hybrid inguinal hernia repair technique are excellent, with low recurrence rate out to a mean of over 11 years. Patient satisfaction is high. This technique has a comparable recurrence rate to that of standard tension free repair.
ACUTE INSULIN SURGES LEAD TO BRAIN HYPOPERFUSION IN HUMAN METABOLIC SYNDROME

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Support: Shapiro Summer Research Program; Cardiovascular Research Center

Background: The high metabolic demand of the human brain requires precise coordination between neuronal activity and cerebral blood flow (CBF). Human metabolic syndrome (MetS), which is linked to cognitive impairment, neurodegenerative disease, and stroke, has been shown to represent a state of diminished global CBF.\(^1\) Although several studies have highlighted that the cerebral atherogenic and microstructural changes seen in metabolic syndrome are regionally distributed, the regional specificity of this change in CBF and its mechanism have largely been unexplored.\(^4\)\(^-\)\(^5\) Moreover, given the high incidence of sleep apnea seen in conjunction with MetS and the well-established vascular endothelial dysfunction found in diabetes mellitus, it is unclear if individuals with metabolic syndrome have an intact hypoxic cerebral vasodilatory response and whether this too is regionally distributed. The current study had a two-fold hypothesis: (1) basal CBF would be lower in individuals with metabolic syndrome in vessels supplying neuronal regions (frontal and temporal lobe) known to be involved in executive functioning, memory, and visuospatial abilities.\(^6\) (2) the endothelial-mediated hypoxic cerebral vasodilatory response would be impaired in subjects with metabolic syndrome.\(^7\)

Methods: Twelve healthy controls (29 ± 6 yrs) and 7 subjects with Metabolic Syndrome (37 ± 7 yrs) were recruited to partake in the study. Four-dimensional flow magnetic resonance imaging (PC VIPR) was used to quantify cerebral blood flow, cerebral vascular conductance, and shear stress simultaneously in 11 arteries at room air and steady state hypoxia (FiO2 = 0.11). Heart rate, blood pressure, oxygen saturation (SpO2), and end-tidal CO\(_2\) were monitored throughout the study time. Scans were reconstructed analyzed using a center-line tool.

Results: Global CBF was significantly attenuated in the MetS group compared to controls (Ctrl 691 ± 45 mL/min vs MetS 531 ± 60 mL/min), however, there was no difference from normoxia to hypoxia in either group. When analyzed for regional distribution, the MetS group was found to have decreased cerebral blood flow in their right-sided cerebral vasculature including the anterior cerebral (ACA), internal carotid (ICA), middle cerebral (MCA), posterior cerebral (PCA), and vertebral arteries (VA). CBF was also depressed compared to controls in the basilar and left middle cerebral arteries. Total cerebral oxygen delivery (arterial oxygen concentration x total CBF) was calculated and was significantly depressed in individuals with MetS (Ctrl 123 ± 8 mL/min vs MetS 99 ± 11 mL/min). In response to hypoxia, the right and left MCA in MetS displayed a significantly smaller change in cerebral vascular conductance (velocity/mean arterial pressure) compared to controls suggesting a disruption in endothelial-mediated cerebral hypoxic vasodilation in these vessels. Baseline wall shear stress (WSS) measurements were lower in the left MCA in MetS compared to controls (Ctrl 3.7 ± 0.7 Pa vs MetS 3.0 ± 0.1 Pa).

Conclusion: The data collected suggest that global cerebral blood flow is significantly attenuated in individuals with MetS thereby suppressing oxygen delivery. This decline in oxygen delivery may be contributing to neurodegeneration or may support evidence toward a lower basal brain metabolism in this population.\(^8\) The regionally right-dominant decline in flow is of unclear significance is will require ASL scanning to better elucidate the areas this distribution is affecting. The diminished hypoxic vasodilatory response in bilateral MCAs, in addition to the decrease in blood flow and wall stress in these vessels, may suggest that these vessels are especially susceptible to remodeling and therefore are close to their hypoxic-mediated vasodilatory vasodilation at baseline. Overall, this study suggests that MetS in conjunction with hypoxia seen in CSA may have detrimental effects to areas of the brain supplied by the MCAs.
INSUFFICIENT IRON STORES DISRUPT IRON METABOLISM MORE THAN INFLAMMATION IN OVERWEIGHT ADOLESCENTS

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Background: Overweight and obese adolescents are at increased risk for iron deficiency (ID), and inflammation in obesity can worsen iron availability. Hepcidin may distinguish between ID due to insufficient iron stores and ID due to inflammation. The aim of this study is to better define the etiology of ID in this population. Methods: 77 ethnically diverse male and female adolescents (11-14 years) with body mass index (BMI) >85th percentile participated in this cross-sectional study. Demographic data, BMI, and fasting blood samples were obtained to analyze markers of iron and metabolic status. Results: 91% of subjects were iron-deficient (71.4% had low ferritin; 70.1% had low transferrin saturation). Subjects were analyzed in 4 groups: iron-sufficient, stage 1 ID, stage 2 ID, and inflammatory-mediated ID. BMI, homeostasis model of assessment-insulin resistance (HOMA-IR), iron indices, and hepcidin differed significantly across all four groups, while markers of metabolic syndrome (HOMA-IR, p<0.0002; adiponectin, p<0.04) and inflammation (C-reactive protein, p<0.02) differed between subjects with low and normal transferrin saturation, and plasma hepcidin differed between subjects with low and normal ferritin (p<0.002). Conclusions: Disordered iron metabolism in overweight and obese adolescents appears multifactorial and insufficient iron stores may contribute more than inflammatory processes to ID in this cohort.
IMPACT OF SIMVASTATIN ON CEREBRAL BLOOD FLOW, PULSATILITY INDEX, AND ALZHEIMER’S DISEASE BIOMARKERS: A CLINICAL TRIAL

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Support: Study funding was provided by an award from the University of Wisconsin School of Medicine and Public Health Department of Medicine and the Herman and Gwendolyn Shapiro Foundation. Additional support provided by the SHARP study AG031790, UW ADRC P50 AG033514, CTSA UL1 TR000427 10, F30 AG054115, T32GM008692, T32GM007507. This material is the result of work supported with resources and use of facilities at the William S. Middleton Memorial Veterans Hospital, Madison, Wisconsin.

Background: Vascular risk factors contribute significantly to cognitive decline and progression of Alzheimer’s Disease (AD). Epidemiologic and animal studies suggest that lipid-lowering agents such as statins may be effective in reducing amyloid burden, possibly via improving amyloid beta (Aβ) clearance and reducing its production. It is unknown whether statins, via their effects on cerebral blood flow (CBF) and pulsatility index (PI), can mediate cerebral spinal fluid (CSF) Aβ in a middle aged population at risk for AD. Methods: This 18-month randomized, double-blind, placebo-controlled study was conducted in a population of 88 middle-aged individuals with a family history of AD. Participants were randomized to receive 40mg simvastatin daily or placebo. At baseline, month 12, and month 18, all participants underwent an MRI including phase contrast vastly undersampled isotropic projection imaging (PC-VIPR) 4D flow sequences for CBF and PI, lumbar puncture, and cognitive assessments. Results: The simvastatin treatment group had lower venous PI in the straight and superior sagittal sinuses than the placebo group at month 18 compared to baseline (p<0.05). A trend was observed indicating increasing CBF over time with simvastatin in petrous (p=0.063) and cervical (p = 0.095) internal carotid artery segments. There was no significant difference between treatment and placebo groups in measurements of CSF Aβ change from months 12 and 18 to baseline. Conclusion: In this study, 18-month simvastatin therapy in a middle-aged population decreased venous PI but did not significantly impact Aβ burden. Treatment with simvastatin also showed trends towards beneficially increasing blood flow in cerebral arteries. This study supports previous studies indicating that cerebrovascular dysfunction may be an early step in AD pathogenesis, occurring before amyloid accumulation or cognitive dysfunction. Future studies are warranted to investigate the effects of longer duration simvastatin treatment on AD pathology over time.
SYSTEMATIC ANALYSIS OF LONG-TERM OUTCOMES IN BIOMET METAL-ON-METAL COMPARED TO METAL-ON-POLYETHYLENE TOTAL HIP ARTHROPLASTY

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Support: Shapiro Summer Research Program; Department of Orthopedics

Introduction: Total hip arthroplasty (THA) is a frequently performed procedure with a low rate of complications that can be performed using metal-on-metal (MOM) designs, as well as metal-on-polyethylene (MOP) designs. However, when compared to MOP, there is increasing concern of high failure rates in several MOM THA designs, and the large number of MOM implants used in the past emphasizes the need to investigate the long-term clinical outcomes of MOM designs. The purpose of this study is to compare the long-term clinical outcomes of a specific Biomet MOM design with a MOP design.

Methods: Retrospective chart review was completed on Biomet MOM patients (n = 161) and MOP patients (n = 155) who underwent THA at the same institute during 2006-2011 with a minimum follow-up interval of 5 years. Patient demographics, clinical failure, clinical outcomes, and radiographic outcomes were compared between the groups. Clinical failure was defined as revision surgery, pending revision surgery, moderate to severe persistent pain, or severe bone loss on radiographic analysis. Clinical outcomes included rates of dislocation, reason for failure, blood chromium and cobalt levels, and patient reported outcomes, including the modified Harris Hip Scores (mHHS). Statistical analysis was performed by Scott Hetzel, the departmental staff statistician. Demographic analysis was completed using between group t-tests and chi-squared tests where appropriate. Clinical outcomes and rates of failure between groups were compared using both a univariate analysis, as well as multivariate analysis controlling for age, gender, surgery date, skin to skin time, and head size.

Results: Patient demographics were significantly different with regard to surgery date, surgeon, age, gender, skin to skin time, and head size (p < 0.05). These variables were controlled for in the multivariate analysis. At a minimum of 5-year follow-up, rates of revision were higher in the Biomet MOM group (9.3%), compared to the MOP group (5.8%), which approached significance but did not reach it (p = 0.065). Composite rate of failure, including rates of revision and progressive bone loss on radiographic analysis again approached significance, but did not reach it (p = 0.063). Dislocation rate was significantly lower in the MOM group (0%) compared to the MOP group (5.2%, p = 0.003). Modified Harris Hip Scores were significantly different between groups both pre-op (p = 0.002) and post-op (p < 0.001), with the MOM group having higher functionality. However, the net difference of post-op minus pre-op mHHS within groups was not statistically significant between groups (p = 0.132). Causes of failure and blood ion levels are still currently under investigation.

Conclusion: As expected, there is a higher rate of revision and a significantly lower rate of dislocation in the Biomet MOM group when compared to the MOP group. Rates of bone loss were slightly higher in the Biomet MOM group (3.7% vs. 1.3%), but when this was included in the rate of failure analysis, the rate of failure still did not reach significance. The MOM group has a significantly higher pre-op mHHS and post-op mHHS, but the difference between pre-op and post-op mHHS is not significantly different compared to the MOP group, suggesting the MOM group started at a higher mHHS baseline since they were slightly younger and predominately male. However, of the MOM failures, there is a higher pre-failure mHHS (μ = 89.4) compared to the MOP failures (μ = 63.6), suggesting the MOM failures are more often asymptomatic prior to failure. Since MOM has a higher rate of failure and they are often asymptomatic, this emphasizes the need for increased patient education, surveillance, and long-term follow-up of Biomet MOM patients.
EVALUATION OF SURGICALLY PLACED TAP CATHETER ANALGESIA FOLLOWING RENAL TRANSPLANT

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Mentors: Shelly Borden, MD; Martin Dib, MD

Support: Shapiro Summer Research Program

Background: Allogeneic renal transplantation (RT) is the gold-standard treatment for end-stage renal disease (ESRD), improving quality of life and survival relative to long-term dialysis (Wolfe, 1999). Opioids have largely been used in the setting of RT, but are associated with significant, unwanted side-effects such as nausea, vomiting, constipation, pruritis, respiratory sedation, psychological addiction, and physical dependence. Transversus abdominis plane (TAP) block, a regional anesthetic technique indicated in surgical procedures of the abdominal wall, is a promising candidate for post-RT opioid-sparing analgesia. TAP block has been shown to improve analgesia in abdominal surgeries (e.g., laparotomy) (Abdallah et al, 2012). Post-RT, TAP block has been shown to reduce pain and/or opioid consumption (Parikh et al, 2015); however, there have been studies that failed to report a significant reduction in pain and opioid consumption (Kuruba et al, 2014). To address this inconsistency, our group is performing a case-control study comparing patients receiving surgically placed TAP block post-RT to a historical control group of patients that received only hydromorphone PCA post-RT. The primary outcome measured in this study is total hydromorphone consumption. Secondary outcomes measured are visual analog scale pain scores (movement/rest), nausea and vomiting scores, length of stay, and incidence of peritonitis and ileus. We hypothesize that patients receiving TAP catheter analgesia will have less hydromorphone consumption than the control hydromorphone-only PCA group.

Methods: In this IRB-approved, retrospective case-control study, we collect perioperative information from patients receiving surgically placed TAP catheter analgesia in addition to hydromorphone PCA post-RT during 2017 (n=60) and patients that received hydromorphone PCA post-RT from 2012-2017 (n=1624). Exclusion criteria include multi-organ transplantation, less than 18 years of age, ipsilateral incision, midline incision, and sequential kidney transplantation. All data is obtained electronically from the EMR. Preoperatively, patients to receive RT are consented to receive TAP block. Post-RT surgical placement of the TAP catheter is performed as previously reported (Parikh, 2015). Following closure of the surgical site, ropivacaine bolus 8 mL/hour (0.2%) is administered via TAP catheter. Postoperatively, pain scores on movement and at rest and nausea/vomiting scores are recorded. At the final time point of 72 hours, total opioid consumption is recorded. Total length of stay is recorded after discharge. Standard demographic is also recorded. Data analysis is performed using the Statistical Package for the Social Science, with a p-value of less than 0.05 will be considered to be statistically significant.

Results: Official data analysis has not yet been performed being that more TAP block samples are presently being collected (n=55).

Conclusions: Next steps include completing data collection and analyzing the data. This study will be published regardless of the efficacy of surgically placed TAP block. If TAP block is shown to be efficacious in this case-control study, the results may prompt a randomized control trial further investigating TAP block in RT.
ASSESSING THE RELATIONSHIP BETWEEN HUMAN RIGHTS VIOLATIONS AND PERINATAL HEALTH OUTCOMES IN WOMEN OF RURAL NORTHERN THAILAND

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Support: Shapiro Summer Research Program; Department of Pediatrics; National Institute of Aging Grant T32 AG00129, core grants to the Center for Demography and Ecology at the University of Wisconsin-Madison (P2C HD047873) and to the Center of Demography of Health and Aging at the University of Wisconsin-Madison (P30 AG017266)

Background: Hundreds of thousands of Shan villagers have fled to Thailand to escape civil conflict and economic instability in Eastern Myanmar, where maternal and infant mortality ranks among the highest worldwide.1-3 It is unclear what drives poor perinatal health outcomes among this population after arrival in Thailand, though exposure to HRVs has been a critical suspect in displaced populations.4 Describing the health of this region may inform a socioecological framework for identifying perinatal risks. The purpose of this study was to identify and categorize HRVs facing women in Chiang Mai Province, Thailand, and describe how these exposures relate to adverse perinatal outcomes (APOs).

Methods: Questionnaire-based interviews on health and HRVs were conducted with mothers residing in two Chiang Mai Province village clusters along the Myanmar border. Data was entered into Microsoft Access using a pre-coded system. We defined APOs as having ever experienced a miscarriage, stillbirth, major pregnancy complication, or neonatal death. Stata software was used to describe the sample and perform staged logistic regression models to elucidate the relationships between risk of APOs and social factors, namely migration history and HRV exposures. Results: Women who had experienced any HRVs had more APOs than women who had not experienced HRVs (p<0.02). Women exposed to HRVs related to labor exploitation and social and material resource deprivation experienced more APOs than women who had not had these HRV exposures (p<0.10). Migrant status was associated with greater odds of experiencing an APO. Staged logistic regressions suggest that this relationship is partially accounted for by greater risks of exposure to HRVs related to labor exploitation and resource deprivation among migrants in the study population. Conclusion: Migrants experienced disproportionately high risk of APOs, which is related to their disproportionately high risk of experiencing HRVs—specifically those related to labor exploitation and resource deprivation. Whether the relationship between HRV exposures and APOs is causative cannot be discerned from this study. Further analysis including health insurance status and legal status could identify social or physiological mechanisms through which HRV exposures and APOs are related. Describing the perinatal health of migrants as it relates to HRV exposures is crucial to drive health improving policy changes.
EVALUATION OF TUMOR-SELECTIVE GADOLINIUM-ALKYLPHOSPHOCHOLINE CHELATE FOR MRI BY MASS SPECTROMETRY

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Mentors: John S. Kuo, MD, PhD; Jamey P. Weichert, PhD

Support: Shapiro Summer Research Program; Department of Neurological Surgery

Introduction: Alkylphosphocholine (APC) analogs are a suite of compounds that display tumor-specific uptake and high retention in a broad range of human cancers. They possess modulable moieties that confer multimodal diagnostic and therapeutic potential. Previously reported modifications with fluorescent agents and radiolabels preserve tumor uptake and retention while enabling in vivo imaging. Magnetic resonance imaging (MRI) has high soft tissue resolution compared to other imaging modalities, but current contrast agents are found to accumulate non-specifically in brain tissue for extended periods of time. The chemical flexibility of the APC carrier region motivated the synthesis of a macrocyclic gadolinium-APC analog (Gd DOTA-APC) as an MRI contrast agent. Previous studies have shown that this compound exhibits strong MRI contrast and tumor uptake. High resolution mass spectrometry (MS) enables further analysis of chemical stability and tissue distribution. This study assesses the stability and tissue distribution of Gd DOTA-APC analogs in rodent and human tumor models in mice, along with the analytical methods for identifying the chemical nature of Gd in tumor and normal tissue. Methods: DOTA was conjugated to an APC analog. Gd was then chelated onto the DOTA-APC. Mice with U87 flank xenografts of > 3mg were injected intravenously with the DOTA-APC drug. After 24 hours, tumors and reference tissue were excised, homogenized, and embedded in gelatin. Matrix deposition was performed on the samples and subsequently imaged using matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-MS). Determination of chemical species was performed using the mass-to-charge peaks in the obtained spectra. Results: MS studies demonstrate that uptake of Gd DOTA-APC chelate analogs is preserved in the tested tumor models. Mass-to-charge peaks demonstrate the presence of intact analogs and analog adducts in tissue. Conclusion: These data suggest that the Gd DOTA-APC analog is an MRI contrast agent which localizes to tumor tissue and maintains structural integrity after uptake. The selectivity and stability of these compounds, coupled with their high and prolonged MRI contrast, makes them promising candidates for diagnosing and localizing soft tissue malignancies in regions such as the brain. Future studies will utilize mass spectrometric imaging techniques to spatially identify the chemical species of residual Gd deposits in the brain and other tissues.
ANALYSIS OF PULMONARY VASCULATURE DEFECTS IN PBX CKO MICE USING MICRO CT

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Mentor(s): Naomi Chesler, David McCulley

Support: Shapiro Summer Research Program; Department of Biomedical Engineering

Background: Pulmonary Hypertension (PH) is a major complication contributing to high mortality rate of patients with Congenital Diaphragmatic Hernia (CDH), a birth defect affecting 1 in 3000 births. Developing tools that demonstrate the pulmonary vascular (PV) defects responsible for PH is necessary for better understanding disease mechanisms and to identify new treatment approaches. Decreased pre-capillary pulmonary artery (PA) number and pre-capillary PA size caused by PV smooth muscle hypertrophy and abnormal smooth muscle contraction contribute to PH in CDH patients. Deletion of Pbx1 and Pbx2, transcription factor genes required for normal diaphragm development, causes lethal PH in Pbx CKO mice. 2D histology experiments suggest PH occurs in Pbx CKO mice due to abnormal smooth muscle contraction; yet it is unclear if reductions in vessel number play a role. In order to better evaluate pre-capillary PA number and volume, we sought to develop a micro CT approach to image the pulmonary vasculature of Pbx CKO mice. With this approach we aim to determine if PH in Pbx CKO mice is caused by abnormal PV development or abnormal PV smooth muscle contraction.

Methods: Initial experiments were conducted on adult wild-type mice to determine optimal surgical approach, PA cannula size, vascular contrast perfusion, and imaging technique. Experiments were conducted using isolated lungs from 2-week old Pbx CKO and littermate control mice (4-5 mice per group). The PA of isolated lungs was cannulated and perfused with saline and Perfluorocarbon contrast, generating arterial pressures 12-15mmHg. The X-ray beam obtained images at 1° increments to generate 360 planar images that were reconstructed using Inveon imaging software (Siemens, Germany). A 3D surface mask of the PA tree was generated; volume calculations were performed.

Results: During this largely methodological experiment, we developed an approach to generate 3D-images of the PA tree in Pbx CKO and control mice. In preliminary experiments we found that PV volume and PA branching are both decreased in Pbx CKO mice compared to controls. Due to the challenging nature of this technique and variation between imaging experiments, statistical analysis of this data will require future imaging studies.

Conclusion: Obtained imaging results demonstrate reductions in Pbx CKO pulmonary arterial volume and branch number. Future work may elicit how these and additional pulmonary vascular defect findings are responsible for PH.
NOVEL CARDIAC FIBROBLAST-DERIVED EXTRACELLULAR MATRIX EDUCATES MONOCYTES INTO ALTERNATIVELY ACTIVATED MACROPHAGES WITH LOW INFLAMMATORY MARKER EXPRESSION

Authors: Keith Spinali, Eric G. Schmuck, Sydney Walker, Anisa Dhillon, John Kink, Debra Bloom, Peiman Hematti, Amish N. Raval

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Mentors: Eric G. Schmuck, PhD; Amish N. Raval, MD

Support: Shapiro Summer Research Program; Cardiovascular Research Center

Background: Heart failure is a common cause of death in the United States. When medication therapy fails or is poorly tolerated, patients may require ventricular assist devices or transplant; however, infection, stroke and organ shortages prevent these advanced therapies. Our group has bioengineered a novel cardiac fibroblast derived extracellular matrix (CF-ECM) from isolated human cardiac fibroblasts. In previous work, CF-ECM was shown to prevent post myocardial infarction (MI) adverse remodeling in rodent MI models. We hypothesize that CF-ECM can educate circulating monocytes into alternatively activated (M2) macrophages with low pro-inflammatory marker expression as a potential mechanism through which CF-ECM exerts its therapeutic effect. Methods: Monocytes were collected from human donors and cultured on D-lysine coated plastic, gelatin, or decellularized CF-ECM scaffolds synthesized in vitro by cardiac fibroblasts obtained from human donor hearts. After three days, the cells were stained with fluorescent antibodies and analyzed via flow cytometry for expression of CD14, CD16, CD163, CD206, PDL1, CD86, and HLA-DR. This study was performed four times with monocytes collected from three different donors. Results: Compared to macrophages cultured on plastic and gelatin, macrophages cultured on CF-ECM exhibited a unique flow cytometry profile with significantly lower expression of macrophage markers associated with inflammation. Specifically, i) HLA-DR (gelatin to CF-ECM comparison: P<0.01; plastic to CF-ECM comparison: P=0.99), and ii) CD-86 (gelatin to CF-ECM comparison: P<0.01; plastic to CF-ECM comparison: P<0.01; plastic to gelatin comparison: P=0.99). Macrophages grown on CF-ECMs also had significantly lower combined expression of HLA-DR and CD86 (gelatin to CF-ECM comparison: P<0.01; plastic to CF-ECM comparison: P=0.99). Finally, macrophages grown on CF-ECM exhibited lower combined expression of CD163 and CD206, which are markers associated with M2 macrophages; (gelatin to CF-ECM comparison: P=0.04; plastic to CF-ECM comparison: P=0.26; plastic to gelatin comparison: P=0.47). Conclusion: These results suggest that culturing macrophages on decellularized cardiac fibroblast-derived ECM scaffolds results in a unique macrophage profile that is low in markers associated with inflammation. Future work will examine the therapeutic potential of these macrophages to stimulate regeneration of myocardial tissue in animal models of heart failure.

Citations:
MENTAL ILLNESS AND OPIOID MISUSE AT 4 WEEKS POST-DISCHARGE FOLLOWING TRAUMATIC INJURY

Authors: Bailee Stark; Randall Brown; Christopher Nicholas

Department: Department of Family Medicine and Community Health, University of Wisconsin School of Medicine and Public Health

Mentor: Randall Brown

Support: Shapiro Summer Research Program; Department of Family Medicine and Community Health

Background: Opioid misuse and related complications have been steadily rising in the United States, and have recently reached the point of epidemic\(^1\). Research has shown that victims of traumatic injuries comprise a group at particular risk for misusing opioids or developing opioid use disorders, with substance misuse in this population up to 6 times that of the general population\(^2\). Mental illness complicates this even further, as mental illness is an independent risk factor for both unintentional traumatic injury\(^3\) and opioid use\(^4\). Given this interaction, mental health prior to injury may be an important clinical predictor of opioid misuse following traumatic injury. It is hypothesized that higher scores on the baseline mental health surveys will be correlated with higher 4-week post-discharge Current Opioid Misuse Measure (COMM) scores, indicating that persons with mental health issues are at increased risk for misusing their opioids post-discharge. Methods: This prospective study included 55 participants recruited from the Trauma and Orthopedic Inpatient Services at the University of Wisconsin Hospital. Mental health was assessed via two forms during admission, one examining depression (PHQ-9) and one examining anxiety (GAD-7). Opioid misuse was measured via Current Opioid Misuse Measure (COMM) scores obtained 4 weeks post-discharge. Relationship between mental health measures and COMM scores was analyzed using a linear regression model. Results: Preliminary linear regression models corrected for age demonstrated that COMM scores were significantly associated with both PHQ-9 and GAD-7 scores, with GAD7 being a stronger predictor. No other significant relationships were observed on preliminary analysis. Conclusion: It was found that, following traumatic injury, persons with higher levels on both anxiety and depression scales were more likely to be currently misusing their opioid medications 4 weeks after discharge from the hospital. The evidence that mental health issues, especially anxiety, are associated with opioid misuse 4 weeks post-discharge after a traumatic injury should give rise to future preventative clinical measures, including early screening, diagnosis, and interventions.

COMBINED INNATE AND ADAPTIVE IMMUNOTHERAPY EFFECT ON MYELOID-DERIVED SUPPRESSOR CELL POPULATIONS IN A MURINE MODEL OF PANCREATIC CANCER

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Support: Shapiro Summer Research Program

Background: Myeloid cells represent a lineage that includes a variety of the leukocytes responsible for the body's first line of defense against pathogens. In addition, their descendant cells normally play a role in the immune response against cancer. Over the past decade, much attention has been paid to a pathologic subset of immature myeloid-derived cells, myeloid-derived suppressor cells (MDSCs), which inhibit cytotoxic T lymphocyte (CTL)-mediated anti-tumor responses. Immunotherapy represents a promising new treatment modality for certain cancers, including melanomas and lymphomas. Pancreatic adenocarcinoma, however, has demonstrated a disappointing response to most immunotherapeutic techniques and continues to carry a devastatingly poor prognosis. Interestingly, patients with pancreatic adenocarcinoma have been shown to have greatly increased percentages of MDSCs in the tumor microenvironment. The purpose of this study is to determine if depletion of MDSCs in a mouse model of pancreatic adenocarcinoma can promote a more robust response to immunotherapy.

Methods: Tumors were established in female B57BL/6 mice by subcutaneously injecting 0.1 mL of 2.4 x 10^7 Panc02 cells/mL. Mice received combinations of following treatments: 12 Gy irradiation, 0.1 mL intratumoral (IT) injections of 5 mg/mL PBS Hu14.18-IC (GD-2 antigen linked to IL-2), 0.5 mL IP (intraperitoneal) injections of 4.8 mg/mL PBS gemcitabine, 0.5 mL IP injections of 1.6 mg/mL PBS abraxane, 0.2 mL IP injections of 1 mg/mL PBS anti-CTLA4 mAb. Tumor volumes were reported by measuring perpendicular diameters of the tumor and calculating (1/2) x tumor length x tumor width^2. For in vitro studies, Panc02 cell cultures were maintained in RPMI 1640 supplemented with 10% FBS and 2 mmol/L L-Glutamine and housed in a humidified incubator at 37° C with 5% CO2. Spleens were harvested from naïve mice and splenocytes were diluted to a concentration of 1 x 10^6 cells/mL with sterile PBS. Panc02 cells were diluted to a concentration of 2.0 x 10^6 cells/mL with sterile PBS. Populations of splenocytes were assessed after single cell suspension, antibody staining, and flow cytometry via MacsQuant analyzer (Miltenyi Biotec) and analysis on FlowJo software (FlowJo, LLC). An unpaired t test and ANOVA test were used to determine significance, utilizing Prism software (GraphPad Software, Inc.)

Results: Our in vivo studies did not provide evidence that IP Gemcitabine administration increased the efficacy of anti-tumor immune responses to radiation therapy and 14.18-IC. No difference in effect was observed between groups with smaller (average 116.81 mm^3) or larger (average 240.33 mm^3) tumor burdens. However, groups with concomitant Gemcitabine treatment showed improved survival. Preliminary data suggest that anti-CTLA4 mAb may be effective at depleting MDSCs among tumor-infiltrating lymphocytes.

Conclusion: While there is an established correlation between MDSC population and immunosuppression, it is unclear whether depletion of MDSCs in murine models of pancreatic adenocarcinoma can lead to improved response to in situ vaccination. More assays are warranted to determine the most effective chemotherapeutic or biologic agent against MDSCs in vivo before designing follow-up experiments.
A SYSTEMATIC REVIEW AND META-ANALYSIS OF PATIENT OUTCOMES IN VERTEBRAL INFECTIONS

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Mentor(s): Paul Anderson, MD

Support: Shapiro Summer Research Program; Department of Orthopedics and Rehabilitation

Background: Vertebral infections are a spectrum of disease that are complex and difficult to manage. The experience at our institution with spinal infections has revealed heterogeneity of care, poor outcomes, delays in diagnosis, and inadequate treatment. There is a lack of data on patient outcomes following treatment for spinal infections. The purpose of this study was to address this gap in knowledge and to characterize the various outcomes of patients treated for vertebral infections in hopes of improving quality of care for all patients. Methods: A systematic search and meta-analysis was performed across 3 databases (PubMed, SCOPUS, and Cochrane Central Register of Controlled Trials). Due to changes in medical care, antibiotic use, treatment strategies, development of new surgical techniques and increasing antibiotic resistance, we focused on studies within the last 10 years. The search was screened for relevant articles based on our inclusion and exclusion criteria. Data extracted included demographics, microbiologic spectrum, mortality, neurologic deficits, pain, reoperations, readmissions, recurrence, and length of stay. A random effects model was used for all effect sizes. Results: Thirty-six studies of 3133 patients were included with an average age of 61.2 and 60.8% male predominance. The majority of infections occurred in the lumbosacral spine (53.9%). Median follow up of the various studies was 23 months. Infection-related mortality within one year was 5.92%. All-cause mortality was 9.72%. Average length of stay was 25.6 days. Overall, 20.5% of patients reported neurological deficits at follow up and 22.4% had persistent pain. Readmissions (22.8%), reoperations (12.3%), and recurrence (8.16%) were common in our meta-analysis. Staphylococcal Aureus was the most commonly isolated organism (45.5%) with a large proportion of culture negative isolates as well (22.7%). Conclusion: Vertebral infections are complex conditions requiring multiple providers and significant coordination of care. Patients diagnosed with spinal infections experience significant morbidity and mortality. These patients are resource-intensive and place significant burden on the healthcare system. Timely consultation, stat imaging, and daily neurological exams may be helpful in improving outcomes. Efficient standardization and coordination of care is vital to improving care. Further studies focusing solely on medical management will be beneficial in supplementing the literature on this topic.
GPI-ANCHORED MEMBRANE PROTEINS AS A BIOMARKER OF RESPONSE TO IMMUNE CHECKPOINT BLOCKADE THERAPY IN METASTATIC MELANOMA

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Mentors: Mark R. Albertini, MD; Cindy L. Zuleger, PhD

Support: Shapiro Summer Research Program; Department of Medicine, UW School of Medicine and Public Health.

Background: Melanoma is the deadliest form of common skin cancer. While metastatic melanoma is usually incurable, immune checkpoint blockade therapy (e.g., ipilimumab, pembrolizumab, nivolumab) has demonstrated durable tumor regression in some patients. However, not all patients respond to immunotherapy, and the therapy is associated with high incidence of immune-related adverse events. The X-linked phosphatidylinositol glycan class A (PIG-A) gene encodes for an enzyme that synthesizes glycosylphosphatidylinositol (GPI) anchors for many membrane-bound proteins. We hypothesized that because immune checkpoint blockade therapy promotes T cell proliferation, a higher frequency of spontaneous PIG-A gene mutation would occur in T cells following therapy. The purpose of this study was to develop a flow cytometry assay using GPI-anchored proteins (GPI-AP) as a surrogate to detect PIG-A mutant T cells as a biomarker for an effective response to immunotherapy in metastatic melanoma patients.

Methods: Normal donors and melanoma patients were enrolled in study OS12601, approved by the UW Health Sciences IRB. Blood samples were collected from four normal donors and six melanoma patients. Among the melanoma patients, three had marked disease regression based on imaging and dermatologic findings, and three had disease progression. Peripheral blood mononuclear cells (PBMCs) were stained with Ghost 450 and antibodies against CD3, CD14, and CD19, and T cells with GPI-AP were identified with FLAER and CD48 antibody. Flow cytometry was performed on LSRII, and the data were analyzed with FlowJo X. FLAER/CD48- double negative T cells were considered as PIG-A variants, and the variant frequency (VF) was compared pre- vs post-treatment.

Results: Using PBMCs from normal donors, we reproducibly measured FLAER/CD48- double negative VF in the range of 5x10^-6 to 16x10^-6. In all six patients, we saw an increase in the percentage of T cells, demonstrating that immune checkpoint blockade induced T cell proliferation. However, we did not observe an increased PIG-A VF post-treatment, whether the patients responded to immunotherapy or not. In patients with disease progression, we observed a decrease in the median fluorescent intensity of CD48 post-treatment.

Conclusion: A flow-based assay of GPI-AP was developed and demonstrated an increased frequency of T cells in melanoma patients after immunotherapy. In this small study, we found that an increase in T cells does not necessarily correlate with a positive response to immunotherapy. All three patients who did not benefit from immunotherapy had a decreased post-treatment level of CD48, a protein important in T cell activation. Due to the exploratory nature of these studies, formal statistical analysis has not been performed. We suggest use of this flow-based assay to study PIG-A variant T cells as a biomarker of response to immunotherapy.
MATERNAL OBSTETRIC KNOWLEDGE, PRACTICES, AND CARE UTILIZATION: A CROSS-SECTIONAL STUDY AMONG RURAL HOUSEHOLDS IN SOUTHERN ETHIOPIA

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Support: Student Summer Research and Clinical Assistantship Program; Department of Family Medicine

Background: Ethiopia has made progress improving maternal health in recent decades; however, its maternal mortality rate is still high, as an estimated 1 in 283 Ethiopian women still die during or due to complications of childbirth. Maternal obstetric knowledge and utilization of health services are associated with improved maternal health outcomes. The objective of our study was to investigate knowledge about obstetric danger signs, practices, and health care utilization during pre-partum, pregnancy, and post-partum periods among mothers of reproductive age who had at least one child between 6-59 months.

Methods: A cross-sectional survey was conducted among 295 mothers in July 2014 from the Sidama and Wolayta zones of the Southern Nations, Nationalities and Peoples Region (SNNPR) of Ethiopia. Trained enumerators conducted structured interviews in the local language with mothers to collect demographic and health data. Basic descriptive statistics identified prevalence of responses for key study areas, with data further disaggregated to the woreda (district) level to consider geographic variation.

Results: Sixty-three percent and 54% of mothers surveyed in Sidama and Wolayta, respectively, were knowledgeable about obstetric danger signs. Prolonged labor, fever, and severe vaginal bleeding were the most frequently cited danger signs in both zones. Respondents in Sidama utilized family planning and antenatal care (ANC) at higher rates than those in Wolayta. 87% and 57% of households in Sidama and Wolayta, respectively, reported having used birth control. 82% and 77%, respectively, received the WHO-recommended number of four or more visits. The top source of ANC in both zones was health extension workers, while the most frequent attendants at birth were untrained in Sidama and traditional in Wolayta. 99% of respondents had access to a health facility, while 4% were >5km away from their nearest facility.

Conclusion: Maternal knowledge of danger signs was low in the study area. The results suggest increasingly available family planning and obstetric care in SNNPR; however, inadequate use persists, particularly in the realms of institutional delivery, skilled attendance at birth and attendance of at least four ANC visits. Strategies to address this could include improving the quality of health education about danger signs and promoting institutional delivery during ANC visits.
αB-CRYSTALLIN EXPRESSION IN BREAST CANCER CORRELATES WITH POOR CLINICAL OUTCOMES.

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Mentors: Vincent L Cryns, MD; Christopher Flynn, MD, PhD


Background: Triple Negative Breast Cancers (TNBCs) are a group of breast cancers characterized by the absence of the estrogen receptor (ER), human epidermal growth factor receptor-2 (HER-2), and progesterone receptor (PR). TNBCs have an especially poor prognosis, with a one-year survival rate of less than 20%. The presence of αB-crystallin (ABC), a small heat shock protein involved in apoptosis inhibition, has been shown to be associated with lung and brain metastasis in mouse models and poor survival in patients. We investigated the link between ABC expression in breast cancer patients and clinical outcomes, including metastasis. 

Methods: We conducted a study using breast tissue samples from a cohort of 372 female patients diagnosed with breast cancer. Tissue was subsequently stained using immunohistochemistry staining for ABC, and samples were scored based on the amount of ABC present (0, 1+ or 2+ staining).

Results: ABC expression correlated with several clinical and pathological features, including tumor size (p < 0.0001), advanced stage (p = 0.003), proliferation (p = 0.0015) and TNBC status (p < 0.0001). In addition, ABC expression was associated with poor clinical outcomes, such as an increase in treatment with chemotherapy (p = 0.002), site of metastasis (p = 0.02), breast cancer-specific mortality (p = 0.002) and overall mortality (p = 0.002).

Conclusion: Overall, breast tumors expressing ABC exhibited more aggressive phenotypes, suggesting ABC plays a critical role in TNBC progression. Future studies will focus on examining the role of ABC in cancer stem cell survival, and potential therapeutic targets.
AUTOIMMUNITY AND POLLUTION: IDENTIFYING TOOLS FOR ASSESSING POLLUTION SAMPLES FOR AUTOIMMUNE PROMOTING ACTIVITY

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Mentor: Joshua Mezrich, MD

Support: Shapiro Summer Research Program; Department of Surgery

Introduction: Autoimmune diseases have been dramatically increasing in incidence worldwide with over 80 recognized diseases. Particulate matter (PM) from airborne pollution has been strongly associated with aggravating autoimmunity in humans, but it has been difficult to characterize mechanisms for aggravation of disease and identify which exposures are most pathological. Our group studies the role the aryl hydrocarbon receptor (AHR) on T-cell differentiation and effector function. Our previous studies suggest that inhalation of polycyclic aromatic hydrocarbons (PAHs) found in PMs may impact autoimmune disease through the AHR. We hypothesized that different pollution samples will induce varying, yet predictable effects on autoimmune disease depending on the balance of the fractions of chemicals in the sample. To characterize this, mice were exposed to inhaled pollution samples (urban dust particle (UDP) and two diesel emission particles (DEP1 and DEP2)) and control two weeks prior to induction of experimental autoimmune encephalomyelitis (EAE). Inhalation of both diesel samples significantly aggravated EAE, while exposure to UDP trended towards ameliorating disease. In this study we explored in vitro assays that could characterize the pathologic effects of different exposures.

Methods: Splenocytes of 2D2 mice, transgenic for a T-cell receptor specific to MOG (the antigen that mice respond to in EAE), were stimulated with MOG peptide and LPS (to mature DCs). Dilutions of the three samples were added to the cells. The cells were cultured for 4-5 days and the supernatants of the cultures were harvested. ELISA was used to measure IFNg and IL-10 levels, as measures of immune activation. Cytokine bead arrays were also used to measure additional cytokines. We cultured bone-marrow derived dendritic cells (BMDC) in another assay, exposed them in culture for 24 hours with pollutants or control, and assayed them for cytokine production. Results: In the MOG assay, all three PMs led to decreased levels of IL-6. Diesel exposure increased IFNg, but decreased IL-10 expression, a cytokine known to suppress immune responses. In contrast, UDP had no effect on IFNg expression, but increased IL-17 and IL-10 expression. In the BMDC assay, exposure to UDP increased levels of IL-10 production while the diesel samples did not. UDP also increased IDO expression in DCs, an enzyme involved in the production of regulatory T cells. Conclusion: The current data suggests that the in vitro assays may have potential for screening the autoimmune promoting activity in samples of pollution. UDP, which is made up of multiple different sources of pollution, is known to include a complex mixture of chemicals, which may affect many different cell-types, whereas diesel samples, derived from single sources of pollution, may have more predictable and specific consequences on T-cell differentiation and disease. Further characterization of this will allow improved strategies for avoidance and remediation of polluted environments.
POTENTIAL SEX BIAS EXISTS IN INTERVENTIONAL AND DIAGNOSTIC RADIOLOGY BASIC SCIENCE AND TRANSLATIONAL RESEARCH

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Background: Potential sex bias has been demonstrated in general surgery basic science and translational research, with unequal representation of male and female specimens. Because basic science research forms the foundation for clinical studies on which patient care is based, it is important for this research to consider both sexes. The purpose of this study was to determine if potential sex bias exists in the basic science and translational interventional radiology (IR) and diagnostic radiology (DR) literature. Methods: A systematic review was conducted of all articles published in 1996, 2006, and 2016 in two influential IR journals (Journal of Vascular and Interventional Radiology (JVIR) and CardioVascular and Interventional Radiology (CVIR)). A systematic review was also conducted of all articles published in 1986, 1996, 2006, and 2016 in two influential DR journals (Radiology and American Journal of Roentgenology (AJR)). All original research articles utilizing animals, cells, or cadavers were included. The data abstracted included study type, sex of specimen studied, and presence of sex-based reporting of data. Distributions of variables were compared using the Fisher Exact test, with significance defined as p < 0.05. Results: Of 1427 articles reviewed for IR, 97 (7%) were included: 86 animal or cell-based studies (89%) and 11 human cadaver-based studies (11%). Overall, authors in 58 studies (60%) did not report the sex of animals, cells, or cadavers used. Of 39 studies (40%) in which the authors did report sex, 13 (33%) utilized male only, 16 (41%) utilized female only, and 12 (31%) utilized both sexes. Of those studies that used both sexes, authors in only 4 studies (25%) reported sex-based results. Of 39 studies (40%) in which the authors did report sex, 13 (33%) utilized male only, 16 (41%) utilized female only, and 12 (31%) utilized both sexes. Of those studies that used both sexes, authors in only 4 studies (25%) reported sex-based results. A subanalysis of articles across 3 decades revealed a significant increase in studies specifying sex from 1986 to 2016 (16% in 1986 vs. 58% in 2016; p<0.0001). Conclusions: Potential sex bias exists in both IR and DR basic science and translational research, with many studies not specifying sex of specimens. The number of studies utilizing only male or female specimens outweighs those using both sexes. Encouragingly, there has been an increase in reporting of sex of specimens over the past three decades.
CLINICAL UTILITY OF HENDRICH II SCORES IN PREDICTING OUTPATIENT FALLS

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Background: Falls among older adults are a major public health concern associated with significant morbidity, mortality, and cost. Despite guidelines and quality measures, screening for fall risk remains inconsistent in the primary care setting. The emergency department (ED) offers an ideal additional site to capture high risk patients as patients presenting to the ED have an increased risk of future falls when compared to the general population. While many ED patients are currently screened for inpatient falls using the Hendrich II Fall Risk instrument, this instrument has yet to be studied with regards to its ability to predict outpatient falls. The objective of this study was to evaluate the utility of routinely collected Hendrich II fall scores in predicting returns to the ED for falls within 6 months. We performed a retrospective observational study using patient Electronic Health Record (EHR) data at a single academic medical center ED with level 1 trauma center accreditation. Our outcome of interest was a visit to the ED within 6 months of an initial index ED visit. Index visits were comprised of all ED visits resulting in discharge among patients 65 years of age or older. A logistic regression model was built to evaluate the association between the Hendrich Score II score assigned at a given visit and return for fall within 6 months, both alone and including other variables with potential additional predictive value or confounding. Results: Among visits with a completed Hendrich II score, the return rate for fall within 6 months was 8.3%. Within this population each additional point on the Hendrich score had an odds ratio (OR) of 1.23 (95%CI 1.19-1.28) on 6-month return. Area under the ROC curve (AUROC) for this model was 0.64. When included in a model with other potential confounders or predictors of fall, the Hendrich II score remains a significant predictor of return for fall with an AUROC of 0.75. Conclusion: In this analysis, we sought to determine the effectiveness of the Hendrich II inpatient fall screening instrument for the prediction of serious outpatient falls. We found that the instrument did have some predictive power with an AUC of 0.64, but given the sensitivity and specificity at each particular Hendrich II cutoff value, Hendrich II would likely have little usefulness if instituted as a stand-alone fall risk screen. However, when combined with extractable covariates, the screen performs better with an AUC of 0.75 for these returns. These results highlight the potential utility of EHR data for outpatient fall risk screening.

References
THE IMPACT OF METFORMIN ON SURVIVAL OF DIABETIC VETERANS ON ANDROGEN DEPRIVATION THERAPY FOR PROSTATE CANCER RECEIVING DOCETAXEL CHEMOTHERAPY

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Mentors: David Jarrard, MD; Kyle A. Richards, MD FACS

Support: Shapiro Summer Research Program; Herbert Brendler, MD Research Fund

Background: Prostate cancer (PCa) is the most common male malignancy in the United States and the second leading cause of cancer-related death. Metastatic castration resistant prostate cancer (mCRPC) is highly mortal, and treatment options remain limited. A growing body of evidence suggests metformin, a commonly used drug to treat type II diabetes, possesses antineoplastic properties and has the potential to be an effective treatment for a variety of cancers, including prostate, with direct effect on tumor growth or as a chemosensitizer. Epidemiological evidence has associated metformin use with decreased PCa risk, PCa specific mortality, and development of mCRPC. A recent study examined metformin's synergistic chemosensitization effects with docetaxel treatment in diabetic men with mCRPC but found no survival benefit. Given the increasing evidence of metformin's potential ability to benefit diabetic patients undergoing cancer treatment, this study sought to examine the effect of metformin with docetaxel therapy for men in a Veterans Administration population undergoing treatment for mCRPC.

Methods: We performed a retrospective observational cohort study using the Veterans Affairs database recruiting men with PCa on androgen deprivation therapy (ADT) from the years 2000-2008. Patients were stratified into 3 groups based on their diabetes status: non-diabetics, diabetics with metformin, and diabetics without metformin. The primary outcome measured was overall survival; secondary outcomes included PCa specific mortality and skeletal-related events. Overall survival, PCa specific survival, and skeletal-related events were calculated and plotted using Kaplan-Meier survival curves and compared between groups using the log rank test. Multivariable Cox proportional hazards regression models were performed adjusting for covariates using the nondiabetics as the referent group.

Results: 2,895 patients with prostate cancer treated with ADT and docetaxel chemotherapy were identified: 1,803 non-diabetics, 508 diabetics without metformin, and 584 diabetics with metformin. Metformin use was not associated with increased overall survival in diabetic patients compared to nondiabetics (HR 0.79, CI 0.62-1.01, p=0.06). Metformin use did not have any statistically significant effect on skeletal related events (HR 1.17, CI 0.61-2.225, p=0.64) or PCa specific mortality (HR 0.81, CI 0.59-1.13 p=0.22).

Conclusion: Our data did not find a significant association of metformin with an improvement in overall survival among diabetic men with PCa on ADT. However, given the low cost and toxicity of this agent and growing epidemiological and laboratory evidence supporting the antineoplastic effects of metformin, continued investigation is warranted as a potential adjunctive therapy in treating PCa.
THE ASSOCIATION BETWEEN PRE-OPERATIVE EXECUTIVE FUNCTION AND POST-OPERATIVE DELIRIUM

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Mentor: Dr. Robert D. Sanders, BSc (Hons) MBBS PhD FRCA

Support: Shapiro Summer Research Program, Department of Anesthesiology

Background: Delirium is a common complication of hospitalization and can result in a higher incidence of deleterious hospital acquired conditions, longer hospital stays and an increased financial burden on both the patient and health care system\(^3,4\). An episode of delirium predisposes patients to subsequent episodes of delirium, and may potentially lead to dementia\(^1,2\). Existing delirium prediction models use executive function. The ability to predict delirium may facilitate early implementation of prevention measures as well as further the research currently surrounding delirium pathology. The purpose of this project is to examine the relationship between different tests of executive function and delirium incidence in non-cardiac surgery patients over the age of 65.

Methods: Patients undergoing non-cardiac surgery were recruited and consented at UW hospital and clinic locations in Madison, WI. Tests of executive function including Trail Making Test A (TMTA), Trail Making Test B (TMTB), and Stroop test were performed prior to surgery. Demographic data was gathered from the EMR and entered into the ACS NSQIP surgical risk calculator to provide a measure of mortality risk. Delirium was assessed with the CAM and DRS 98 tests on post-operative days one through four. Patients that remained delirious at day four were assessed twice daily until delirium resolved. We tested various logistic regression models to build the most robust model to predict a participant’s delirium status, including variable predictors such as age and gender, scores on TMT A, B, and Stroop, and NSQIP mortality risk. Stata 14 was used to create predictive logistic regression models.

Results: We enrolled and consented 83 participants. The mean age of participants was 71 years. The participant pool consisted of 47 men (56.6%) and 36 (43.3%) women. Of the 83 we gathered preoperative data on, 26 became delirious (31.7%), 56 were non-delirious (68.3%), and 1 passed away during surgery. The mean length of delirium was 0.7 days. Before surgery, delirious patients were slower than non-delirious on both TMTA (49.21+/−23.21 vs. 37.73+/−13.02, p=0.0325) and TMTB (117.04+/−53.22 vs. 88.98.13+/−55.13, p=0.0261), but not for Stroop cognitive interference (2.34+/−0.80 vs. 2.22+/−0.95, p=0.6312). The model that was able to differentiate best between delirious and non-delirious patients was a stepwise regression with forward selection with predictive variables of TMTB, SCI, Sex, and NSQIP mortality risk (Probability >chi^2 = 0.0013, Pseudo R^2= 0.2792, AIC= 1.196, area under the ROC curve= 0.8296). Preoperative TMTB and NSQIP mortality risk were both found to significantly correlate with onset of delirium with p values of .003 and .038 respectively. Conclusions: Our results indicate that two measures of executive function, along with sex and mortality risk, may provide a moderate predictive model with a ROC of 0.8296 for the incidence of delirium in non-cardiac surgical patients over the age of 65. This may point to a complex interplay between executive function, surgical severity, and delirium and informs future analyses with this data.

MODELING PHYSIOLOGIC FLOW VARIATION IN TOTAL CAVOPULMONARY CONNECTION WITH 4D FLOW MRI AND PHYSICAL MODEL EXPERIMENTS

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Support: Shapiro Summer Research Program; Department of Radiology

Altered total cavopulmonary connection (TCPC) hemodynamics can cause long-term complications. Patient-specific anatomy hinders generalized solutions but can be studied with advanced flow imaging techniques. Previous work has studied TCPC with computational simulation but these results have relied on assumptions and are dependent on accurate boundary conditions. In vivo imaging can be used to assess patient-specific flow dynamics, but it does not allow for the manipulation of resistance and flow, which are needed to simulate exercise states. This study modeled physiologic flow variation in 6 patients with TCPC using 4D flow MRI and patient-specific physical models. Images were segmented from MR scans of TCPC patients and three-dimensional (3D) geometries were generated from angiography scans and used for physical model construction through additive manufacturing. These models were connected to a perfusion system, circulating water through the vena cava and exiting through the pulmonary arteries at two flow rates to simulate resting conditions and an exercise-induced state. Models underwent 4D Flow MRI and image processing and the data was processed for visualization and quantification of velocity and flow. A significant difference in flow distribution (p=0.01) and pathline distribution (p=0.03) was observed between normal and exercise conditions. Flow pattern metrics of vorticity and helicity did not increase with the same magnitude as the flow increase and strong inflow jets were observed at the inlet connections. Results of this study display the feasibility of analyzing varying physiologic conditions in patient specific vascular anatomy. Furthermore, significant differences in flow metrics between exercise and rest conditions suggest altered TCPC performance in patients during exercise.
ELECTROPHYSIOLOGICAL ANALYSIS OF SPINAL CORD NERVE FIBERS IN ADULT RATS WITH ADMINISTRATION OF PANCURONIUM BROMIDE AND DIHYDRO-BETA-ERYTHROIDINE BROMIDE

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Mentors: Amgad Hanna; Daniel J Hellenbrand

Support: Shapiro Summer Reaserch Program; Department of Neurosurgery

Background: It is estimated that there are 270,000 individuals in the United States living with a spinal cord injury (SCI). Recently, there has been an increase in research into potential therapies for these debilitating injuries and a parallel need for techniques that can effectively characterize the regeneration of neuronal networks and function. Axonal regeneration can be evaluated with two methods: direct visualization or detection of new axon sprouting and physiological evaluation of axonal function. There have been various studies that evaluate the regrowth patterns of axons, but there is less research that investigates the physiological properties of the regenerated axons. In this study, we used an electrophysiological technique to look at the conductive properties of axonal populations in the spinal cords of healthy and injured rats. Electrophysiological techniques that analyze the spinal cord axons can shed light on their conductive properties through the analysis of several parameters of the resulting compound action potential (CAP).

Methods: For this study, we used a needle stimulating electrode on the thoracic spinal cord and a recording electrode 15 mm downstream to measure the resulting CAP. We used 8 rats in two groups of 4: one uninjured group and one with spinal contusions. Each rat underwent three complete procedures that included stimulation with currents ranging from 100 uA to 400 uA. After one complete procedure, we injected the rat with a neuromuscular blocker, pancuronium bromide (1 mL/kg), and repeated the recording. This was followed with injection of a synaptic blocker, dihydro-beta-erythroidine bromide (1 mL/kg) and subsequent recording. Results: Untreated rats showed three distinct peaks for the CAP; however, upon injection of pancuronium bromide, the resulting CAP displayed one distinct peak. The addition of the synaptic blocker resulted in no subsequent change in the CAP. We found no significant difference in conduction velocities between healthy and injured groups, however, there was a significant, and expected, decrease in CAP amplitudes in the injured rats compared to the healthy rats.

Conclusion: As shown by the single peak CAP, the use of a neuromuscular blocker is essential to eliminate noise and obtain information specifically from the conduction of the action potential through the nerve fibers. Electrophysiology can be a helpful tool in analyzing the conduction properties of axons and evaluating physiological recovery.
THE ASSOCIATION OF FRONTAL CORTEX NEURODEGENERATION AND POSTOPERATIVE DELIRIUM

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Support: Shapiro Summer Research Program; Department of Anesthesiology

Background: Delirium is an acute brain dysfunction characterized by fluctuating states of cognition and consciousness, precipitated by an acute event such as surgery. This syndrome has significant associations with long-term neuropsychological and cognitive deficits and increased mortality risk independent of other causes. By investigating the pre-delirium brain state in a cohort design coupled with neuroimaging, we hope to provide further data on how patients become predisposed to delirium. We hypothesize that postoperative delirium is associated with reduced frontal cortical thickness. Methods: Patients >65 years undergoing noncardiac surgery with a hospital stay of approximately two days or more were recruited. Patients underwent initial cognitive testing, including the Confusion Assessment Method (CAM) and Delirium Rating Scale-Revised-98 (DRS-98: measurement of delirium symptoms), followed by an MRI on a 1.5 or 3.0 Tesla machine. After surgery, delirium was assessed twice daily with the CAM and DRS-98 (AM/PM) from postoperative day 1 through postoperative day 4. If the patient was delirious on the last assessment, delirium assessments continued until the delirium resolved. Patients who score CAM positive at any point are classified as delirious. Cortical thickness analysis was performed with the Freesurfer brain imaging suite, using its QDEC interface to make statistical maps of cortical thickness. Correction for multiple comparisons was done with a Monte Carlo Simulation, setting the P-value <0.01.

Results: Our cohort included 69 subjects for analysis, of which 19 were delirious (Mean age: 72, 9-M, 10-F) and 50 were not delirious (Mean age: 71.2, 29-M, 21-F). Preoperative scans were completed on 48 patients and postoperative scans were completed on 21 patients. The average maximum DRS-98 score for the non-delirious and delirious patients was 4 and 24 respectively. General Linear Model analysis comparing cortical thickness between delirious and non-delirious revealed that the rostral middle frontal cortex (cluster size: 731.38 mm²) and the precentral gyrus (cluster size: 542.16 mm²) were significantly thinner in delirious compared with non-delirious in the left hemisphere. The left hemisphere also yielded two structures where cortical thickness negatively correlated with maximum DRS-98 score: the rostral middle frontal cortex (cluster size: 883.11 mm²) and the postcentral gyrus (cluster size: 744.43 mm²). The average thickness of each cortical structure did not significantly differ in the right hemisphere between the groups and there were no significant correlations between DRS-98 and right hemisphere cortical thickness. Conclusion: These findings suggest portions of the left prefrontal cortex are thinner in those patients who experience postoperative delirium than those who do not. In future analyses we will look to account for confounding variables including age, gender and average hemisphere cortical thickness. We hope to provide further understanding in this area as we collect data from more delirious patients.

References:
COMPARISON OF USE OF A SHORTENED AIR-Q SP VERSUS THE WILLIAMS INTUBATING AIRWAR FOR SINGLE-OPERATOR FLEXIBLE BRONCHOSCOPIC INTUBATION

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Mentor: Richard E. Galgon, MD, MS

Support: Shapiro Summer Research Program; Department of Anesthesiology

Background: Flexible bronchoscopic intubation, also known as fiberoptic intubation (FOI), is an effective and well-established technique for gaining airway access in patients with difficult airways (1). Successful airway management during FOI is highly dependent on the ability to visualize the patient’s vocal cords. In patients with difficult anatomy, laryngeal edema, or general obesity, a second operator can externally manipulate the larynx by applying one or more maneuvers (e.g. jaw thrust or lingual retraction) that provide an improved view of the vocal cords (2). With the vocal cords in sight, the first operator is then better able to guide the flexible bronchoscope through the patient’s upper airway and into their trachea. This procedure can occur with or without the use of a conduit airway for fiberoptic intubation (e.g. the Williams, Ovassapian, or Berman Intubating Airway). The air-Q SP is a commercially available supraglottic airway (SGA) that can be used as a primary airway device and also as a conduit for intubation, similar to the Williams, Ovassapian, and Berman Intubating Airways (3). Previous trials comparing the air-Q SP with other commercially available SGAs have found that the air-Q SP bowl design provides a partial or full view of the vocal cords in 80-92% of patients without requiring any maneuvers involving a second operator (4)(5). The high rate of vocal cord visualization allowed by the air-Q SP gives reason to believe that successful tracheal intubation can be achieved without the need for a second operator when using the air-Q SP. However, further analysis will be required to demonstrate this. Consequently, our study will compare the single operator intubation success rate when utilizing a version of the air-Q SP versus the Williams airway.

Methods: The entire summer was spent working with the UWSMPH IRB to achieve study approval. I worked closely with Dr. Galgon to submit updated proposals to the IRB as requested. I utilized the UW ARROW system for viewing IRB comments and making the necessary changes to the study proposal. In addition, I was able to shadow Dr. Galgon as he engaged in his clinical duties, inside and outside of the operating room. Results: IRB approval of the study was achieved at the end of the summer. However, I was unable to initiate the study and collect data as my allotted time with the project ended and my second year of medical school began shortly after achieving approval. Conclusion: This study has yet to be initiated, but I plan to be involved in some capacity as the study is rolled out.
**INVESTIGATION OF THE MECHANISM OF NEUTROPHIL INHIBITION BY CANDIDA BIOFILMS**

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**Mentors:** Jeniel Nett, MD, PhD; Chad Johnson, PhD

**Support:** Shapiro Summer Research Program; Department of Medicine

**Background:** Medical devices, including endotracheal tubes, central venous catheters, and pacemakers, are vital components for the treatment of patients. However, these devices are prone to serve as a major source of nosocomial infections that are particularly difficult to treat due to biofilm formation.¹ Biofilms refer to the attachment, adherence, and growth of microorganisms onto a surface. They are highly resistant to clearance by the immune system defenses as well as to clearance by antibiotics.²,³ The fungal pathogen *Candida albicans* is a common causative agent in forming biofilms on medical devices and causing bloodstream infections.⁴ The mortality rate of patients affected by invasive candidiasis is almost 30%.⁵ Thus, it is an extremely serious health problem. Non-biofilm *Candida*, i.e. planktonic *Candida*, is more easily eradicated by the host immune system compared to *Candida* in a biofilm state.⁶ The critical immune system components in the process of killing non-biofilm *Candida* are neutrophils. Neutrophils release neutrophil extracellular traps (NETs) that capture and kill microorganisms. NETs are composed of proteins, DNA, and histones.⁷ Interestingly, neutrophils only release NETs in response to non-biofilm *Candida* and not in response to *Candida* biofilms. The inability of neutrophils to release NETs when exposed to *Candida* biofilms enables the fungal pathogen to persist by evading killing by the host immune system. A potential mechanism by which *Candida* biofilms inhibit NET release by neutrophils is through the display of sialic acids that mimic host cell glycans. Sialic acids were hypothesized to serve as an inhibitory signal to neutrophils via Siglec receptors.⁸ My overall objective was to identify the NET inhibitory pathway induced by *Candida* biofilms focusing on 1. the hypothesis that biofilms impair NETs by engagement of Siglec inhibitory receptors on neutrophils and 2. identifying other neutrophil receptors that potentially interact with biofilms. **Methods:** I measured NETs produced by neutrophils in response to *C. albicans* biofilms in the presence and absence of antibodies to Siglecs 5 and 9, as well as with soluble Siglecs 5 and 9. This was accomplished through the use of Sytox Green, an impermeable nucleic acid stain. I also used sialidase to cleave sialic acids on biofilms to investigate this effect on neutrophil NET release. Additionally, I used phospho-immunoreceptor arrays to identify neutrophil receptors activated after interaction with biofilms. **Results:** Siglecs 5 and 9 did not appear to play a major role in NET inhibition. However, neutrophil response to biofilms in these experiments was variable based on the neutrophil donor. **Conclusion:** There are other receptors and pathways to consider in the mechanism of neutrophil inhibition by *Candida* biofilms including FcγRIIB and DCIR/CLEC4A. Future studies will focus on studying these other receptors. Overall, multiple pathways are likely involved in the inhibition of NETosis by *Candida* biofilms, and receptors for these pathways could be variably expressed in donors.
IMPACT OF RACE AND SOCIOECONOMIC STATUS ON TREATMENT AND OUTCOMES OF BLUNT SPLENIC INJURIES.

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Introduction: Racial, ethnic, and socioeconomic disparities exist in trauma patients. There is little information on disparities in patients with blunt splenic injuries (BSI). This study assessed the effect of race and insurance status on physician treatment plans and outcomes in blunt splenic trauma.

Methods: The National Trauma Data Bank was used to study patients aged 15-89 with BSI from 2013-2015. Variables of interest were compared across groups using Chi-Square tests, and those with significant associations were used in multivariate regression models for each outcome of interest to control for confounding variables. Results: We analyzed 13,537 BSI patients. Uninsured patients had increased odds of mortality (OR 1.6, p>0.001), more splenic operations (OR 1.6, p<0.001), and were less likely to have non-operative management (OR 0.63, p<0.001). Uninsured patients were also twice as likely to be discharged home and three times as likely to leave AMA. (OR 0.35, OR 0.33; p<0.001). Blacks and Hispanics had higher mortality (OR 1.5; p=0.035, p=0.029 respectively). Blacks had more splenic operations (OR 1.23, p=0.03) and were 0.5 times less likely to receive angioembolization (p<0.001), while Hispanics had less splenic operations (OR 0.81, p=0.032). Conclusion: Noteworthy differences exist in the management of splenic trauma patients based on race/ethnicity and socioeconomic status, despite controlling for demographics and injury characteristics. Insurance status and race affect surgical treatment plans and mortality, particularly for uninsured, Black and Hispanic patients.
TRENDS IN ED EVALUATION OF PEDIATRIC PATIENTS WITH MENTAL HEALTH COMPLAINTS

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Support: Shapiro Summer Research Program;

Background: Emergency room visits with a mental health component make up a significant proportion of overall patients who present in the emergency department (ED). The objective of this study was to examine trends in mental-health related visits to EDs in the U.S. from 2005-2014. Methods: Data from 2005-2014 were extracted from the National Hospital Ambulatory Medical Care Survey using criteria for mental-health visits based upon ICD-9-CM diagnosis codes, V codes, and injury E codes, and National Center for Health Statistics reason-for-visit codes. Trends over time were depicted for overall visits, demographic makeup, and mental health case-mix. Trends in length of visit and number of laboratory tests were modeled using regression. Results: There was a weighted total of 90,302,144 mental-health related visits identified from 2005 to 2014. Median length of visit increased from 180 minutes, 95% CI [65, 199] in 2005 to 201 minutes, 95% CI [182, 223] in 2014. Adults had the longest median length of stay; however, no significant time trends were found when adjusting for continuous age (P=0.24). The three most prevalent diagnoses were mood disorder, anxiety disorder, and substance use disorder. Median number of tests for all patients of all years was 2 tests. The median number of tests was significantly associated with age and diagnosis, and increased for all diagnoses except anxiety disorders (p<0.01). Median length of visit was significantly associated with age and number of diagnostic tests, and increased for all diagnoses except anxiety disorders (p<0.01). Additional descriptives forthcoming. Conclusion: Mental health visits continue to make up a significant portion of visits to the ED. From 2005-2014, LOV increased slightly. There was no significant change in median number of tests ordered.
EFFECTS OF PRE-OPERATIVE OPIOID USE ON POST-OPERATIVE PATIENT OUTCOMES AFTER ORTHOPEDIC KNEE SURGERY

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Introduction: Opioids are popular pain medications that are often prescribed for patients with knee pain. However, opioid prescription before knee replacement surgery is associated with longer hospital stays, more post-surgical pain, a higher need for additional procedures, and a higher rate of complications. Despite the growing evidence against opioids, they remain one of the most popular pre-operative pain management prescriptions. The purpose of this study is to clearly examine the effects of both length and dosage of pre-operative opioid use on orthopedic knee surgeries and post-operative outcomes/complications.

Method: This was a retrospective study and the patients all underwent orthopedic knee surgery at UW hospitals between 5/1/2014 and 4/30/2015. We randomly selected 197 patients and divided them into two groups that had pre-operative opioid dosages of either <= 180 mEq morphine (low dose) or >180 mEq morphine (high dose). We harvested pre-operative and post-operative data including pain scores and knee range of motion from patient charts in EPIC. We then statistically analyzed the data using Statistical Package for the Social Sciences (SPSS), utilizing two-tailed T-tests for numerical data and Chi-squared tests for categorical data.

Results: Of the 197 patients, 100 were in the low dose morphine group while 97 were high dose. The cutoff at 180 mEq morphine was calculated to be the median dosage across all patients. We did not find many significant (P<0.05) differences between the groups with regards to surgical outcomes and complications. However, we did find several interesting associations such as the low dose group being on a shorter opioid prescription, getting higher dosages of intraoperative opioids, and being more likely to have hypertension than the high dose group.

Conclusion: Patients with high dose pre-operative opioid treatment, both in terms of chronological length of treatment and dosage of treatment, do not have worse post-operative outcomes and complications as compared to a group of similar patients with low dose opioid treatment undergoing orthopedic knee surgery. Increasing the sample size may be required to reach a more definitive understanding of opioid effect on surgical outcomes.
IMMEDIATE VISUAL FEEDBACK AND ITS EFFECT ON TECHNICAL SKILLS AND CONFIDENCE DURING COMPLEX TOURNIQUET APPLICATION

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Support: Shapiro Summer Research Program

Introduction: Junctional hemorrhage is a leading cause of preventable military death. Tourniquets exist for these difficult anatomical regions and are approved by the FDA to stop bleeding until arrival at a medical facility. The purpose of this study is to compare preferences and changes in performance when using a newly designed visual bleeding feedback system (VBFS) in training novices. We hypothesize that users will indicate higher levels of confidence after training and greater improvements in training time with the bleeding feedback system compared to those who train without feedback (WF). Methods: Medical students (N=15) and community emergency medics (N=4) with no junctional tourniquet experience were randomized in a single-blind, crossover, controlled study to start either in the VBFS group or the WF group. All subjects underwent training in the following order: instructional videos, hands on practice, 3 recorded skill trails in their randomized start group, VBFS or WF and crossover to VBFS or WF for 3 more recorded skill trails. Participant agreement with statements asserting confidence in efficient and accurate tourniquet application and usefulness of the VBFS was assessed using a pre-and post-Likert scale with ratings from 1 to 7, with 1 being least agreement and 7 being most. Video and audio data were also collected and analyzed to assess total trail time and tourniquet application time. Group confidence scores and trial times were calculated via paired t-test. Results: Participants indicated very high ratings for VBFS usefulness (6.37/7.0 +/- 1.25) and recommendation to others (6.74/7.0 +/- 0.56). There was no statistical difference in pre and post 1st training set user confidence before the crossover, but there was a significant reduction in overall application times between the 1st and 6th trial (80.5 s vs 44.4 s, p = 0.032) after crossover. It is also notable that participants in the in the VBFS spent more time than the WF groups (37.9 s vs 21.4 s, = 0.56) indicating active use of the visual feedback system. It is also noted that participants started with a comparably high confidence levels in the pre-training phase compared to confidence after the 6th trial, (5.11/7.0 vs 5.37/7.0, p = 0.35). Conclusion: Trial times were increased when using the VBFS and all users rated VBFS highly. Participants were equally confident in tourniquet application after just watching a video compared to finishing the entire training with its six applications on a bleeding and non-bleeding model. Given that most participants were novices to this type of tourniquet, it is possible that they were overly confident in their original self-assessed abilities. This over confidence necessitates the need for developing effective scenario based training curricula for this deceptively straightforward life-saving task.
IMPROVING SCREENING, DIAGNOSIS AND TREATMENT OF IRON DEFICIENCY ANEMIA IN INFANCY

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Support: Shapiro Summer Research Program; Department of Pediatrics. UW Cardiovascular Research Center Medical Student Fellowship.

Background: Iron deficiency (ID) is the most common micronutrient deficiency. Infantile iron deficiency anemia (IDA) can cause sensory, motor, cognitive and social/behavioral deficits. Since early detection of ID can prevent long-term consequences, universal screening for IDA at 12 months and risk assessment at 4 months of age are recommended. Two aims were developed to prevent IDA by decreasing variation in IDA screening. 1. Website: Prospective observational study to disseminate IDA resources to families/providers. 2. Neonatal intensive care unit (NICU) screening: Retrospective observational study analyzing screening rates for IDA at 1st month and 6th month of life. Methods: Website: Develop a website that provides comprehensive data on screening, risk factors, diagnosis and treatment of childhood IDA. Serial interventions were performed to increase website views, which were tracked after the following interventions: June: Notified colleagues through email. July: Meriter NICU parent class, Meriter website, Meriter Facebook and flyers in Meriter NICU. August: UW-Health Healthy Kids blog article. NICU Screening: Data from 110 NICU graduates included 1st and 6th month ferritin levels as the index of iron status. Screening compliance was assessed. Risks for IDA were summed and included prematurity, overweight or underweight, multiple gestation, maternal obesity, maternal anemia, maternal diabetes, minority status and Badgercare insurance. Statistics included unpaired t-tests, \( \chi^2 \) and simple regression analyses. Results: Website: Visits to the website fell (160, 35 and 29) over the 3 months \( p<0.01 \), but many visitors were returnees. Visits lasted 3-6 minutes and pages with the most views were Providers, Families and Handouts. NICU Screening: 1st month ferritin was below cutoff in 12% of babies, with lower ferritins as risk factors increased, \( p<0.025 \). Mean risk factor number was 2.7. Ferritin at 1 month was unrelated to ferritin at 6 months and none were below the 6th month cutoff value, although only 29% had 6th month screening performed. Conclusion: Barriers to IDA prevention and early identification were observed in this project. Website: Visits were less than expected. NICU Screening: Rates of 6th month screening were low, but a lack of relationship between 1st and 6th month ferritin suggests that current interventions may effectively prevent IDA. Additional interventions to improve website utilization and awareness of IDA screening practices are planned.