2014 Student Research Forum Abstracts
(listed alphabetically by student last name)
PATHOLOGY ASSESSMENT OF COLLAGEN ORGANIZATION AND STRUCTURE IN PANCREATIC DUCTAL ADENOCARCINOMA

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Support: Shapiro Summer Research Program; Department of Surgery, University of Wisconsin School of Medicine and Public Health

BACKGROUND: Pancreatic ductal adenocarcinoma (PDAC) is one of the most dismal cancers in the U.S.; it is one of the few human cancers with nearly 100% mortality and a median survival time of less than 6 months. Cancer progression is governed largely by the interplay between neoplastic cells and components of the tumor microenvironment. Of particular interest is the extracellular matrix protein collagen, which is a significant component of the stroma in many cancer types. A number of studies have demonstrated that the organization of collagen fibers in the stroma has biological and clinical (i.e. diagnostic and prognostic) relevance. The imaging technique for stromal collagen analysis has traditionally been second-harmonic generation (SHG), a laser-scanning microscopy method that can visualize collagen in specimens without the need for labeling. However, collagen characterization has yet to be implemented into the clinical setting largely because SHG is technically challenging and requires expensive instrumentation.

OBJECTIVE: To compare and contrast SHG microscopy and Picrosirius Red staining with particular interest in visualizing and quantifying collagen formations, dimensions, and organization to determine if a surrogate method exists for collagen analysis as part of the clinical evaluation of cancer tissues.

METHODS: De-identified tissue specimens were obtained for 3 patients that underwent surgical resection for PDAC. The tissues were histologically processed for standard H&E and Picrosirius Red staining and regions rich in collagen fibers and representative of the grade of cancer were annotated (6-8 per section). Each region was imaged using both SHG and polarized brightfield microscopy. Image quantification for the different modes of collagen contrast was completed using the CT-Fire software.

RESULTS: Comparative results from the Picrosirius Red stain and SHG are currently being analyzed with CT-Fire software. The results will help us determine if there are any characteristics uniquely visible in a particular visualization technique or if there is a more efficient histopathological method to evaluate stromal collagen.

CONCLUSIONS: In the initial study design, we intended on analyzing a total of 5 stains but that proved to be difficult as some stain ingredients interacted negatively under laser scanning microscopy. Future directions of this project would be to determine more stains that can be used to analyze collagen and to increase the sample size.
RISK EVALUATION OF ORGAN DONATION FROM DONORS WITH PRIMARY MALIGNANT GLIOMAS

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BACKGROUND: Progress in organ transplantation to treat end-stage organ disease has resulted in organ demand greatly outpacing supply. The escalating organ shortage and rising mortality rates for the estimated 123,000 patients on the U.S. organ wait-list motivated our reevaluation of common practices related to organ donation from individuals with primary central nervous system (CNS) tumors. Malignancy is generally considered a contraindication to organ donation, with rare exceptions including non-metastatic primary brain tumors (PBT). Glioblastoma multiforme (GBM) is a WHO grade IV glioma that accounts for over 45.2% of malignant PBTs in the U.S. Therefore, less than 0.5% of 13,000 U.S. patients dying from malignant gliomas annually serve as organ donors. Although a hallmark feature of GBM is infiltration into surrounding brain, metastatic capacity outside the CNS is poorly documented

OBJECTIVE: Evaluate and assess the implications of available data on the rarity of extra-neural metastasis (ENM) of GBM as it pertains to metastatic transmission following organ transplantation.

METHODS: Using literature review of all available papers reporting on GBM and extra-neural metastasis, we evaluated and assessed the implications of available data on the rarity of extra-neural metastasis (ENM) of GBM regarding the risk of donor-derived transmission (DDT) of cancer to organ recipients. We evaluated and present recent reports on DDT rates among recipients of cadaveric organs from GBM patients. RESULTS: Careful screening of papers for only pathologically confirmed metastatic events were considered high quality, reliable data. Literature review revealed only clinical case reports suggesting a maximum incidence of metastasis that is likely significantly lower than 2%, and highlights that such rare GBM metastatic events preferentially target pulmonary, lymph, hepatic and bone tissues.

CONCLUSIONS: These findings imply that kidneys from donors with GBM may be considered for transplantation, and the morbidity and possible mortality of wait-listed renal allograft recipients may outweigh the apparent small risk of DDT from donors with GBM. Further studies are required to validate this implication before implementing any changes in donor evaluation policy. Furthermore, re-evaluation of policies regarding other lower grade primary brain tumors are being considered for study in order to support the goal of increasing donor organs.
DOES LEVOTHYROXINE ADMINISTRATION IMPACT PARATHYROID LOCALIZATION?

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BACKGROUND: Proper localization is crucial in performing minimally invasive parathyroidectomy for primary hyperparathyroidism (PHPT). Ultrasonography (US) and Tc-99m sestamibi (MIBI) scintigraphy are common methods used for localization. As the appearance and activity of the thyroid gland may impact parathyroid localization, the purpose of this study was to determine how exogenous use of the thyroid hormone, levothyroxine (LT), affects parathyroid localization. OBJECTIVE: To determine the effect of levothyroxine on parathyroid localization. METHODS: Adult patients with non-familial PHPT who underwent initial parathyroidectomy from 2001 to 2014 were retrospectively identified. Levothyroxine (+LT) and non-levothyroxine (-LT) patients were matched 1:3 based on age, gender, presence of goiter, and pre-operative parathyroid hormone levels. Further subgroup analysis was performed on patients previously treated with radioactive iodine (RAI) and patients undergoing single adenoma (SA) resection. RESULTS: Of the 1,737 patients that met inclusion criteria, 286 were on LT at the time of localization and were matched to 858 –LT patients. There was no difference in gender, age, or pre-operative labs between the two groups. Use of LT did not impact the percentage of correct MIBI localization scans when compared to -LT patients (p =0.83). 31 of the 286 +LT patients were post-RAI treatment and this did not impact localization by MIBI either (p=0.55). Interestingly, use of LT significantly hindered parathyroid localization by US in comparison to the –LT group (48.4 vs 62.2%, p <0.01) regardless of the reason for LT supplementation (post-RAI: 22.2 vs 67.4 %, p=0.02). Additionally, for the 73% of patients having SA resection, the percentage of correct US localization was significantly less for +LT compared to –LT patients (56.7 vs 71.8%, p<0.01) while MIBI localization accuracy was not significantly different (p=0.31). When examining only patients where a single upper gland was removed, the +LT group was less likely to have a correct US compared to the –LT group (50 vs. 72.8%, p<0.01). There was no difference in percentage of correct US for patients who only had a single lower gland removed (p =0.51). CONCLUSIONS: Exogenous levothyroxine is associated with impaired parathyroid localization with US but not MIBI. This effect could be due to the thyroid’s echotexture in patients with hypothyroidism limiting the ability to detect more posteriorly located upper glands with US.
THE SHARED SAVINGS PAYMENT MODEL AS A PATHWAY TO IMPROVING HEALTH CARE QUALITY AND VALUE IN WISCONSIN

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BACKGROUND: While many alternatives to fee-for-service reimbursement are being tested in Wisconsin and nationally, the Centers for Medicare and Medicaid Services (CMS) has put considerable weight behind the Shared Savings payment model through the Medicare Shared Savings Program (MSSP) and the Pioneer Accountable Care Organization (ACO) program. Over the last two years, hundreds of organizations across the country have entered into Shared Savings agreements with CMS. Like other payment reform models, Shared Savings is designed to support and facilitate higher quality care for patients at a lower cost for payers and purchasers. When Medicare ACOs improve quality and reduce costs, participating provider organizations become eligible to share in a portion of the costs that CMS “saves” as compared to expected expenditures. In Wisconsin, seven ACOs are currently participating in the Medicare Shared Savings program and one ACO is participating in the Pioneer ACO program. Organizations began entering into three year Shared Savings agreements with CMS in 2012, and additional organizations joined program in 2013 and 2014. Many provider organizations have now completed at least one full year under an ACO agreement with CMS, and health care leaders now have first-hand experience with the implementation of the Shared Savings model. These experiences are providing valuable insights as health care leaders and CMS consider the keys to successfully operating an ACO. OBJECTIVE: This research will explore the ways in which Medicare ACOs (both MSSP and Pioneer) have improved the quality and value of health care in Wisconsin. It further offers recommendations gleaned from the perspectives of Shared Savings participants on the future of this payment model as a pathway to greater health care value. METHODS: Semi-structured interviews will be conducted with the executives from selected ACOs operating in Wisconsin. These interviews will be transcribed and coded for review. Additionally, data made available through CMS will be used to analyze ACO performance. RESULTS: The interviews with ACO executives and other health care leaders are ongoing. Results are not yet available. CONCLUSION: Since the Patient Protection and Affordable Care Act (ACA) was signed into law in 2010, much attention has been given to the newly created ACOs, but little information is available directly from the health care leaders who have been at the forefront of implementing the Shared Savings payment model along with significant transformations in clinical practice and patient engagement. By conducting interviews with ACO executives and health care leaders we seek to bring together the unique experiences of different health care organizations in Wisconsin to highlight best practices, lessons learned, and areas of improvement that can guide future payment reform and quality improvement efforts.
REDUCING CENTRAL-LINE ASSOCIATED BLOODSTREAM INFECTIONS THROUGH A SOCIOADAPTIVE INTERVENTION

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BACKGROUND: Central-line associated bloodstream infections (CLABSI) are a major cause of hospitalized patient morbidity and mortality and generate substantial excess healthcare costs. Most reduction efforts have focused on interventions to standardize central line insertional practices in the intensive care unit (ICU) setting. While successful, contemporary studies have shown that a majority of CLABSIs now occur outside the ICU setting where time-to-event often occurs 7 days after insertion – demonstrating a need to focus on line maintenance practices. OBJECTIVE: This poster provides evidence of the impact of a central-line maintenance bundle within ICU and non-ICU settings at the University of Wisconsin Hospitals and Clinics (UWHC). The UWHC employed several strategies to reduce CLABSI rates, including chlorhexidine bathing, hospital-wide education focused on a central-line maintenance bundle and an intensive socio-adaptive intervention focused on training and supporting unit-based champions whose purpose was to improve safety culture and care-related behaviors associated with central lines. The primary objective of this project was to evaluate the impact of a unit-based champion training intervention on observed CLABSI rates while accounting for the other interventions implemented during the same time. METHODS: CLABSI rates were tracked using standardized methods recommended by the CDC’s National Healthcare Safety Network. The unit-based champion intervention was implemented across different units at UWHC using a stepped-wedge design. Multivariate Poisson regression was used to calculate the impact of unit-based champion training on observed CLABSI rates while accounting for the influence of other previously implemented interventions. RESULTS: Rates decreased significantly after implementation of the CBT initiative from 2.36 to 1.52 per 1,000 CLABSI days (OR = 0.59 [0.42, 0.85]). Although rates decreased for both education campaigns as well, these results were not statistically significant. CONCLUSIONS: These results demonstrate that a socio-adaptive model focused on modifying culture and ensuring sustainability of proper CLABSI maintenance practices is effective in reducing CLABSI rates. Additional studies should be done to examine differences in rates between units to determine if specific characteristics of the units and champions affect infection rates in order to better understand the underlying mechanisms behind the decrease in infections.
READTHROUGH OF AN IN-FRAME NONSENSE MUTATION ASSOCIATED WITH LEBER'S CONGENITAL AMAUROSIS

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BACKGROUND: Leber’s Congenital Amaurosis (LCA) is a congenital blindness affecting 20% of the kids attending schools for the blind. LCA16 is a subtype associated with a mutation of the KCNJ13, which codes for the Kir7.1 inwardly-rectifying potassium channel. Kir7.1 is found at the apical membrane of Retinal Pigment Epithelial (RPE) cells and is a major component of the apical membrane K+ conductance required for the transport function of this epithelial cell monolayer. OBJECTIVE: The group recently identified an LCA patient with a novel non-sense mutation, c.158G>A (p.W53X), in the KCNJ13 gene. We sought to assess the ability of gentamicin along with readthrough compounds 13 and 14 (RTC13,14), previously shown to enable readthrough of in-frame nonsense mutations, to recover the expression of functional Kir7.1 protein in the context of the W53X mutation and the R166X mutation, another in-frame nonsense mutation that occurs downstream in KCNJ13. METHODS: To evaluate the function of the ion channel, we heterologously expressed plasmid vectors of Kir7.1, W53X, and R166X mutations in Chinese hamster ovarian (K1) cells. The drugs were administered directly through the cell culture medium 12 hours after transfection. Whole-cell patch-clamp electrophysiology was performed on cells cultured on glass coverslips to register current responses after 36 hours of drug treatment. Data was analyzed off-line and statistical analysis was performed. RESULTS: Both W53X and R166X transfected cells that received no drug treatment exhibited no Kir7.1 channel current with a depolarized membrane potential and served as controls. W53X cells treated with RTC14 showed recovery of Kir7.1 current, unlike gentamicin and RTC13 treated cells. Similarly, R166X cells treated with RTC13 did not show Kir7.1 current, however, R166X cells treated with the higher dose (10uM) of RTC14 showed a Vm (-44 mV) closer to recovered Vm (-62 mV). CONCLUSIONS: The initial goal of the study was to assess gentamicin, an FDA approved medication, as a possible future therapy for LCA. Despite the fact that the study does not support this possibility, the findings regarding RTC14 are significant. Although it is currently not an approved therapeutic, our results support investigation of RTC14 as a possible therapy for LCA. Furthermore, our study provides more evidence in favor of continuing investigation of readthrough compounds for the treatment of conditions involving in-frame nonsense mutations.
BACKGROUND: HIV is more prevalent in incarcerated populations than in the general U.S. population, and many patients first receive HIV-specific care while in prison. However, individuals living with HIV face numerous challenges to successful reintegration into society after leaving the prison system that may negatively impact the ability of patients to engage with HIV care within the community and to remain adherent to antiretroviral treatment regimens. To date, there is a lack of qualitative research that explores the specific barriers and facilitators to optimal HIV care following release from prison. OBJECTIVES: This study aims to describe the experiences of individuals with HIV prior to incarceration, during incarceration, and through the initial six months after release from prison. The ultimate goal of this research is to inform clinical practice and social service provision for former prisoners with HIV as they transition back into the community. METHODS: Eligible participants were patients receiving care at the UW HIV Comprehensive Care Clinic while incarcerated in a Wisconsin prison. The qualitative component of the study consisted of semi-structured interviews conducted several days prior to release from prison and again six months following release. The interview was designed to elicit knowledge, attitudes, and beliefs about HIV as well as legal, financial, and social challenges to reintegration. RESULTS: In this ongoing investigation, four participants have completed the study and 21 have completed a pre-release assessment. Two of the four participants having completed the study were incarcerated 20 years; the other two were incarcerated less than five years. Prior to release from prison, participants described optimism regarding their ability to transition smoothly into their community after release from prison, including confidence in their ability to maintain optimal HIV care. During the follow up interview six months after release, participants described unanticipated intrinsic and extrinsic barriers to reintegration, and mentioned management of HIV as a top personal priority. CONCLUSIONS: Despite the tremendous challenges facing individuals in this cohort, initial findings show good adherence to HIV-specific medical care. This study provides evidence that with adequate social support, individuals living with HIV can be retained in care and maintain medication adherence during the transition from prison back into the community.
PREDICTORS OF SURGICAL SITE INFECTION AFTER DISCHARGE IN PATIENTS UNDERGOING MAJOR VASCULAR SURGERY

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Support: Shapiro Summer Research Program; Department of Surgery, University of Wisconsin School of Medicine and Public Health

BACKGROUND: Surgical site infection (SSI) after vascular surgery is one of the most common post-operative complications and is the leading cause of unplanned, potentially preventable hospital readmissions among surgical patients. Transitional care interventions to detect SSI after hospital discharge may help stem the burden of readmissions and morbidity associated with SSI; however little is known regarding the classification of patients at high-risk for development of SSI occurring after hospital discharge (postSSI). OBJECTIVE: The objective of this study is to determine the unique predictors of postSSI in order to better direct transitional care interventions. METHODS: Patients who underwent major vascular surgery from 2005-2012 were identified from the American College of Surgeons National Surgical Quality Improvement Program Participant Use Files. Patients were categorized as having no SSI, SSI while in-hospital (preSSI), or postSSI. Multivariable logistic regression was performed using patient demographics, preoperative health characteristics and comorbidities, and operative variables to predict preSSI and postSSI. RESULTS: Of the 50,091 patients who underwent major vascular surgery, 4,481 (9.0%) were diagnosed with SSI (2.1% preSSI; 6.8% postSSI). Predictors unique to patients who experienced preSSI include totally dependent functional status (odds ratio [OR]: 2.7; 95% confidence interval [CI]: 1.8-4.0), emergency case (OR: 2.5; CI: 1.9-3.1), chronic obstructive pulmonary disease (OR: 1.4; CI: 1.1-1.8) and prolonged operative time (OR: 1.3; CI: 1.0-1.7). Predictors unique to patients who experienced postSSI include female gender (OR: 1.4; CI: 1.3-1.5), overweight vs. normal BMI (OR: 1.3; CI: 1.2-1.5), insulin dependent and non-dependent diabetes mellitus (OR: 1.4; CI: 1.2-1.5) (OR: 1.3; CI: 1.1-1.4), dyspnea with moderate exertion (OR: 1.1; CI: 1.0-1.3), rest pain/gangrene (OR: 1.4; CI: 1.3-1.5), coronary artery disease (OR: 1.1; CI: 1.0-1.2), hypertension requiring treatment (OR: 1.2; CI: 1.1-1.4), peripheral vascular disease (OR: 1.3; CI: 1.2-1.4), smoking (OR: 1.2; CI: 1.1-1.3) and neurological disease (OR: 1.1; CI: 1.0-1.3). CONCLUSIONS: Predictors of preSSI after major vascular surgery are largely acute non-modifiable conditions whereas predictors of postSSI are primarily chronic comorbidities. Appropriate identification of these different sets of risk factors may improve both in-hospital wound surveillance and subsequent transitional care efforts to improve wound monitoring.
COORDINATING CARE COORDINATION? OBSTACLES, OPPORTUNITIES, AND ACTIONS IN THE UW HEALTH SYSTEM

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BACKGROUND: In recent years, greater attention has been placed on super-user patients. These are patients who frequently utilize emergency department and in-patient hospital services. Due to their high health care costs and overall poor health outcomes alongside the fiscal reforms presented by the implementation of the Affordable Care Act (ACA), the barriers faced by super-users must be addressed by health care systems. OBJECTIVE: We sought to characterize UW Health’s approach to super-user patients. METHODS: We conducted 10 semi-structured key-informant interviews, with interviewees selected based on involvement as leaders or frontline workers involved in super-user interventions within UW Health or the Madison community. Key informants were asked to describe their affiliated super-user programs, including how super-users were defined and identified, specific interventions, collaborations, and perceived strengths and weakness. All interviews were conducted in-person by two members of the interdisciplinary research team. Qualitative analysis of the recorded interviews was performed using the Grounded Theory Method. RESULTS: The following three major themes were elucidated from interviews: 1) health care reform and its impact on super-user interventions, 2) a need for comprehensive, multi-level approaches to working with this population, and 3) understanding and addressing the complexity associated with super users. Multiple, distinct super-user programs were identified, though these programs included substantial patient overlap. Programs emerged from an almost universal awareness of the need for an appropriate super-user intervention; however, stakeholders showed an inconsistent and incomplete awareness of other programs. Furthermore, to address complexity, the most successful interventions included multilevel collaboration, patient accompaniment, individualized programming, a focus on social determinants of health, and a strong community presence. CONCLUSIONS: Multiple efforts to address issues of super-users are underway within UW Health, including targeted efforts that focus on specific populations. However, there remains a silo-like nature surrounding some of these efforts that might be attributed to the short existence of some programs and limited interdepartmental communication. In order to maximize resources and impact, strong consideration should be given to increasing collaborative super-user program efforts across UW Health and within the community.
EXPRESSION OF SIGIRR/TIR8, AN INHIBITOR OF TLR-IL-1R SIGNALING, IS REDUCED IN BENIGN PROSTATIC HYPERPLASIA

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BACKGROUND: Benign prostatic hyperplasia (BPH) is the result of hyperproliferation of epithelial and stromal cells in the prostate gland and often leads to prostate enlargement. Around 60% of men over the age of 60 and 80% of men over the age of 80 develop BPH, which frequently leads to lower urinary tract symptoms (LUTS) such as difficulty in urination. Nuclear factor-kappa B (NF-κB) is a well-known protein complex involved in inflammation and cellular functions like survival, proliferation, and cell-cycle control, and it has been shown that NF-κB is elevated in patients with BPH. Well-characterized initiators of NF-κB induction are members of the toll-like receptor-interleukin-1 receptor (TLR-IL-1R) superfamily. It has more recently been shown that the protein SIGIRR (Single immunoglobulin interleukin-1 receptor-related molecule), also known as TIR8, inhibits TLR-IL-1R induction of NF-κB.

OBJECTIVE: To date, SIGIRR expression has not been characterized in human prostate tissue. Given that NF-κB appears to play a role in prostate growth, this study aims to compare SIGIRR expression between normal prostate and BPH tissue. We hypothesized that SIGIRR expression would be decreased in BPH.

METHODS: The expression of SIGIRR within prostate tissue was evaluated using a tissue microarray (TMA) in conjunction with immunohistochemistry and multispectral imaging. Normal prostate tissue obtained from radical prostatectomy specimens (96 cores from 48 patients) was compared to tissue from patients with BPH (48 cores from 24 patients) obtained from transurethral resection of the prostate (TURP). Immunohistochemistry was performed with a SIGIRR antibody (polyclonal rabbit antibody, Abcam) with 3,3’-Diaminobenzidine (DAB) using an automated immunostainer (Leica Bond) and counterstained with hematoxylin. The Vectra multispectral imaging platform was used to perform automated scanning of the TMA. Pattern recognition software (inForm, PerkinElmer) was trained to recognize and segment epithelium vs stroma sections of tissue as well as nuclei vs cytoplasm within cells. Unmixing of the chromagen signals (DAB and hematoxylin) and measurement of optical density was performed using inform software. Student’s t-test was used to compare normal prostate and BPH with a two-sided p-value <0.05 considered significant in all analyses. GraphPad Prism (La Jolla, Ca) was used for statistical analysis.

RESULTS: Compared to normal prostate tissue, SIGIRR expression was significantly decreased in stromal nuclei, epithelial nuclei, and stromal cytoplasm, but not epithelial cytoplasm, at a p<0.05 levels. Epithelial expression of SIGIRR was significantly higher than stromal expression of SIGIRR in both normal and BPH tissue.

CONCLUSION: Three out of the four tissue types analyzed supported our hypothesis that SIGIRR expression would be decreased in BPH tissue compared to normal. These findings identify SIGIRR as a potential marker of BPH. There is a need for further research into the mechanism of SIGIRR action in the development of BPH.
RISK FACTORS FOR ADVANCED STAGE GRADE 1 ENDOMETRIAL ADENOCARCINOMA: A RETROSPECTIVE ANALYSIS

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BACKGROUND: Endometrial cancer is the most common gynecologic malignancy in the United States with a lifetime risk of 2-3%. The majority of endometrial cancer is grade 1, and 73% of these are stage IA. Patients with grade 1 stage IA endometrial cancer have an 88% 5 year survival rate as compared to 15-75% for stage IB and greater. Risk factors for endometrial cancer are well documented, but few studies have explored risk factors specific for advanced stage disease or advanced histology. In particular, no studies have explored gynecologic procedures that may disrupt the endometrium or myometrium, including endometrial ablation, dilation and curettage, myomectomies, or cesarean deliveries, as potential risk factors for advanced stage endometrial cancer. OBJECTIVE: The primary aim is to determine risk factors of advanced stage grade 1 endometrial adenocarcinoma, specifically exploring previous gynecologic procedures. The secondary aim is to determine if endometrial ablation increases the risk of advanced disease. We hypothesize that endometrial ablation is a risk factor for presentation with advanced stage disease due to delay in presentation and diagnosis. METHODS: A retrospective chart review was performed of endometrial cancer patients from the University of Wisconsin Tumor Registry. The Tumor Registry was queried for patients with a diagnosis of endometrial cancer and all stages. Demographic and clinical data were extracted from the medical records and recorded in the GOLDCUP database employed through RedCAP software. Patients were then subdivided into two groups: 1) stage IA grade 1 and 2) stage IB or greater grade 1 based on the 2009 FIGO staging system. RESULTS: Data was collected via the GOLDCUP database. This database was recently launched through the Division of Gynecologic Oncology. We are currently maturing the data for conversion to the proper format for statistical analysis. Final results will be available when this has been completed CONCLUSION: The effect of previous gynecologic procedures on risk of advanced stage endometrial cancer will be the target of our statistical investigation. If an association is found, further exploration into these procedures in patients who have additional risk factors for endometrial cancer should be explored.
LONG-TERM CLINICAL OUTCOMES OF MANUAL VERSUS ROBOTIC-ASSISTED UNICOMPARTMENTAL KNEE ARTHROPLASTIES

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Mentor(s): Richard Illgen, MD

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BACKGROUND: Manual navigation and placement of unicompartmental knee arthroplasty (M-UKA) has been the standard procedure for decades with good long-term outcomes. With advancements in technology, robotic-assisted UKA (R-UKA) is becoming more common despite minimal knowledge of long-term clinical outcomes. OBJECTIVE: The purpose of this study is to determine if using R-UKA has an advantage over M-UKA for long-term pain and functional outcomes. METHODS: A retrospective chart review was conducted on all patients who underwent a UKA performed at UW Health from 2001 through 2013. Outcomes from the patients’ most recent postoperative evaluation at a minimum of 10 months after surgery were compared for patients who underwent R-UKA versus M-UKA. Outcome measures used to assess pain and function included: Short Form-12 Health Survey Mental Component Summary (SF-12 MCS) and Physical Component Summary (SF-12 PCS), Western Ontario McMasters Universities Arthritis Index (WOMAC), and the University of California Los Angeles (UCLA) Activity Score. Statistical analysis was performed using a Student’s two-tailed paired t-test, adjusted for follow up times. RESULTS: Postoperative data from 251 patients following manual (n=125, 58 males, 59.1 ±9.0 yrs old, 6.4 ±2.5 yrs post-op, 28.9 ±5.4 kg/m²) or robotic (n=126, 67 males, 59.1 ±9.9 yrs old, 2.5 ±1.1 yrs post-op, 28.9 ±4.5 kg/m²) UKA was used for this study. At the patients’ latest postoperative evaluation, no significant difference was observed between patients who underwent a R-UKA or a M-UKA as determined by the SF-12 MCS (p=0.79), SF-12 PCS (p=0.88), and WOMAC scores (p=0.35). The UCLA Activity Score demonstrated significance (p=0.04) with those who underwent a R-UKA self-reporting a higher level of activity post-surgery. CONCLUSIONS: This study demonstrates there are minimal significant differences in long-term patient outcomes following a R-UKA or a M-UKA. However, a significant difference in UCLA Activity Score shows promise that R-UKA may have better long term postoperative outcomes due to the UCLA Activity Score’s limited ceiling effect. Future work consists of investigating the relationship of Knee Society Score outcomes between groups. For a more accurate analysis, a matched pair analysis using similar follow up times between groups is suggested.
THIRTY-DAY ORTHOPEDIC READMISSIONS: RISK FACTORS, CAUSES, & DATA VALIDITY

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Support: Shapiro Summer Research Program; Department of Orthopedics and Rehabilitation, University of Wisconsin School of Medicine and Public Health

BACKGROUND: The Centers for Medicare & Medicaid Services now include hip and knee replacements in the Hospital Readmission Reduction Program. The 30-day readmission rate is being used to penalize hospitals with readmission rates above a national benchmark. Therefore, reducing the 30-day readmission rate has become a top priority in orthopedic quality assurance not only for improving patient care but also for reducing costs and repayment penalties. OBJECTIVE: We examine our academic hospital to determine: What is the 30-day readmission rate stratified by subspecialty? What are the risk factors and causes of 30-day readmission? What potential strategies can be identified to lower the 30-day readmission rate?

METHODS: We retrospectively examined the hospital’s quality improvement database and identified 4,792 discharges from the department of orthopedics during a 24 month period. Demographics and comorbidities were extracted from the database and subjected to univariate and multivariate analysis to determine risk factors for 30-day readmission. Further chart review was conducted on all cases of 30-day readmission to identify causes. RESULTS: The all-cause 30-day readmission rate was 4.2 (95% confidence interval (CI): 3.8-4.8) percent. The unplanned readmission rate was 3.3 (95% CI: 2.8-3.8) percent. Multivariate analysis, controlling for age, gender, and insurance type, demonstrated that length of stay (odds ratio (OR): 1.10, p-value < 0.001), ASA score (OR: 1.89, p-value < 0.001), and care under trauma (OR: 2.55, p-value < 0.001) or “other” (OR: 1.65, p-value = 0.009) subspecialty significantly increased the risk of readmission. Of the 157 unplanned readmissions, 93 (59%) were surgical and 64 (41%) were medical. There was poor agreement (Fleiss’ kappa = 0.120) between three definitions of planned readmission. CONCLUSIONS: Medical comorbidities should be optimized prior to surgery. Surgical site complications represent a target for 30-day readmission reduction strategies. Definitions used for coding should be made clearer and more clinically relevant if used for reimbursement penalties.
MILWAUKEE IMMUNIZATION RATES: PRACTITIONER NEEDS ASSESSMENT

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Mentor(s): Paul Hunter, MD

Support: Shapiro Summer Research Program; Farrell Public Health Scholars Program Award, Public Health and Primary Care Innovations in Medical Education (PRIME), University of Wisconsin School of Medicine and Public Health; Department of Family Medicine Compassion in Action Award- Dr. and Mrs. Zorba Paster

BACKGROUND: Though the city of Milwaukee has seen gains in immunization rates in recent years, immunization rates still lag significantly compared to rates statewide. In 2012, 57% of children aged 24 months had completed their primary series (4:3:1:3:1:3:1:4) compared to 69% statewide. Immunize Milwaukee! (IM!), a community-wide coalition, seeks to prevent morbidity and mortality from vaccine preventable illnesses by focusing collective efforts of member organizations on continuing to improve vaccination rates in Milwaukee. OBJECTIVE: This project assessed the needs of Milwaukee practitioners in improving immunization rates. Health care personnel were asked to prioritize their needs and describe what they would value most from a community coalition such as IM!. METHODS: Key-informant interviews of health care personnel were used to assess the needs, experiences, and knowledge around immunization practices. Individuals with various roles within health care were targeted as stakeholders for in-person interviews, especially if they had been engaged or shown interest in IM!. A post-questionnaire assessed familiarity with and prioritization of evidence based interventions recommended by the Community Preventive Services Task Force. RESULTS: In discussing current needs, stakeholders spoke most commonly about 1) strong and consistent recommendations for vaccination by clinicians, 2) determining vaccinations needed at every clinic visit by consistent use of the Wisconsin Immunization Registry (WIR), and 3) practice time constraints. CONCLUSIONS: Review of evidence-based guidelines and qualitative analysis of the key-informant interviews supports the following recommendations to IM!. 1) The IM! Board should request health systems to provide incentives to clinicians and nursing staff to assess immunization status of every patient at every clinical visit. 2) The IM! Vaccination Practice Work Group should encourage and train clinicians to draft and update standing orders for administering ACIP-recommended vaccines. 3) The IM! Vaccination Practice Work Group should encourage and train nursing staff to use standing orders to vaccinate patients at every clinical opportunity.
QUALITY OF ONLINE INFORMATION TO SUPPORT SHARED DECISION MAKING IN BREAST CANCER SURGERY

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Support: Shapiro Summer Research Program; Building Interdisciplinary Research Careers in Women’s Health Scholar’s Program, Department of Surgery, University of Wisconsin School of Medicine and Public Health

BACKGROUND: Decision-making for breast cancer surgery relies heavily on women’s preferences. To reach an informed decision, women require treatment information that is complete, easily understandable, and encourages them to consider their values in the context of treatment options. OBJECTIVE: To assess the quality of online information available to support shared decision making for breast cancer surgery. METHODS: Four breast cancer surgery-related queries were done on Google and Bing, and websites from the first two search pages reviewed. Two investigators evaluated each website for content pertinent to breast cancer surgery using an investigator generated list. The DISCERN instrument was used to evaluate: 1) websites’ structural components that influence publication reliability, 2) quality of information on treatment choices. Scores on this 16-item validated questionnaire were normalized to a 5-point scale, with scores of 4/5 considered “good”. RESULTS: 45 unique websites were identified and reviewed (kappa 0.80). Websites were general information/health-care portals (48%), .GOV sites (13%), non-profit foundations (18%), hospitals (18%), and Youtube.com (2%). Websites satisfied a median 5/9 (range 0-9) content questions, with 2.2% covering all topics. Commonly omitted topics included: most women being candidates for both breast conservation and mastectomy (67%), the potential for a 2nd surgery to obtain negative margins after breast conservation (60%), post-surgery recovery times (58%), and equivalent survival regardless of surgery (53%). Websites had a median DISCERN score of 2.9 (range 2.0-4.5). Websites achieved higher scores on structural criteria (median 3.57 [2.07-4.71]), with 24.4% rated as “good”. In contrast, scores on treatment choice questions were lower (2.56 [1.3-4.38]), with only 6.7% scoring “good”. Four websites (all non-profit foundations) rated highly on both. However, reviewers perceived these websites to be challenging to navigate, with significant effort required to find key content. CONCLUSIONS: Although numerous online sources of breast cancer information exist, most websites do a poor job providing women with essential information necessary to play active roles in treatment decision-making. Even highly ranked websites provided information that was difficult to navigate and did not facilitate easy comparison of the treatment choices in the context of women’s values. Access to high quality online breast cancer information that is balanced and approachable for Internet users of all experience levels would improve the quality of care provided to breast cancer patients.
BARRIERS AND FACILITATORS TO PREVENTIVE CANCER SCREENING IN LIMITED ENGLISH PROFICIENT PATIENTS

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Support: Shapiro Summer Research Program; University of Wisconsin Carbone Comprehensive Cancer Center; NIH/NCI P30 CA014520; Health Innovation Program; Wisconsin Partnership Program; Clinical and Translational Science Award (CTSA) program, previously through the National Center for Research Resources (NCRR) grant 1UL1RR025011, and now by the National Center for Advancing Translational Sciences (NCATS), grant 9U54TR000021

BACKGROUND: Limited English proficient (LEP) patients receive fewer recommended preventive screenings than their English-speaking counterparts. While qualitative studies have explored patients’ perceptions of barriers to care, little research has characterized physicians’ perceptions and understanding of the disparity. OBJECTIVE: To describe primary care physicians’ perception of the barriers and facilitators to preventive cancer screening in LEP patients. METHODS: We conducted qualitative interviews with eight primary care physicians from UW Health using a semi-structured interview guide. Each interview was transcribed and systematically coded to illuminate important themes across interviews. RESULTS: A wide variety of barriers specifically hinder LEP patients’ receipt of cancer screening, including poor language proficiency and communication, lack of transportation, unfamiliarity with the concept of prevention, culture, complex scheduling systems, poor interpretation by ad hoc and phone interpreters, and limited physician time to discuss preventive care. While physicians identified many factors that facilitate preventive screening in general, they mentioned few that are specific to LEP patients. CONCLUSIONS: We found that primary care physicians attribute the low rates of preventive cancer screening among LEP populations to a variety of patient, provider, interpreter, and system factors, most of which go beyond simple language barriers. Interventions developed to reduce these barriers and enhance the impact of identified facilitators will need to be multi-level and designed to engage primary care physicians.
FUNCTIONAL OUTCOMES AFTER ROBOTIC TOTAL HIP ARTHROPLASTY COMPARED WITH MANUAL TECHNIQUE AT MINIMUM 1-YR FOLLOW-UP

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Mentor(s): Richard L. Illgen II, MD

Support: Shapiro Summer Research Program; Department of Orthopedics and Rehabilitation, University of Wisconsin School of Medicine and Public Health

BACKGROUND: Clinical outcome and long-term durability of total hip arthroplasty (THA) is affected by many factors including precise component positioning and accurate restoration of hip biomechanics. Robotic-assisted THA (rTHA) has been shown to improve accuracy of component positioning, but impact on functional outcomes has not been demonstrated. OBJECTIVE: This study compared functional outcomes following rTHA with manual THA (mTHA) at minimum 1-year follow-up. METHODS: In this retrospective cohort study, a single-center database was used to identify all patients who underwent primary THA since introduction of rTHA at our institution (April 2012). Validated patient-reported outcome measures (PROMs) following rTHA (n=100) were compared with consecutive mTHA cases (n=100) performed prior to adoption of rTHA by the same fellowship-trained surgeon at minimum 1-year follow-up. PROMs included the Short-Form 12 Health Survey mental (SF12-MCS) and physical (SF12-PCS) component summaries, UCLA Activity-Level Rating (UCLA), total WOMAC Osteoarthritis Index (WOMAC), and modified Harris Hip Score (HHS). Statistical analyses included chi-squared, Wilcoxon rank-sum, and two-tailed t-tests with significance set at P < 0.05. RESULTS: There were no statistical demographic differences between groups. No significant differences in pre-operative mean HHS, SF12-MCS, WOMAC, or UCLA scores were observed between groups. The mTHA group demonstrated a lower mean pre-operative SF12-PCS score relative to the baseline score observed in the rTHA group (P = 0.006). All PROMs metrics showed significant improvement in both cohorts at minimum 1-year follow-up (P < 0.001) aside from SF12-MCS scores in both rTHA and mTHA groups. Analysis of post-operative PROMs data revealed significantly higher mean HHS (92.1 ± 10.5 vs. 86.3 ± 16.3, P = 0.003) and UCLA (6.3 ± 1.8 vs. 5.8 ± 1.7, P = 0.032) scores in the rTHA group compared to the mTHA group. Differences in post-operative SF12-MCS, SF12-PCS, and WOMAC scores between groups were insignificant. CONCLUSION: Excellent functional outcomes were noted for both rTHA and mTHA at 1-year clinical follow-up. rTHA demonstrated significantly improved post-operative modified HHS and UCLA scores compared with mTHA. To our knowledge, this is the first study to evaluate functional outcomes following primary rTHA. Further study is needed to determine if improved PROMs associated with rTHA will result in improved functional outcomes at long-term intervals.
CELLULAR AND MOLECULAR PLASTICITY OF THE AGING BRAIN AND RESPONSE TO ISCHEMIC STROKE

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Support: Shapiro Summer Research Program; Department of Neurological Surgery, University of Wisconsin School of Medicine and Public Health

BACKGROUND: Stroke is the fourth leading cause of death in the United States and the leading cause of disability. While strokes occur in people of all ages, the prevalence of stroke is much higher in those 65 years of age and older. In addition to the disproportionate occurrence in older individuals, the response and subsequent recovery following ischemic stroke is worse. A systematic investigation of the cellular and molecular characteristics of the aged brain is imperative to understanding its plasticity following an ischemic episode.

OBJECTIVE: Using immunofluorescence staining and PCR, we examined the change in number and distribution of the various neuronal and glial cell types, as well as the expression of the genes involved in cellular motility and migration.

METHODS: A mouse model of transient focal cerebral ischemia (middle cerebral artery occlusion - MCAO) was used. Six animals were assigned to 3 groups to represent the aging brain: 2-3 months, 5-6 months, and 11-12 months. In each group, MCAO or sham surgery was performed under stereotaxic control. Mice were subjected to 60 minutes of left middle cerebral artery occlusion using the intraluminal filament method, with 24-hour reperfusion. Animals were sacrificed and half of the brain tissue samples were embedded in paraffin and sectioned at 5-micron thickness. Immunohistochemistry was performed on brain coronal sections, using antibodies for 4 cellular types: neurons (NeuN), neuronal progenitors and neuroblasts (DCX), astrocytes (GFAP), and microglia (Iba1). The other half of the animal brain samples was processed for RNA extraction. A RT2 Profiler PCR Cell Motility Array encompassing 84 genes involved in cell motility was run using the extracted RNA from each age group and compared using QIAGEN software. Remaining samples were stored for future processing.

RESULTS: Data is currently being gathered and processed. A Keyence fluorescence microscope is being used to capture images of our immunofluorescence data, and examine the distribution and number of the various cell types in the ischemic brain. Results of our PCR motility array revealed one gene, RHOGDI, an inhibitor of a G-protein involved in actin cytoskeleton regulation, was up-regulated 2 fold in the brain of older animals versus young animals.

CONCLUSIONS: Our initial studies in a mouse model indicate an alteration in gene expression levels as a function of age. Particularly, increase in the expression levels of RHOGDI, implicate this gene in regulating migratory processes, which play an important role in injury and repair.
DOES PROCEDURE URGENCY EFFECT OUTCOMES IN COLORECTAL SURGERY?

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Support: Shapiro Summer Research Program; Department of Surgery, University of Wisconsin School of Medicine and Public Health

BACKGROUND: Reimbursement for surgical care is based upon Current Procedural Terminology codes for a ninety-day global period regardless of patient presentation: elective or acute. It is generally accepted that care for acutely ill patients is more involved than that of their less emergently presenting counterparts; however, the long term ramifications of timing of surgical intervention is not considered by payers or hospital systems. Our objective was to characterize the preoperative condition, cost, and complexity of care for elective versus urgent/emergent patients. METHODS: A retrospective chart review of patients who underwent colectomies at the University of Wisconsin Hospital and Clinics between February 2013 and February 2014 was performed. Patient comorbidities, insurance status, American Society Anesthesiologists (ASA) score, and length of hospital stay (LOS) were recorded along with mortality, hospital readmissions, emergency room visits, physician charges, and adverse postoperative events within a ninety-day postoperative period. Comparisons were made between patients undergoing elective procedures and those undergoing urgent/emergent operations. RESULTS: A total of 273 patients were included in this study. Of these, 183 underwent elective procedures while 90 required urgent/emergent operation. Emergent/urgent patients had a higher ASA score (2.73 vs. 2.17; p<0.001), longer LOS (12.66 days vs. 5.89 days; p<0.001), and greater number of adverse postoperative events (4.79 vs. 1.63; p<0.001). Physician charges were found to be significantly less in urgent/emergent patients ($6865.00 vs. $7342.64; p<0.01), while no significant difference was observed in patient comorbidities between the two groups (Charlson comorbidity index score 4.26 vs. 4.47; p=0.554). CONCLUSIONS: Emergent/urgent colectomy patients have a higher ASA score, a longer postoperative LOS, and experience more negative postoperative events. These patients require a greater investment of physician resources and time to optimally treat; however, physician charges associated with emergent/urgent colectomy patients are less. This disconnect between acute care surgeon effort and compensation may negatively impact the field’s ability to recruit the most competitive residents and ultimately provide the best possible patient care. Lobbying efforts aimed at rectifying the inequity in payment for amount of work performed should be initiated with the Center for Medicare and Medicaid Services, as well as with private insurers.
EXPANDING DAILY CHLORHEXIDINE BATHING BEYOND THE ICU: A WORK SYSTEM ANALYSIS OF HOSPITAL-WIDE IMPLEMENTATION

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Support: Shapiro Summer Research Program; Department of Medicine, Division of Infectious Disease, University of Wisconsin School of Medicine and Public Health; Infection Control Department, University of Wisconsin Hospital and Clinics; NIH National Center for Advancing Translational Sciences Grant #UL1TR000427

BACKGROUND: Much evidence has shown that daily bathing of patients with chlorhexidine gluconate (CHG) is efficacious in preventing healthcare-associated infections. There is need for research to study the translation of this intervention into effective healthcare. Using the Systems Engineering Initiative for Patient Safety (SEIPS) model framework, this study assessed house-wide key implementation issues for daily chlorhexidine bathing in an academic teaching hospital. METHODS: Direct observations of the bathing process as well as provider and patient surveys assessed implementation of daily chlorhexidine bathing. This occurred in the setting of adult inpatient units at a large academic medical center (566 beds) which began performing daily CHG bathing house-wide using liquid 4% chlorhexidine six months prior to this study. The observations and surveys were developed using the SEIPS model to analyze the entire work system. RESULTS: Twenty-eight CHG baths performed by a nurse and/or nursing assistants (NAs) were observed in the 17 adult inpatient units that followed the standard CHG daily bathing protocol. Of these units, four were Intensive Care Units (ICUs) and 13 were non-ICUs. Overall, 105 surveys were completed by nursing staff and 86 surveys were completed by patients. Of all the observed baths, 57.1% (16/28) were fully compliant, 35.7% (10/28) were partially compliant, and 7.1% (2/28) were non-compliant. There were no statistically significant differences in level of compliance between ICUs and non-ICUs or between fully versus partially assisted bathing. All patients interviewed who were partially and fully assisted with bathing agreed or strongly agreed that the bathing process took an appropriate amount of time. CHG bathing was very well tolerated by patients and none of them experienced any adverse events. The most common barrier to CHG bathing mentioned by nursing staff was that the bathing process is time consuming. Bathing supplies were adequate and always available. CONCLUSIONS: This study assessed the implementation of house-wide daily chlorhexidine bathing in an academic teaching hospital. Low compliance to the chlorhexidine protocol was a key finding in this study. Time was the main barrier identified by the nursing staff. There is a need for larger multisite studies to investigate the implementation process for durations longer than six months and to conduct surveillance for issues such as the possibility of resistance to chlorhexidine following house-wide implementation.
ONE YEAR OUTCOMES FOR MEDICAID VS. NON-MEDICAID PATIENTS UNDERGOING LAPAROSCOPIC ROUX-EN-Y GASTRIC BYPASS

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Support: Department of Surgery NIH T35 DK062709 grant, University of Wisconsin School of Medicine and Public Health

BACKGROUND: The Medicaid system pays for nearly half of obesity-related medical costs in the U.S. with 45 states providing bariatric surgery coverage to varying degrees. Given that Medicaid services have expanded significantly since the passage of the Affordable Care Act in 2010, understanding bariatric surgery outcomes and costs for Medicaid patients is critical. The purpose of this study is to compare one-year surgical outcomes and costs between Medicaid and non-Medicaid patients who underwent laparoscopic Roux-en-Y gastric bypass surgery. METHODS: Our study is a retrospective review that included all patients who underwent a primary laparoscopic Roux-en-Y gastric bypass from January 1, 2010 to June 1, 2013 at the University of Wisconsin Hospital and Clinics (220 patients). Of these patients, 33 Medicaid patients were identified and matched with 99 non-Medicaid patients (1:3 study design). Ninety-day and one-year outcomes and complications were extracted from the electronic health record. One-year facility costs (inpatient, outpatient, and emergency department) were obtained from the UW information technology division. Fisher’s exact and students T-tests or Wilcoxon rank sums were used to compare categorical and continuous variables, respectively. RESULTS: Medicaid patients were younger (age 39.0 vs. 48.7; p<0.001) but had similar preoperative body mass indices when compared to non-Medicaid patients (49.6 vs. 47.1; p=0.09) and similar preoperative comorbidities with the exception of hyperlipidemia (24.2% vs. 50.5%; p=0.01). Length of stay (2.2 vs. 2.3 days; p=1.00) and 90-day overall complication rates (42.4 vs. 31.3; p=0.29) were similar between Medicaid and non-Medicaid patients, respectively. Emergency department visits (48.2% vs. 27.4%; p=0.06) and hospital readmissions (37.0% vs. 14.7%; p=0.01) were more common for Medicaid patients. Medicaid patients had less overall excess body weight loss (50.7% vs. 65.6%; p=0.01) but had similar rates of comorbidity resolution one year following surgery. Median overall costs during the one-year follow-up period were lower for Medicaid patients compared to non-Medicaid patients although this difference was not statistically significant ($21,160 vs. $24,215; p=0.92). There were no deaths during the one-year follow-up period. CONCLUSION: One-year outcomes following laparoscopic Roux-en-Y gastric bypass were similar between Medicaid patients and non-Medicaid patients at our institution. Emergency department visits and readmissions were more common for Medicaid patients but this did not translate into increase costs for the Medicaid system. State Medicaid programs that are considering bariatric surgery coverage can expect to have similar costs for Medicaid and non-Medicaid patients.
CORRELATION OF METABOLIC SYNDROME AND LIVER DENSITY IN ASTHMA PATIENTS

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Support: Shapiro Summer Research Program; NIH grant #R01HL069116, Department of Radiology, University of Wisconsin School of Medicine and Public Health

BACKGROUND: About 24 million people in the US suffer from asthma. Asthmatics may also develop metabolic syndrome (MetS), defined by at least three of the following: a large waistline, high triglycerides, low HDL-cholesterol, high blood pressure, and elevated fasting blood glucose. MetS identifies patients at risk for cardiovascular disease, stroke, kidney disease, and type 2 diabetes mellitus. MetS has also been associated with nonalcoholic fatty liver disease (NASH). OBJECTIVE: We sought to determine if MetS was correlated with liver density in asthma patients. METHODS: This was an IRB approved and HIPAA compliant study involving 173 patients enrolled in the Severe Asthma Research Program. There were 21 normal volunteers, 72 non-severe asthmatics, and 79 severe asthmatics (age range 2 - 72 years). Each patient’s diastolic blood pressure, BMI, total cholesterol, triglyceride levels, HDL, LDL, fasting glucose, and steroid dosage per day were recorded. Using the PACS workstation (McKesson), liver density (LD), trabecular density at vertebrae levels T12 and L1, and paraspinal muscle density were collected using region-of-interest Hounsfield unit (HU) measurements. RESULTS: Patients with MetS had lower LD than those without MetS (p-value = 0.002). Asthma severity was correlated with MetS: 0% - normal, 7.7% - non-severe, and 21% - severe asthmatics. Severe asthmatics had lower liver HU (p-value = 0.002), lower trabecular HU (p-value = 0.0006), and lower paraspinal muscle HU (p-value = 0.00002) when compared with normal and non-severe asthmatics. Steroid dosage per day did not correlate with liver density or MetS. A low LD, lower T12 and L1 bone trabecular density, and lower paraspinal density was found in severe asthmatics. The use of inhaled or oral steroids was not found to be associated with MetS or LD. CONCLUSIONS: MetS is more commonly seen in severe than in non-severe asthmatics. The concept that MetS defines an inflammatory state is supportive of the fact that those with severe asthma are more likely to have this comorbidity. Severe asthmatics and MetS can also be defined by an imaging biomarker of lower than normal liver HU density on HRCT exams.
INSTRUMENT DEVELOPMENT AND TESTING TO IDENTIFY INEQUITIES IN INITIATION OF PRENATAL CARE IN BUCARAMANGA, COLOMBIA

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Support: Shapiro Summer Research Program; Farrell Public Health Scholars Program Award, University of Wisconsin School of Medicine and Public Health

BACKGROUND: The timely initiation of prenatal care, defined as occurring within the first 12 weeks of pregnancy, provides better opportunities for the detection and management of risk factors and education for a healthy pregnancy. In Colombia, healthcare reforms have addressed inequity in healthcare access, but as in other developing countries, disparities remain in prenatal care. In Bucaramanga, the fifth largest city and our study site, a 1998 study reported that only 32.8% of pregnant women began prenatal care in the first trimester. This study aims to deepen current understanding of barriers and inequities in the timing of initiation of prenatal care through the development of an instrument and its use in a pilot study.

OBJECTIVE: Develop and test an instrument to identify barriers to the timely initiation of prenatal care in Bucaramanga. Characterize the women interviewed in the pilot study to inform the full investigation.

METHODS: Using current literature and existing surveys, a questionnaire was designed to identify barriers related to 9 categories. The instrument was tested in simulations by the study team and in a test with 5 subjects. After revisions, a questionnaire with 96 questions was used in the pilot cross-sectional study. 32 pregnant women, 18 years of age and older, were consented and interviewed at local health institutions, hospitals, or their homes in June and July 2014. Data was entered into an EpiData database and analyzed using Stata 11. RESULTS: The mean age of subjects was 25.94. This was the first pregnancy for 53.1% of the women. Of 15 multiparous women, 12 attended prenatal care visits. Of the 31 women who had attended a visit for the current pregnancy, the mean initiation time was 12.13 weeks with 64.5% initiating prenatal care within the first trimester and 35.5% initiating prenatal care late. Cited reasons for late initiation included not being aware of the pregnancy and problems with insurance.

CONCLUSIONS: The successful implementation and completion of the pilot study suggests that a larger study is feasible with the developed instrument. The variety of barriers suggested by the results calls for greater statistical power to identify the most relevant barriers and any inequities. The large percentage of women who initiated prenatal care late suggests that while timely use of prenatal care has improved over the last decade, this is still a significant problem in Bucaramanga.
EVALUATION OF FLAT-PANEL COMPUTED TOMOGRAPHY FOR COCHLEAR IMPLANT IMAGING

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Support: Shapiro Summer Research Program; Department of Surgery; Department of Radiology; NIH grant #NCATS 9U54TR000021 - KL2 Award and P30 HD003352, University of Wisconsin School of Medicine and Public Health

BACKGROUND: Audiological outcomes of cochlear implantation have some variability and are influenced by a number of factors. Device related factors that can influence outcomes include the scalar position of the electrode array and its depth of insertion. Measurement of these variables using conventional multi-detector CT (MDCT) may be complicated by image artifact created by the metallic components within the electrode and insufficient resolution. Flat-panel CT (FPCT) has been shown to improve upon the resolution of MDCT while reducing the appearance of artifacts. Most studies of FPCT cochlear implant imaging have employed isolated cadaveric temporal bones, prototype imaging equipment and have not systematically evaluated radiation exposure. OBJECTIVE: We sought to compare the ability to resolve cochlear implant scalar location and radiation exposure of a commercially available FPCT scanner to MDCT using whole cadaveric heads

METHODS: Cochleae of four cadaver heads were accessed via transmastoid posterior tympanotomy. Seven multi-channel electrode arrays were inserted via the round window, with one array inserted via scala tympani cochleostomy. Implants were cut at the facial recess and fixed in place with cyanoacrylate. The implanted heads were imaged using MDCT and FPCT. During each scan thermoluminescent detectors (TLDs) were used to measure radiation dose to the ocular lens. Subsequently, the implanted cochleae were isolated and imaged with micro-CT to allow for comparison. All images were analyzed by two neuroradiologists and graded on various measures of image quality.

RESULTS: Localization of electrode arrays to the scala tympani was correctly reported by the readers 75% of the time for FPCT and 0% for MDCT. Correct localization to the lateral wall was 100% and 25% for FPCT and MDCT respectively. FPCT showed less metallic artifact than MDCT. Radiation dose measured at the ocular lens with FPCT was 54% that of MDCT for full field of view scans and 6.9% and 4.4% at the ipsilateral and contralateral eyes respectively for small field of view scans. CONCLUSION: Reduced metallic artifact in the FPCT images allows for improved localization of the electrode array within the cochlea with minimal distortion of surrounding structures. Importantly, FPCT provides lower radiation doses than MDCT. Given these results, FPCT may offer advantages when used to evaluate cochlear implants in patients.
EVALUATION OF TAXANE SENSITIVITY IN METASTATIC BREAST CANCER

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Mentor(s): Mark Burkard, MD, PhD

Support: Shapiro Summer Research Program; Department of Medicine, University of Wisconsin School of Medicine and Public Health

BACKGROUND: Breast cancer is the second most common cause of death in women in the US. Paclitaxel (a type of mitotic inhibitor) has proven to be effective in 50% of patients that are treated with it. Currently, there is no way to predict Taxane effectiveness in breast cancer patients. However, preliminary data from Dr. Mark Burkard and Dr. Beth Weaver suggest that cancer cells demonstrating chromosomal instability (abnormal numbers of chromosomes) are more susceptible to treatment with taxanes.

OBJECTIVE: Our ultimate hypothesis was to determine if breast tumor cells demonstrating chromosomal instability would show greater sensitivity to Taxane treatment compared to tumor cells with stable genomes. I was able to determine whether specific subtypes of breast cancer have distinct sensitivities to Taxol therapy, which will eventually be correlated with the rate of chromosomal instability in these subtypes.

METHODS: 1. Patients were considered eligible for this study if they had metastatic breast cancer, received taxane therapy (Paclitaxel, Docetaxel, or nab-Paclitaxel), and had radiologic images and tumor samples at UW Hospital for later analysis. We found 37 eligible female patients. 2. In eligible patients, metastatic tumor response was measured from analysis of radiologic images (CT, MRI) using RECIST 1.1 criteria (Response Evaluation Criteria In Solid Tumors). 3. Data was collected to determine whether there were any clinical predictors of Taxane response (hormone receptor status (ER/PR), HER2 oncogene amplification, time to treatment, number of prior chemotherapies, prior hormonal therapy, and others).

RESULTS: This is an ongoing project, and tissue samples have not yet been assessed for chromosomal instability. However, from the clinical data, it was determined that breast cancer subtype (ER/PR/HER2 status) did not correlate with Taxane response. Additionally, patients that received prior chemotherapy did not respond differently to taxane therapy.

CONCLUSIONS: As expected, there was no apparent correlation between breast cancer subtype and response to taxane therapy. Fluorescent in situ hybridization will be performed on formalin fixed paraffin embedded specimens from the subjects to determine chromosomal instability status. If our hypothesis holds true that cancer cells demonstrating chromosomal instability are more susceptible to treatment with taxanes, these results could have profound implications for better tailoring our treatments for patients with metastatic breast cancer.
IDENTIFYING GAPS AND METHODS FOR IMPROVEMENT OF BED NET COVERAGE AMONG WOMEN & CHILDREN OF THE SHEEMA DISTRICT, UGANDA

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Mentor(s): Ajay Sethi, PhD, MPH

Support: Shapiro Summer Research Program; Department of Pediatrics, University of Wisconsin School of Medicine and Public Health

BACKGROUND Malaria is the leading cause of morbidity and mortality in Uganda with 13,591,932 suspected cases (37.4% of the total population) and 6,585 malaria-attributed deaths recorded in 2012. Malaria is hyperendemic in the rural Sheema North district of southwest Uganda, from which the data for this study were collected. In the same region, mobile phone penetration is high, but only about half of the surveyed women have a bed net in the household, compared to a national estimated household average of 64% in 2012. A mobile health (mHealth) initiative taking advantage of the relatively high access to mobile phones may be an effective intervention strategy for increasing bed net coverage and usage by childbearing-aged women and children of this region and, thus, a positive step towards the achievement of the WHO’s Millennium Development Goals 5 (a commitment to maternal health) and 6 (a commitment to reverse the incidence of worldwide malaria). OBJECTIVE This study aims to describe factors associated with bed net and mobile phone usage by childbearing-aged women in Uganda and to identify opportunities for using mHealth initiatives to increase bed net ownership and usage among Ugandan women, children, and other household members. METHODS The data consist of responses from 1000 cross-sectional surveys from a cohort of childbearing-aged women living in the Sheema North district. Indices based on asset and livestock ownership were created to estimate the wealth of households. These indices and variables related to health, mobile phone usage, and socioeconomic factors were compared bed net ownership using Chi2 and logistic regression tests. RESULTS Bed net ownership correlated positively with household wealth, but was not increased among households with at least one member at-risk for malaria as defined by the WHO, i.e. infants under the age of one year, children one to five years old, individuals with HIV/AIDS, and pregnant women. CONCLUSIONS Our results indicate that targeted bed net distribution programs have not eliminated the economic disparities in bed net ownership in the Sheema North district and have not increased bed net ownership among at-risk groups. Given that 25.2% of the childbearing age women in the Sheema district own a personal or shared a mobile phone, an mHealth program to supplement the current bed net distribution programs may be an effective means of increasing bed net coverage among women and their families.
THE EFFECT OF BODY MASS INDEX ON OUTCOMES OF CERVICAL LYMPHADENECTOMY

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Support: Department of Surgery NIH T32 DC 009401 grant, University of Wisconsin School of Medicine and Public Health

BACKGROUND: Cervical lymph node metastasis is a marker of advanced stage head and neck cancer and has a significant impact on the prognosis and treatment rendered. Cervical lymph nodes are located in specific, adipose rich regions. The identification of surgical landmarks and extirpation of the fibrofatty packet of lymphatic tissue is technically more difficult to remove in obese patients. Thus, the effect of BMI on neck dissection outcomes is of interest. OBJECTIVE: To determine which factors, including body mass index (BMI), affect the outcomes of neck dissections as it relates to lymph node yield and post-operative complications. METHODS: This study was a retrospective cohort study at an academic medical center. A chart review was performed on 354 subjects who had undergone a neck dissection between 1992 and 2010. Body mass index, type of neck dissection, lymph node yield, demographic information, comorbidities, cancer histology, and history of radiation were identified. Univariate analyses of variances and independent t-tests were performed to determine the effects of BMI on the lymph node yield and post-operative complications of neck dissections. RESULTS: There was an association between increased BMI and increased lymph node yields after controlling for history of radiation (p=0.001). Patients who were categorized as obese (BMI>=30) had significantly higher lymph node yield compared to those with a BMI less than 30 (p=0.005). Obese and non-obese patients averaged 8.44 and 6.95 nodes per neck level dissected, respectively. There were no associations between post-operative complications and an increased BMI. The average number of lymph nodes per neck level dissected for patients with N1, N2a, N2b, N2c, and N3 staged cancer were 8.52, 7.81, 7.21, 6.56, and 5.34, respectively. CONCLUSION: These results show an increase in lymph node yields in patients with elevated BMI, no history of radiation, and an earlier N-staged cancer. There is no consensus on what constitutes an adequate lymph node yield in neck dissections. This study demonstrates that patient and disease specific features that may impact the lymph node yield.
ALTERATIONS IN GRAY MATTER VOLUME AND CORTICAL MEASURES IN PEDIATRIC POST-TRAUMATIC STRESS DISORDER

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Support: Shapiro Summer Research Program; Department of Psychiatry; American Academy of Child 298 and Adolescent Psychiatry Junior Investigator Award (RJH); NARSAD Young Investigator Grant (RJH); 299 University of Wisconsin Institute for Clinical and Translational Research Translational Pilot Grant Award 300 (RJH); National Institute of Mental Health Career Development Award (K08 MH100267, RJH)

BACKGROUND: Currently, few neuroimaging studies have examined Post-traumatic Stress Disorder in the pediatric population. These studies have found an overall reduction in cerebral brain volume, but mixed results with respect to specific brain regions. Additionally, no studies have examined surface-based measures such as cortical thickness and surface area in pediatric PTSD. There is increasing evidence that these measures may be more sensitive than gray matter volume in identifying neural substrates in illnesses and have potential implications for treatment and PTSD. OBJECTIVE: The present study utilizes structural MRI statistical analyses to investigate differences in cortical thickness, gray matter volume, and gray matter surface between PTSD participants and non-trauma controls.

METHODS: Twenty-eight PTSD participants (mean age=13.9), as diagnosed by the DSM-IV, and thirty non-traumatized healthy youth (mean age=14.1) were scanned with a 3D T1-weighted MRI structural sequence. Cortical reconstruction, volumetric segmentation, and group comparisons of the structural data were performed in Freesurfer, controlled for age and sex. Secondary analyses were conducted using SPSS 12.0. RESULTS: Consistent with the studies on normal development, age predicted cortical thinning in widespread brain regions across all youth. Several group by age interactions emerged, however. Healthy youth exhibited greater age-related increases in cortical thickness in right precuneus and left superior temporal cortex. With regard to cortical surface area, age negatively predicted surface area in healthy youth but positively predicted surface area in PTSD youth for bilateral superior frontal, left parahippocampal, left lingual, left precentral, and right inferior parietal cortex. CONCLUSIONS: To our knowledge, this is the first reported study to examine detailed measures of cortical gray matter in pediatric PTSD. Our findings suggest that pediatric PTSD is characterized by altered cortical gray matter development, as indicated by age-dependent abnormalities in cortical thickness and surface area. Age-related expansion of cortical surface area in pediatric PTSD, compared to contraction in healthy youth, may suggest a reduction in synaptic pruning in PTSD youth. Further work will be needed to characterize cortical gray matter changes longitudinally, and determine whether they may play a direct role in the pathophysiology of pediatric PTSD.
NOTCH2 HAS AN OPPOSITE ROLE TO OTHER NOTCH ISOFORMS IN NEUROENDOCRINE TUMORS

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Support: Shapiro Summer Research Program; Department of Surgery, University of Wisconsin School of Medicine and Public Health

BACKGROUND: Notch signaling involves in various aspects of mammalian biology such as cellular differentiation, cell-cycle regulation, metabolism and apoptosis. Among the four identified mammalian Notch receptors, the role of Notch1 and 3 as tumor suppressor in neuroendocrine tumor cells (NET) have been elucidated. Nevertheless, the function of Notch2 signaling still remains unclear in NETs.

OBJECTIVE: The aim of this study was to access the role of Notch2 in gastrointestinal (GI)NETs (carcinoids).

METHOD: pcDNA4/V5-His plasmid, containing constitutively expressed human active portion of Notch2 (NICD2), was transiently transfected into GI carcinoid (BON) cells. The same plasmid without NICD2 was used as a control. Transfection efficiency was assessed by cotransfection with plasmid expressing the green fluorescent protein (GFP). The expression of NICD2 was confirmed by quantitative RT-PCR and Western Blot. Next the functional activity of NICD2 was analyzed by measuring the degree of CBF-1 binding by luciferase reporter assay. Cell viability was then tested by MTT (3-(4, 5-Dimethylthiazole-2-yl)-2, 5-diphenyltetrazolium bromide) assay after 24, 48, 72 and 96 hours after transfection. To investigate the potential effects of NICD2 on BON cells proliferation, cell cycle and anti-apoptotic markers such as X-linked inhibitor of apoptosis (XIAP), cyclin D1, and c-Myc were examined by Western Blot analysis.

RESULTS: The expression of NICD2 was detected over all time points of transfection on both mRNA and protein levels. CBF-1 binding assay showed increased luciferase activity indicating functional activation of NICD2. In contract to Notch1 and 3 which are tumor suppressive, NICD2 transfected cells did not reduce proliferation comparing to the cells transfected with control plasmid. Moreover, Western blot analysis showed an increase of anti-apoptotic markers XIAP, C-Myc, and Cyclin D1 with the overexpression of NICD2.

CONCLUSIONS: Carcinoid tumor cells have paucity Notch2. For the first time, we demonstrate the growth – promoting function of Notch2 receptor in carcinoid cancer with concomitant upturn of anti-apoptotic markers XIAP, c-Myc and cyclin D1. This opposing role of Notch2 isoform in NE cancer progression warrant further investigation.
EVALUATING PRIMARY CARE VIEWS ON SURVIVORSHIP CARE PLANS GENERATED WITHIN AN ELECTRONIC HEALTH RECORD SYSTEM

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BACKGROUND: Survivorship care plans for cancer survivors may address inadequate provider-to-provider communication, however, primary care provider (PCP) perspectives on care plan provision and use is limited, especially when care plans are electronic health record (EHR) generated. We sought to examine PCPs perspectives regarding EHR-generated care plans. **OBJECTIVE:** The purpose of this research is to report on the development and results of a survey evaluating PCP viewpoints on care plans. We specifically addressed care plan impact on: clinical workflow, clinical behavior, preferred method of care plan delivery and preferred timing of delivery. A secondary aim of our study was to assess the views of PCPs in rural practice. **METHODS:** PCPs in the Wisconsin Research and Education Network listserv received a sample 10-page plan (Cohort 1), and PCPs of survivors enrolled on two of our clinical trials received a plan tailored to the survivor (Cohort 2). Both cohorts received a survey after reviewing the plan. **RESULTS:** 46 and 26 PCPs completed the survey in Cohorts 1 and 2, respectively. PCPs regarded EHR-generated plans as useful in coordinating care (88%), understanding treatments (94%), understanding treatment side effects (89%) and supporting clinical decisions (82%). Few felt using an EHR-generated plan would disrupt clinic workflow (14%) or take too much time (11%). Most (89%) preferred receiving the plan via EHR, reporting consistent provision (81%) and standard location in the medical record (89%) as key facilitating factors. A significant minority wanted an abbreviated care plan, ideally 1-3 pages (32%) and/or care plans specifically written for PCPs (57%). **CONCLUSION:** Plans were viewed as useful for coordinating care and making clinical decisions. However, PCPs desired shorter, clinician-oriented plans accessible within an EHR, delivered and located in a standardized manner.
INHIBITION OF STAT1-BCL2 PATHWAY IN T CELL ACUTE LYMPHOBLASTIC LEUKEMIA CELLS AS CANCER THERAPY

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Support: Shapiro Summer Research Program; Alex's Lemonade Stand Foundation Pediatric Oncology Student Training Program

BACKGROUND: While childhood acute lymphoblastic leukemia (ALL), the most prevalent form of pediatric cancer, boasts an overall survival rate of >80% at 5 years, the early subtype of T-cell ALL maintains a dire prognosis of <20%. Thus, developing more effective therapies for problematic subtypes of cancer, like early T-cell ALL, is needed. Previous research showed that novel drug therapies targeting cell apoptotic regulatory genes can reduce tumor growth in lymphoma and leukemia. The TYK2-STAT1-BCL2 axis plays a major regulatory role in cell apoptosis and tumor progression involved in cancer growth. Gain-of-function TYK2 mutations lead to upregulation of the anti-apoptotic/pro-survival protein BCL2. The early T-cell ALL LOUCY cell line upregulates BCL2 suggesting both BCL2 and STAT1 may be effective markers and targets. This study aims to target BCL2 and STAT1 using gene inhibitors to provide insight into developing a new therapy for the early subtype of T-cell ALL.

OBJECTIVE: In T-cell ALL cell lines, (1) determine relative BCL2 expression and (2) measure the effects of BCL2 and STAT1 inhibition on cell proliferation and apoptosis.

METHODS: LOUCY, JURKAT (T-cell ALL cell lines) and Z138 (mantle cell lymphoma cell line) were treated with ABT-199 (BCL2 inhibitor) and CYT-387 (STAT1 inhibitor). Relative BCL2 levels were determined with mean fluorescence intensity by flow cytometry. Cell proliferation was measured using MTT assays and Trypan Blue Viability counts. Cell apoptosis data was collected by 7-AAD and Annexin V staining. RESULTS: When compared to JURKAT and Z138 cells, LOUCY cells demonstrated a relatively higher BCL2 mean fluorescence intensity. Treatment of LOUCY, JURKAT and Z138 cells with either ABT-199 or high concentrations of CYT-387 resulted in significantly decreased tumor proliferation and viability and increased tumor apoptosis (p<0.05). Treatment of LOUCY cells with both ABT-199 and CYT-387 resulted in less tumor growth compared to CYT-387 alone.

CONCLUSIONS: Treatment of an early T-cell ALL cell line with specific BCL2 and STAT1 inhibitors caused decreased tumor proliferation and viability. The relatively higher BCL2 levels in LOUCY cells led to stronger anti-tumor effects of ABT-199. When combined with ABT-199, CYT-387 demonstrated greater anti-tumor effects on LOUCY cells. Further studies will evaluate the synergistic effects of treating T-cell ALL with both ABT-199 and CYT-387 in vitro and in vivo.
VIRTUAL HLA CROSSMATCHING AS A MEANS TO SAFELY EXPEDITE THE TRANSPLANTATION OF SHIPPED-INPANCREATA

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Support: Department of Surgery NIH T35 DK062709 grant, University of Wisconsin School of Medicine and Public Health

BACKGROUND: Cold ischemia time (CIT) accumulates with shipped-in pancreata and limits utilization and outcomes. Flow cytometric HLA crossmatching (FXM) is used to assess histocompatibility between pancreas and recipient before transplantation. Waiting for a FXM, which is typically done once the organ arrives, prolongs the CIT. A ’virtual crossmatch’ (VXM) can be performed before the transport of the organ using the results of the single antigen bead (SAB) Luminex assay thereby allowing the assessment of recipient donor specific antibodies. OBJECTIVE: This study investigates whether it is acceptable and safe to proceed with transplantation of shipped-in pancreata based solely on VXM results, rather than waiting for a FXM. METHODS: We retrospectively reviewed outcomes of pancreas transplants (n=153 patients) performed from June 2010 to December 2013. Comparisons were made between three patient groups: 1) shipped-in pancreas, VXM only (n=39), 2) shipped-in pancreas, VXM and FXM (n=12), and 3) local pancreas, VXM and FXM (n=102). Graft-survival, patient survival, and CIT were determined. RESULTS: There were 51 shipped-in pancreata: 39 transplants were performed based solely on VXM results and 12 based on FXM results. Transplants that began based on a VXM had a FXM performed retrospectively, all of which were negative. Donor and recipient demographics, immunosuppression regimens and surgical parameters were comparable between groups with the exception of transplantation type. Shipped-in pancreata were primarily solitary pancreas (SP) transplants whereas the local group had primarily SPK transplants (87% SP: Shipped-in VXM only vs. 100% SP: Shipped-in VXM + FXM vs. 13% SP: Local, p < 0.001). Graft survival, death-censored graft survival, and patient survival did not differ between groups. CIT was shorter in the local group than either of the shipped-in groups (15.9h: Shipped-in VXM only vs. 17.5h: Shipped-in VXM + FXM vs. 13.2h: Local, p < 0.001). CIT was compared among pancreata originating from similar destinations. For pancreata shipped in from UNOS regions 3 and 4, proceeding to surgery without a FXM saved 5.1 hours (95% CI [3.25, 6.98]) (p = 0.0001). CONCLUSIONS: VXM enables transplantation to proceed without waiting for a FXM. For shipped in pancreata, CIT can then be minimized without adversely affecting graft or patient survival. This policy, if widely adopted, could increase utilization of pancreas grafts from further distances.
LOCAL SUSTAINED DELIVERY OF INTERLEUKIN-10 TO ATTENUATE SECONDARY DAMAGE AND PROMOTE FUNCTIONAL RECOVERY

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BACKGROUND: After spinal cord injury (SCI), a cascade of cellular and molecular responses culminates into the formation of a dense astroglial scar. This dense glial scar prevents appreciable axonal regeneration. Post-SCI administration interleukin-10 (IL-10), a potent antiinflammatory, has been shown to attenuate the astroglial scar, provide neuroprotection, reduce apoptosis and improve functional recovery. After SCI, oligodendrocytes continue apoptosing for two weeks and the glial scar continues to form for over two weeks. Therefore, it would be beneficial to have a local sustained delivery of IL-10 directly on the injury site for at least 14 days to attenuate these effects. OBJECTIVE: We developed calcium phosphate coated sutures to bind, stabilize, and controllably deliver a localized, sustained quantity of Interleukin-10 which should reduce secondary damage from spinal cord injury and promote functional recovery. METHODS: Calcium phosphate (CaP) was grown on 7-0 Vicryl sutures via incubation in a modified simulated body fluid for 7 days at 37°C. The proteins were then bound by incubating the CaP coated sutures in a solution containing IL-10. To characterize the release profile of IL-10, sutures were placed in simulated body fluid (SBF) and switched into fresh SBF every 2 days for over 2 weeks. An ELISA kit was used to calculate the amount of IL-10 released from the sutures into the solution. RESULTS: Energy Dispersive X-Ray Spectroscopy (EDS) showed 1.70 A.U. X-Ray emissions on the calcium/phosphate mineralized suture demonstrating adequate adsorption, nucleation, and crystal growth on a 7-0 Vicryl suture. ELISA showed a burst release of IL-10 followed by a linear release that continued for over 2 weeks. Furthermore, on day 17 there was still 4.67±1.68 pg/mm of IL-10 being released. The released IL-10 was immune reactive, which suggests that it was biologically active and properly folded upon release. CONCLUSIONS: Calcium phosphate coated sutures have the ability to deliver a sustained amount of biologically active IL-10 for over 2 weeks in vitro. This is encouraging in developing a method to deliver IL-10 and other proteins to sites of spinal cord injury. Studies are currently being conducted using CaP coated suture loaded with IL-10 in combination with sciatic nerve grafts to treat a complete spinal cord transection in an in vivo rat model.
HEALTH AND SOCIAL ISOLATION AMONG LATINAS IN DANE COUNTY

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Support: Shapiro Summer Research Program; Farrell Public Health Scholars Program Award, University of Wisconsin School of Medicine and Public Health

BACKGROUND: During 2000–2010, the Latino population in Dane County nearly doubled, with continued growth expected. Recent trends show new immigrant communities in the Midwest often lack resources and support networks available in communities with larger, more long-standing Latino populations. Studies have clearly demonstrated the protective influence that social support has on health. However, in Dane County little is known about the prevalence and adequacy of social support amongst Latinas. OBJECTIVE: We sought to identify barriers preventing Latinas from establishing social support networks in Dane County and to describe how this may affect their ability or motivation to seek prenatal care. METHODS: Following an initial literature review, a key informant questionnaire was developed, and 11 semi-structured interviews were conducted with staff from community organizations working directly with Dane County Latinas. Initial participants were identified by Public Health Madison & Dane County, with subsequent participants identified through snowball referral. Interviews were recorded, transcribed, and manually coded to identify emerging themes. RESULTS: Almost all participants perceived social isolation as negatively affecting Latinas in Dane County to varying degrees. Barriers to creating and maintaining social networks of support were categorized into four main themes: environmental, cultural, psychosocial, and socioeconomic. Environmental factors included transportation, rural residence, and lack of resources. Cultural factors included language, different ways of life, gender roles, motherhood, resilience, communication, and awareness of resources. Psychosocial barriers included emotional state, mental health, personal characteristics, family separation, difficulty creating friendships, trust issues, and controlling relationships. Socioeconomic factors included work outside the home, work schedules, lack of documentation, and marginalization. Pregnancy and children had an unclear effect on social isolation, and social isolation was not determined to be a major factor in limiting prenatal care. CONCLUSIONS: This study highlights the complexity of creating and maintaining social support networks and its impact on Latina health within Dane County. Furthermore, it illustrates the complex systems-level issues that contribute to these conditions, which likely will require additional research and efforts from multiple Dane County community sectors to fully address.
PREDICTORS OF ADEQUATE PRENATAL CARE IN AMERICAN INDIAN PATIENTS

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BACKGROUND: Compared to general populations, we see poorer birth outcomes in American Indian populations. In order to have the best possible outcome for mother and child, early and regular prenatal care is necessary. Therefore, it is important to understand what factors influence whether American Indian mothers receive adequate prenatal care and are associated with better birth outcomes.

OBJECTIVE: This research project was intended to illuminate maternal factors that predict adequate prenatal care in the American Indian population served by a south central Wisconsin tribal clinic.

METHODS: A chart review was performed at a South Central Wisconsin tribal clinic, using data from 38 American Indian patients who received prenatal care at the clinic during 2012-2013. Data collected on maternal characteristics including the following demographic variables: number of previous pregnancies, tobacco use, pre-pregnancy BMI, weight gain, blood pressure, and status of father involvement. Adequacy of prenatal care was defined using the Kotelchuck Adequacy of Prenatal Care Utilization Index, and birth outcomes were assessed by gestational age and weight at birth. Descriptive statistics were performed, and Chi-square tests were conducted to examine the association between maternal characteristics and both adequacy of prenatal care and birth outcomes. RESULTS: Approximately two thirds of American Indian women received adequate prenatal care. The majority of patients had normal blood pressure, full-term births and paternal involvement. Forty percent of mothers smoked during pregnancy, and 71% were identified as overweight/obesity. No significant relationships were found via Chi-square analyses of the variables examined except for those of mother’s pre-pregnancy BMI and baby’s birth size (p-value= 0.03). CONCLUSIONS: The results indicate the further need for enhancement of smoking cessation advice prior to and during pregnancy and the counseling of overweight/obesity rates in American Indian mothers.
NUTRITIONAL AND PSYCHIATRIC WEIGHT LOSS PREDICTORS FOLLOWING BARIATRIC SURGERY

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BACKGROUND: Identifying morbidly obese patients who will succeed following bariatric surgery remains challenging. While numerous studies have focused on preoperative factors associated with weight loss following bariatric surgery, the critical nutritional and psychological characteristics remain unclear.

OBJECTIVE: The purpose of this study was to examine the association between preoperative nutritional and psychological characteristics and the likelihood of successful weight loss among bariatric patients.

METHODS: Our study is a retrospective cohort study of all patients who underwent primary laparoscopic Roux-en-Y gastric bypass from September 1, 2011 to June 1, 2013 at the University of Wisconsin Hospital and Clinics (124 patients). Patient demographics, comorbidities, nutritional and psychological factors, and excess weight loss were abstracted from the electronic medical record. “Successful” weight loss was defined as a loss of ≥ 50% of excess body weight one year after surgery. To evaluate bivariate associations between predictors and successful weight loss, Fisher’s exact and student’s T-tests were used for categorical and continuous variables, respectively. Variables significant (p<.05) in bivariate analyses were included in a multivariable logistic regression model with successful weight loss as the outcome.

RESULTS: 78% (n=97) of patients had at least one year of follow-up data and were included in analyses. Of those, 69% (n=67) experienced successful weight loss. Mean excess body weight loss was 69.0% (+/- 16.6%) for these patients vs. 39.0% (+/- 9.4%) for patients with suboptimal weight loss (p=0.01). In bivariate analyses, successful weight loss was associated with lower preoperative weight (268.1 vs. 301.4 lbs; p=0.02), a lower maximum past weight loss attempt (40.0 vs. 65.6 lbs; p=0.01), no diabetes history (81.4% of non-diabetics vs. 59.3% of diabetics were successful; p=0.03), being able to quit soda consumption before surgery (81.8% who quit vs. 59.3% with unchanged drinking habits were successful; p=0.04) and greater patient autonomy (mean percentile rank of 68.7% on the Hogan Personality Inventory for successful vs. 38.8% for unsuccessful patients; p=0.01). On multivariate analysis, absence of diabetes and not having a past weight loss of > 50 lbs were associated with success. CONCLUSION: Of the dietary habits and psychological characteristics evaluated in our study, none were associated with weight loss success after adjusting for measurable confounders. Identification of predictive dietary and psychological variables for patients in our program remains elusive. Diabetic patients warrant especially close follow-up after surgery given their propensity to experience suboptimal weight loss.
FACTORS ASSOCIATED WITH IMPROVED RECURRENCE FREE SURVIVAL FOR TRANSURETHRAL RESECTION OF BLADDER TUMORS (TURBT)

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Mentor(s): Tracy Downs, MD, FACS

Support: Shapiro Summer Research Program; Department of Urology, University of Wisconsin School of Medicine and Public Health

BACKGROUND: Superficial bladder cancer accounts for the vast majority of cancers of the bladder and is the fourth most common cancer overall. TURBT is the most common treatment for superficial bladder cancer. TURBT is performed by inserting a cystoscope with resection tools through the patient’s urethra to their bladder and then removing the superficial tumor. A number of guidelines exist for performance of a more complete and permanent removal of cancer. OBJECTIVE: The purpose of this project was to identify predictors of recurrence free and overall survival in the UW Health patient population for patients with superficial bladder cancer. METHODS: A list of UW Health patients who have undergone TURBT since 2001 was compiled for a total of 420 patients and 760 operations. For each of these patients demographics, and details of each TURBT performed compiled. This data was then uploaded into the statistical software REDCap for analysis. Recurrence free survival and total survival were calculated. Hazard ratios were then calculated between survival and the following: Age, Sex, Diabetes and Smoking status, Stage and grade of tumors, number of tumors, recurrence risk group, use of blue-light cystoscopy to allow better detection, use of chemo/immunotherapeutics, presence of muscularis propria in biopsy, and completion of a second-look follow-up TURBT. RESULTS: Of the calculated Hazard ratios, Immunotherapeutic use (HR=0.49), recurrence risk group (HR=1.947), use of blue light cystoscopy (HR=0.57) and completion of second-look (HR=0.73) all had statistically significant effects on survival. These ratios were calculated for the entire database population, specific effects on individual groups have the possibility of significance as well. CONCLUSIONS: This study provides evidence of interventions that are associated with better patient outcomes. It also validates many predictors of patient outcomes in the UW health patient population. Future directions include looking at the effect of these interventions and other predicting factors on specific subgroups. Use of this database would allow physicians to choose treatment options for patients based on their effectivity for people similar to them in the database. In addition, more accurate predictions of recurrence rates and survival can be given to patients regarding their cancer based on their specific characteristics.
PATTERNS OF CANNABIS USE AMONG INTRAVENOUS DRUG USERS IN BALTIMORE

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Support: Shapiro Summer Research Program; Department of Medicine, University of Wisconsin School of Medicine and Public Health

BACKGROUND: Much has been studied and written about patterns of marijuana use among teenagers and young adults with the goal of testing the gateway hypothesis and determining the implications for future drug use and health outcomes. However, there is a dearth amount of information about marijuana use among older drug users, and how this correlates to health and socioeconomic outcomes.

OBJECTIVE: To characterize the patterns of marijuana use among intravenous drug users and relate marijuana use to demographic, socioeconomic, and health variables. METHODS: The ALIVE cohort is a longitudinal study following just under 4000 current and former intravenous drug users from 1988 to the present in Baltimore, Maryland. Originally designed to study the impact of HIV/AIDS in this population, this study also tracked participants’ marijuana use among a multitude of other variables. Marijuana use was classified using latent trajectory modeling. Marijuana use was then correlated with health status and socioeconomic variables using multivariate repeated measures modeling. RESULTS: Approximately 35% of participants did not use marijuana during the study, and among users, low use was the most common pattern (use less than 15 times in the past 6 months). Preliminary analyses indicated that marijuana use decreases with both age and number of years in the study. Trajectory modeling demonstrated a mostly abstinent group (37.9%), an early cessation group (29.3%), a late cessation group (14.5%), an intermittent use group (10.7%), and a chronically high use group (7.6%). Marijuana use was correlated with worse mental and physical health scores, greater general body pain, less education, male gender, incarceration, and polydrug use, but was surprisingly protective for injection drug use. CONCLUSIONS: This analysis characterized patterns of marijuana use among intravenous drug users. Although previous studies have indicated that marijuana use has no impact on the success of methadone treatment, further studies should investigate whether marijuana use increases, decreases, or stays the same among intravenous drug users that quit injecting, and whether marijuana use impacts withdrawal or the likelihood of remission. The impact of chronic marijuana use on neurological function, peripheral neuropathy, and disease progression among HIV positive individuals is another topic for future investigation.
HEPATOSPLENIC CT VOLUMETRY FOR DETECTING CIRRHOSIS: COMPARISON WITH ESTABLISHED LINEAR MEASURES

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BACKGROUND: Liver biopsy is regarded as the standard in diagnosing hepatic cirrhosis. However, the procedure is invasive and can cause potentially life-threatening conditions for a patient. Due to these risks, the liver biopsy is normally not recommended for patients who are asymptomatic. Additionally, biopsy results can be variable and inaccurate due to differences in microscope readings and tissue sample quality. Thus, a non-invasive method with greater precision and accuracy needs to be developed. It has been shown that hepatic and splenic volume ratios can be used to diagnose liver cirrhosis. In a cirrhotic liver, the right lobe and medial left segment of the liver decrease in volume, and the caudate and left lateral segment increase in volume. Other studies have used linear measurements to assess liver morphology, but linear measurements do not fully characterize changes in organ volume. Recent improvements in semi automated CT volumetric methods allow for an accurate and precise measurement of organ volumes. With a large normal and abnormal cohort and using the latest Philips Intellispace Portal Liver Analysis software, this study may address cirrhosis based upon liver volume. Automated steps in the software analysis of CT images reduce significant levels of user variability in the volumetric readings. In practice, the non-invasive nature of a CT scan may enable physicians to diagnose liver cirrhosis early in asymptomatic patients, or track the progress of disease and response to treatment.

OBJECTIVE: To compare volumetric measures of the liver and spleen with established linear measurements for differentiating normal from cirrhotic livers. METHODS: Hepatic and splenic volumes were measured using semi-automated software (Liver Analysis application, Philips Intellispace Portal) on contrast-enhanced abdominal CT scans in 204 controls (potential renal donors; mean age, 46 yrs; 82M/122F) and 108 patients with end-stage liver disease (ESLD; mean age, 55 yrs; 63M/45F). The liver segmental volume ratio (LSVR) was defined as the volume ratio of Couinaud segments I-III to segments IV-VIII. Linear measures included the caudate-to-right lobe (CRL) ratio at the portal bifurcation, and maximal transverse and coronal splenic dimensions. Kruskal-Wallis test and ROC/AUC were used for statistical analysis.

RESULTS: Differences in LSVR between cirrhotics and controls were highly significant (p<0.0001; mean, 0.5496±0.2917 versus 0.2664±0.0702; ROC AUC=0.916). Linear CRL ratio differences were not statistically significant between the two cohorts (p=0.0509; ROC AUC=0.567). Differences in splenic volume were highly significant (p<0.0001; mean, 769.2±448.4 versus 216.5±90.9 ml; ROC AUC=0.938), but maximal linear splenic dimension was also effective (p<0.0001; ROC AUC=0.909). An LVS threshold ≥0.3 had a sensitivity and specificity for cirrhosis of 88.9% and 71.1%, respectively. A splenic volume threshold ≥300 ml had a sensitivity and specificity for cirrhosis of 88.0% and 84.8%, respectively. When combining LVRS and splenic volume together, ROC AUC=0.986.

CONCLUSIONS: Hepatosplenic volumetric changes are more effective than standard linear measures for differentiating normal from cirrhotic livers, especially with respect to changes in hepatic segments I-III versus IV-VIII.
EVALUATION OF BASELINE BIRTH OUTCOMES PRIOR TO THE IMPLEMENTATION OF CENTERINGPREGNANCY AT TWO UW RESIDENCY CLINICS

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BACKGROUND: CenteringPregnancy (CP), group based prenatal care, is an alternative method of prenatal care. CP has been associated with decreased rates of preterm birth and improvements over traditional individual care in patient satisfaction, prenatal visit attendance and pregnancy knowledge. CP was recently implemented in 2 South Madison residency clinics. A chart review was carried out to determine birth outcomes specific to this cohort of patients prior to the implementation of CP and evaluate the potential of the program to effect positive change. METHODS: A chart review was carried out of all patients receiving prenatal care in these 2 clinics 6 months prior to the implementation of the program. Birth outcomes were evaluated for a total of 159 patients. Statistical Analysis was carried out using Chi Squared and Fishers Exact tests for association between demographics of these patients and adverse birth outcomes. RESULTS: Chart review showed rates of low birth weight (LBW) births higher than both the national and Wisconsin averages, but rates of preterm birth that were lower. However, 58% of total preterm births were late preterm births. Additionally, rates of breastfeeding at discharge from the hospital and smoking during pregnancy were worse than both national and state averages, with lower rates of breastfeeding and higher rates of smoking. No association was found between any specific demographics and LBW or preterm birth, although the sample size was small with few total adverse events, reducing the statistical power of the analysis. CONCLUSIONS: Late preterm births (LPTB) tend to be the most effected by perinatal intervention, including CP, because many are preventable (i.e. elective induction) LPTB represents 60% of the preterm births at these clinics. CP has also been shown to have positive results on the initiation of breastfeeding at discharge from the hospital and promoting smoking cessation. These clinics serve a resource limited neighborhood with very high rates of smoking and LBW births. This analysis leads to the conclusion that this institution and its patients seek to benefit from the implementation of the CP protocol, which may help to mitigate some of these adverse outcomes in this population. This baseline data will also be used in the future to monitor birth outcomes after the implementation of this program and to contribute to the growing body of scientific literature on the efficacy and benefits of CP.
FINANCIAL AND ADMINISTRATIVE IMPLICATIONS OF MIGRAINE SURGERY

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BACKGROUND: Migraine headaches are a debilitating neurologic condition that affect up to 15% of the world’s population. The economic consequences of migraine headache have been estimated to exceed $13 billion per year, primarily due to absenteeism and lost productivity. Migraine surgery (MS) offers a novel treatment for patients who are refractory to conventional therapy. Studies to date have demonstrated the effectiveness of MS in up 92% of eligible patients. There is currently no data on surgeon time commitment and reimbursement for migraine headache work-up, operative intervention, and post-operative care. This information would be invaluable in the cost reduction setting of the Affordable Healthcare Act and would add to the large amount of recent literature on procedural cost analysis.

OBJECTIVE: The aim of this study is to analyze the administrative aspects and relative financial value of MS from a surgeon and hospital perspective. Breast reconstruction (BR) is a well-accepted and appropriately reimbursed procedure and serves as an important comparison and control for MS.

METHODS: 55 new MS and BR consultations leading to subsequent surgery were identified from the plastic surgery registry over a 12-month period (January 2013 - 2014). Epidemiological variables were gathered through retrospective chart review. Conversion rates (proportion of initial clinic visits that result in surgery) were determined for each procedure. Physician and hospital billing information were obtained from the Department of Surgery Billing Records. Physician and hospital collection rates were calculated from billing records. Statistical analysis of variables was carried out using t-test and chi-squared test.

RESULTS: Variation in source of referral was found to be statistically significant (p<0.05). The difference in conversion rates was found to be significant (p<0.05) for MS (27.4%) and BR (65.5%). Physician collection rate was found for MS (25.2%) and BR (30.7%). Hospital financial data is currently being analyzed to determine collection rate and revenue. CONCLUSIONS: MS has a lower conversion rate (27.4%) than most other surgical procedures. MS also has a low physician collection rate (25.2%). Analysis of hospital billing information will determine hospital revenue and collection. Determination of the relative value of MS to physicians and hospitals will help to illustrate steps that must be taken to better attract and retain skilled migraine surgeons dedicated to surgical alleviation of migraine headaches.
IN VITRO VANCOMYCIN AND TOBRAMYCIN ELUTION IN DUAL ANTIBIOTIC IMPREGNATED ACRYLIC BONE CEMENT

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BACKGROUND: Infection remains a rare but devastating complication of total joint arthroplasty. The use of dual antibiotic impregnated bone cement has become a common practice in treating infected prosthetic joints. However, little data exists on the elution characteristics of combined vancomycin and tobramycin impregnated acrylic bone cement. OBJECTIVE: To quantify the in vitro antibiotic elution characteristics of Palacos R bone cement (Heraeus Medical GmbH, Wehrheim, Germany) impregnated with varying concentrations of vancomycin and tobramycin over a four week period. METHODS: Twelve different groups of 5 vancomycin and tobramycin loaded cement disks were prepared, varying from 0 to 3 g of each antibiotic. Each disk was incubated in 10 mL of saline at 37°C on a rotary shaker. At 6 hr, 1, 3, 5, 7, 14, 21, and 28 days, the saline was replaced and samples were frozen at -80°C. Antibiotic concentration was quantified by high performance liquid chromatography (HPLC). RESULTS: At a set quantity of vancomycin, an increasing amount of tobramycin correlated with an increase in vancomycin release. However, the maximal release of vancomycin did not occur at maximal loading of both vancomycin and tobramycin. Cumulative release from pellets containing 2 g vancomycin and 3 g tobramycin was 2.409 mg of vancomycin, 47% more than the 1.636 mg from pellets containing 3 g vancomycin and 3 g tobramycin (p=0.01). Tobramycin concentrations are still being determined. CONCLUSION: These findings suggest that tobramycin increases the elution of vancomycin, though the tobramycin elution data is required to better understand these results, since maximal release of vancomycin does not occur with maximal antibiotic loading. Future studies testing the antimicrobial activity of the eluents will be performed.
NON-INVASIVE RIGHT VENTRICULAR EFFICIENCY USING 4D FLOW MRI

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BACKGROUND: Pulmonary arterial hypertension (PH) is a progressive disease of increased resistance to flow through the lungs, leading to right ventricular (RV) failure. MRI is increasingly used to assess right ventricular (RV) function in PH. RV stroke work (SW) based on invasive pressure and volume measurements, is used to assess ventricular work. Determining RV work from MRI could enable a more complete characterization of RV and PA interactions in PH. The purpose of this study was to non-invasively estimate RV work from simultaneously acquired RV volume (VRV) and pulmonary artery flow (QPA) using a 4D flow-sensitive MRI sequence in a canine model. METHODS: After IACUC approval, six adult female beagles were induced with propofol and maintained under anesthesia with isoflurane. Measurements were performed prior to and following induction of acute PH by injection of embolizing micro-beads (150–500μm) into the right atrium. Pre- and post-embolization right heart catheterization (RHC) was performed to measure hemodynamic changes in the RV and PA. 4D flow MRI (Phase Contrast with Vastly undersampled Isotropic Projection Reconstruction – PCVIPR) was performed on 3T clinical scanners (MR750, GE Healthcare, Waukesha, WI) after the intravenous administration of gadolinium-based contrast agents. PCVIPR parameters: FOV=32x32x22cm, isotropic 1.3mm spatial resolution, TR/TE=6.3/2.1ms, Venc=150cm/s, scan time: ~10min using adaptive respiratory gating of bellows and retrospective ECG gating. Post-processing was done using Mimics (Materialise, Ann Arbor, MI) for the segmentation of the VRV from dynamic magnitude images and Ensight (CEI, Apex, NC) for quantification of QPA. RV pressure – VRV loops were generated to assess SW by calculating the area inside the loop. QPA - VRV loops were generated and their area calculated for comparison to the SW calculations (Fig1). Direct comparison was used for the analysis of the results and a student t-test was used to compare the two methods. RESULTS: In all cases embolization induced an increase in SW (180 ± 140 vs 374 ± 210mmHg*cm3). Similarly the calculated area of the QPA - VRV loops increased for all the cases (369 ± 210 vs 785 ± 486 s-1) (Fig2). No significant difference was found between the percent increase of SW and the QPA - VRV loops area (53 ± 15 vs 52 ± 12%, p = 0.95). CONCLUSION: QMPA – VRV loop area estimated noninvasively using 4D flow MRI can be used to evaluate right ventricular stroke work. The results from this study indicate that 4D flow-sensitive MRI with PC VIPR can also be used to estimate PVR, complementing the analysis of alterations in flow patterns in the heart and pulmonary arteries in patients with cardiopulmonary disease, however more studies need to be done for validation of the model.
EVALUATION OF CAPITAL CITY STATE TRAIL FEES AND IMPACT ON ACTIVE LIVING AMONG LOW-INCOME INDIVIDUALS

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BACKGROUND: Decreasing physical activity over recent years has been associated with increasing rates of obesity, heart disease, stroke, cancer, hypertension, and diabetes with heart disease and cancer being the two leading causes of death in the United States. Low-income populations tend to have increased rates of physical inactivity and related health diseases. The federal government released the National Prevention Strategy in June of 2011 in order to initiate a greater focus on prevention of chronic diseases. It contains seven priority areas, including Active Living, which provides guidelines for state and local governments, employers, health care systems, schools, communities, families, and individuals to encourage and support physical activity. Currently, 80% of adults and youths nationwide do not meet physical activity guidelines of one hour per day for youths and 150 minutes per week for adults with similar trends in Dane County, Wisconsin. The local public health department, Public Health – Madison & Dane County (PHMDC), has recently shifted efforts towards Active Living. OBJECTIVE: To explore and prioritize options for PHMDC to encourage and support physical activity in Dane County. METHODS: Policy and systems level approaches to support Active Living in Dane County were identified via literature review, examination of policies in other areas of the country, and through contact with members of PHMDC and other organizations such as the Child Obesity Prevention Collaborative. Interventions relating to Safe Routes to School, Complete Streets, community gardens, parks, and trails were assessed for feasibility and potential impact in Dane County. Ultimately, the bicycle trail fee on the Capital City State Trail (CCST) in Dane County was analyzed for costs, benefits, and policy alternatives. RESULTS: An exemption or sliding fee scale for low-income individuals for the CCST fee may encourage trail use for that population. Potential benefits to health, environment, businesses, and roadways may outweigh potential costs, such as loss of revenue. CONCLUSIONS: The CCST fee may deter low-income individuals from using the trail for commuting or recreation, which could otherwise be a source of physical activity. Further study is needed to estimate the amount that trail use could be increased by creating a policy change for low-income individuals as well as to identify other barriers that discourage or prevent trail use.
LEFT AND RIGHT VENTRICULAR KINETIC ENERGY USING TIME-RESOLVED VERSUS TIME-AVERAGE VENTRICULAR VOLUMES

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BACKGROUND: Four-dimensional flow-sensitive (4D flow) MRI opens the possibility for finding new, non-invasive measures of cardiac function, including kinetic energy (KE). Studies using 4D flow MRI have reported correlations between disease states and altered KE profiles. However, the majority of these studies have relied on the faster, yet potentially less accurate, process of time-averaged segmentation rather than time-resolved segmentation, analyzing volumes determined from reconstructions averaged across the entire cardiac cycle, instead of volumes traced out at multiple phases. OBJECTIVE: The purpose of this study was to see if there are any significant differences between KE profiles determined using the two segmentation methods, specifically in healthy right and left ventricles (RV, LV). METHODS: Time-resolved 4D flow MRI data were acquired from 10 healthy volunteers on a 3T scanner (MR750, GE Healthcare, Waukesha, WI). RV and LV volumes were segmented from time-resolved and time-averaged images using Mimics (Materialise, Leuven, Belgium). Velocity profiles were obtained using Ensight (CEI, Apex, NC), and the total KE in each ventricle was calculated from both the time-resolved and time-averaged data using MatLab (The Mathworks, Natick, MA). KE profiles were then compared using paired Student’s t-tests and Bland-Altman plots. RESULTS: Small yet significant differences in calculated KE were observed between time-resolved and time-averaged segmentation. For both RV and LV, there were significant differences in peak systolic KE (P = 0.016, 0.005) and total KE integrated across the entire cardiac cycle (P = 0.004, 0.001), but not in peak diastolic KE (P = 0.082, 0.044). For both RV and LV, Bland-Altman plots revealed a bias towards higher systolic peak KE (average difference = 0.649 mJ, 0.866 mJ), diastolic peak KE (0.280 mJ, 0.416 mJ), and total integrated KE (250 mJ, 305 mJ) using time-averaged segmentation. CONCLUSIONS: KE profiles for both the right and left ventricles were determined using time-averaged and time-resolved segmentation. Although qualitatively the two methods resulted in comparable results, time-averaged segmentation consistently over-estimated KE, with differences between the two methods being more pronounced during systole and particularly in the LV. Therefore, for a qualitative analysis, using time-averaged image for segmentation is recommended, while a more accurate, quantitative analysis requires a full time-resolved segmentation.
COSTS IN PATIENTS WITH OPIOID-TREATED CHRONIC LOW BACK PAIN: A SECONDARY ANALYSIS OF A MEDITATION RCT

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BACKGROUND AND OBJECTIVE: Opioid-treated chronic low back pain (CLBP), a pervasive and disabling condition, imposes a significant economic burden on the patient and health care system. The goal of this secondary analysis of a randomized-controlled trial was to assess costs in patients with opioid-treated CLBP. METHODS: 35 adults with CLBP, prescribed at least 30mg of morphine-equivalent dose per day, were enrolled. Direct costs were assessed through self-reported medication use, health care utilization (office visits, inpatient days, ER visits, urgent care visits, individual and group mental health visits), and motor vehicle accidents. Indirect costs due to lost productivity were assessed through self-reported missed work days or missed leisure days. RESULTS: Preliminary analyses of participant data (80% women; mean age of 51.8 ± 9.7 years; low back pain duration of 14.2 ± 10.1 years; opioid therapy duration of 7.9 ± 5.7 years; Oswestry Disability Index score of 66.7 ± 11.4; EuroQoL index score of 0.581 ± 0.126) showed that the mean 6-month cost of opioids was $1254 (95% CI: $742-$1766), of health care utilization was $4151 (95% CI: $1931-$6372), of motor vehicle accidents was $143 (95% CI: $59-$345), and of lost productivity was $4862 (95% CI: $2355-$7369), adding up to a total cost of $10410 (95% CI: $6695-$14126) per participant. Other medication cost analyses are pending. CONCLUSIONS: Patients with opioid-treated CLBP are characterized by high costs, with indirect costs comparable in size to direct costs. Despite high spending on health care and medications, health and disability scores were poor.
SELF-OPTIMIZING VENTILATOR WITH HIGH FREQUENCY OSCILLATING FUNCTIONALITY

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BACKGROUND: Acute respiratory distress syndrome (ARDS) is a serious lung condition characterized by inflammation of the lung parenchyma that is estimated to affect 190,000 Americans annually. ARDS patients are typically critically ill and have impaired gas diffusion across alveoli leading to low blood oxygen levels. Mechanical ventilation is necessary to facilitate their respiratory gas exchange. Because of the compromised parenchymal tissue, ARDS patients are at an increased risk for barotrauma. High frequency oscillating ventilation (low tidal volumes with high respiratory rate) is commonly used in especially severe cases of ARDS to achieve maximal levels of ventilation while minimizing the risk of lung over-distension. We have been working on developing a device that combines a standard positive pressure ventilator with a high frequency oscillating ventilator and utilizes a series of algorithms to automatically optimize pulmonary mechanics based on the ventilation goal inputted by a physician. The device is designed to closely monitor a patient’s lung compliance and automatically adjust to optimal levels for the best possible gas exchange while maintaining minimal over-distention from high pressures. One of the biggest benefits of this device would be replacing the cumbersome transition phase between using high frequency oscillating ventilation and normal positive pressure ventilation, which in current practice is much based on guesswork. OBJECTIVE: To conduct preliminary testing of a ventilator prototype and build a pressure controlled test chamber. METHODS: We utilize flow meters and pressure sensors to measure the output of the ventilator prototype and gauge how well it responds based on inputted parameters. A rubber balloon in a pressure controlled chamber serves as an artificial lung with variable compliance and resonant properties. RESULTS: The ventilator design was modified as needed to meet control and output specifications. A test chamber with variable pressure control was fabricated to allow future testing on artificial lungs and porcine cadaver lungs. The chamber will allow for simulating the dynamic changes that occur within an ARDS patient’s lungs. CONCLUSIONS: Our ventilator prototype shows promise in addressing a need for improved mechanical ventilators. More testing will need to be completed on artificial lungs and animal models to refine control algorithms.
WHO GETS IT? A SURVEY OF PHYSICIAN ATTITUDES REGARDING DISASTER RESOURCE ALLOCATION

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BACKGROUND: Resource allocation during disasters poses clinical, administrative and ethical challenges—overwhelming available healthcare resources and obviating the standard of care. The lack of evidence-based standards or consensus-based goals for health care resource allocation in a disaster setting leads to uncertainty for providers being asked to distribute resources. OBJECTIVE: To ascertain the opinions of the health care professionals who will actually be providing care if a disaster strikes.

METHODS: Data was obtained from a brief IRB-approved survey conducted at a quaternary care, academic institution. Personal experiences with disaster planning and awareness, opinions of main goal of crisis care, understanding of possible important disaster resource allocation factors (age, life expectancy, DNR status), and knowledge of triggers for declaring crisis care were ascertained. The confidential survey was electronically distributed to a random sample of faculty physicians and residents. Analysis of descriptive characteristics and for possible relationships between baseline awareness and patterns of allocation was performed. RESULTS: Analysis of physician responses demonstrated a 39% response rate (yield from 1233 surveys distributed). Mean years in practice was 12 years. Thirty-five percent of physicians stated they had been involved in disaster planning, but only 21% knew the institutional disaster plan or where to find these plans. Eighteen percent felt they had received adequate training to receive a large surplus of patients. The majority of physicians said that scope of practice (89%) and legal standards (65%) change during disaster scenarios, and just over half (52%) said ethical norms changed. A minority (24%) of physicians had experience with disasters or resource allocation, and most (82%) do not feel they have received adequate training in this area. CONCLUSION: The majority of physicians at a large academic hospital are ill prepared to deal with resource allocation in disasters. This early single institution analysis provides the first reported insights into baseline physician attitudes and can be a basis for targeting institutional education initiatives and future surveys in disaster planning and management.
SCREENING OF NOVEL SYNTHESIZED ANALOGUES TARGETING HISTONE DEACETYLASE IN AGGRESSIVE THYROID CANCERS

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BACKGROUND: There are currently no effective therapies for aggressive thyroid malignancies including anaplastic and poorly differentiated cancers. Compounds targeting histone deacetylases (HDAC) have shown promising antitumor activities in others cancers. In order to develop novel therapies for these aggressive thyroid cancers, we synthesized a new group of analogues targeting HDACs named AB1 to AB13 which has different linkers between a metal chelating group and a hydrophobic cap. Therefore, the purpose of this study was to screen out the most effective compounds and evaluate the therapeutic efficacy in aggressive thyroid cancers. METHODS: Anaplastic (HTh7 and 8505C) and metastatic follicular (FTC236) thyroid cancer cells were treated with thirteen AB analogues using various concentrations, and the IC50 was determined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The most effective compounds were selected based on the IC50 to further study the molecular mechanisms of growth regulation. Both cell cycle regulatory proteins and apoptosis markers were analyzed by the Western blot. In addition, the expression levels of the thyrocyte-specific genes were quantified by real-time PCR to assess the drug potency of inducing re-differentiation in aggressive thyroid cancer cells. RESULTS: Among all the analogues, AB1, 4, 5, 6, 13 showed very limited cytotoxicity effect while AB7, 8, 9, 11, and 12 presented with moderate efficacy to inhibit cell growth. AB2, AB3, and AB10 demonstrated the lowest IC50 values of the thirteen screened drug analogues. The AB analogues showed less cytotoxicity against human fibroblasts. AB2, AB3, and AB10 treatment resulted in an increase of apoptosis markers including cleaved poly adenosine diphosphate ribose polymerase (PARP) and cleaved caspase 3 in a dose dependent manner in all three cancer cell lines. Additionally, the expression of cell cycle regulatory proteins p21/WAF1 and p27 Kip increased with the treatment of ABs while cyclin D1 decreased dose-dependently. Furthermore, AB2, AB3, and AB10 were able to induce various of thyrocyte specific genes in all the cell lines indicated by increased level of sodium iodide symporter (NIS), paired box gene 8 (PAX8), thyroid transcription factor 1 (TTF1), TTF2, and thyroid stimulating hormone receptors (TSHR). CONCLUSIONS: Novel synthetic HDAC inhibitors AB2, AB3 and AB10 suppress thyroid cancer cell growth via cell cycle arrest and apoptosis. They also induce cell re-differentiation which could make aggressive thyroid cancer cells more susceptible to radioactive iodine therapy. Therefore, these compounds could be new options for patients with aggressive thyroid cancers.
ADOLESCENT ATHLETE’S UTILIZATION AND PERCEPTIONS OF ANKLE TAPING AND ANKLE BRACES TO PREVENT ANKLE SPRAINS

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Support: Shapiro Summer Research Program; Department of Orthopedics and Rehabilitation; UW Sports Medicine Classic Fund, University of Wisconsin School of Medicine and Public Health

BACKGROUND: Ankle sprain injuries are the most common injury that occurs in adolescent sport participants. The efficacy of Ankle Taping (AT) and Ankle Braces (AB) and to prevent ankle sprains is well documented. However, there is limited data as to the extent AT and AB are utilized and perceived by at risk adolescent athletes. OBJECTIVE: To determine the utilization and perceptions of AT and AB in a sample of adolescent athletes. METHODS: A cross sectional study was conducted with data collected during the summer of 2014 at a series of sport camps and club team competitions. A convenience sample of unique adolescent (females = 51%, males = 49%; age = 15.7+1.7 yrs.; grades 9 – 12) basketball, football, soccer and volleyball players enrolled in this study. Subjects completed a survey (paper, in-person) adapted from similar to the survey used previously to quantify coaches' utilization of ankle injury prevention strategies and consisted of a series of dichotomous (Yes, No) and Likert scaled questions. The dependent variables included the percentage of subjects utilizing AT and AB. Fisher's Exact tests were used to analyze responses by sex sport and previous ankle sprain (PAS) and no ankle sprain (NoAS). Wilcoxon Rank Sum tests were used to determine if there were differences in Likert Scale Items. All differences were assessed with p < 0.05. RESULTS: Subjects included Basketball (n = 258), Football (n = 158) Soccer (n = 232) and Volleyball (n = 152) players. A total of n = 217 (27 %) reported a PAI on one or both ankles. Ninety eight (12%) reported taping one (61%) or both (39%) ankles. The top three reasons cited for not utilizing AT were: no need for extra support (59%) followed by no previous injury (22%) and no one to tape their ankles (15%). Six hundred twenty five (78%) agreed that taping would reduce the risk of an ankle sprain with this belief higher in subjects with PAS (p = 0.001) than (NoAS) but lower in soccer players than basketball (p = 0.006), football (p = 0.002) and volleyball (p = 0.009). Subjects with PAS (27%) used AT more often (p < 0.001) than NoAS (7%). Basketball players (19%), were more likely (p<0.001) to use AT than football (9%), soccer (9%) and volleyball (10%) players. Two hundred forty nine (31%) wore lace-up n = 166 (67%) or hard shell n = 56 (23%) brace on one (37%) or both (63%) ankles, 1 to 2 days per week (46%) 3 to 4 days per week (17%) or daily (17%). The top three reasons cited for not wearing AB included: no need for extra support, (73%) followed by no previous injury (26%) and expense (24%). Six hundred thirty nine (81%) agreed that AB would reduce the risk of ankle sprains with the belief higher in females (p<0.001) than males and subjects with PAS (p = 0.029) than (NoAS). Soccer players were less likely to (p<0.001) than basketball, football, and volleyball players. AB use was higher (p<0.001) in subjects with PAS (56%) than NoAS (27%). Soccer players (18%) were less likely (p<0.001) to wear AB than basketball (37%), football (25%) and volleyball (49%) players. The top criteria all subjects would consider for using a specific brand / model of brace was comfort, n= 295 (37%), injury prevention, n = 207 (26%) and if their athletic trainer recommended them, n = 108 (14%). CONCLUSION: The utilization AT and AB varies considerably by sex, sport and previous injury status. Athletic trainers need to consider these variables when recommending and implementing ankle injury prevention strategies.
MEASURING THE BURDEN FROM SMOKING IN WISCONSIN COUNTIES

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Support: Shapiro Summer Research Program; Wisconsin Academy of Rural Medicine (WARM); Department of Population Health Sciences; HRSA Training Grant T85HP24472; Robert Wood Johnson Foundation Grant 69835; University of Wisconsin School of Medicine and Public Health

BACKGROUND: Although the prevalence of cigarette smoking among US adults has declined over the past 50 years, smoking remains the leading cause of preventable death, and marked disparities now exist in smoking rates based on education level, socioeconomic status, race/ethnicity, and geographic location. The purpose of this study was to develop a novel method to measure the relative health burden from smoking in Wisconsin counties.

METHODS: Age-adjusted mortality rates for smoking attributable diseases, current adult smoking prevalence, and the current rate of mothers who smoked during pregnancy were calculated. A single summary measure of smoking burden was created for all Wisconsin counties using z-scores. Each county’s smoking burden was compared to both its demographic characteristics to observe disparities and to the number of registered callers to a quit line as a proxy for tobacco control efforts.

RESULTS: The burden of smoking varied significantly between counties for smoking attributable deaths (2-fold), adult smoking prevalence (5-fold), and smoking in pregnancy (5-fold). The overall burden from smoking was highest in counties with less education, higher rates of poverty, more veterans, and in rural counties. The ranking of a county’s smoking burden was highly correlated with its overall health ranking from the County Health Rankings. Counties with higher smoking burden, particularly those with high adult prevalence, had more registered callers to the quit line per adult smoker in the county.

CONCLUSIONS: The burden from smoking varied markedly across Wisconsin and was highest in the least advantaged counties in the state. Although counties with greater smoking burden appeared to be using quit line services more, additional public health efforts should be directed toward these counties in order to reduce these disparities in the future.
HOW DOCTORS BIRTH: HOW OUR EXPERIENCES SHAPE OUR PRACTICE

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Support: Department of Family Medicine Summer Research and Clinical Assistantship Program; Department of Family Medicine Small Grant Program, University of Wisconsin School of Medicine and Public Health

BACKGROUND: Birthing stories are personal narratives that provide a space for women to share experiences. Much research has been done analyzing thematic norms presented in birth stories to improve healthcare practices and patient experiences. However, very little data has been collected on how physicians’ own birthing stories shape the ways they provide care. One study that successfully captures how personal experiences inform the choices of physicians is Dr. Ken Murray’s “How Doctors Die: It’s not like the rest of us, but it should be”. Murray’s study investigates why physicians often choose less interventional supportive care when faced with a terminal illness, and how that is different from the choice of their patients. How Doctors Birth aims to explore similar discrepancies in delivery preferences by listening to the powerful birth stories of physicians themselves. OBJECTIVE: How Doctors Birth will explore how common clinical practices develop from female physicians' personal pregnancy experiences.

METHODS: Physicians’ birthing narratives were obtained from 30 minute in-person interviews. These stories were coupled with quantitative survey data consisting of information on medical training and family development history. Female Family Medicine physicians and Obstetricians who have received training in labor and delivery were recruited. Survey data was analyzed for correlations between medical training experiences, family development trajectories, and delivery interventions. Data was also analyzed for common breastfeeding practices and perceptions. Content and thematic analysis of interviews was conducted to elicit associations between physician’s birthing experiences and the care they provide.

RESULTS: Quantitative data assessing the way doctors birth demonstrates similar averages to those across the Nation and in Wisconsin. Analyses are still in progress, but suggest that doctors birth in similar ways to other non-physician women. Physicians’ experiences throughout pregnancy have changed their scope of practice in three major ways: increased empathy for patients, increased awareness of social pressure put on women to parent or birth in a particular way, and increased advocacy efforts for patient empowerment. Prenatal counseling, labor support, breastfeeding counseling, and pediatric care all changed as a result of personal birthing experiences. CONCLUSIONS: Personal experiences construct the way physicians approach and counsel patients. Therefore, further research must address the following questions: How successful are physicians with leveraging empathy to address empowerment? and How do we teach non-parents in medical training all that doctors have garnered from personal experiences?
DOES AIRWAY TYPE AFFECT TRANSBRONCHIAL NEEDLE ASPIRATION (TBNA) DIAGNOSTIC YIELD?

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Mentor(s): Richard E. Galgon, MD, MS

Support: Shapiro Summer Research Program; Department of Anesthesiology, University of Wisconsin School of Medicine and Public Health

BACKGROUND: Mediastinoscopy is traditionally used for tissue sampling for staging lung cancer and diagnosing other mediastinal lesions. However, transbronchial needle aspiration (TBNA), guided by endobronchial ultrasound (EBUS-TBNA) or electromagnetic navigational systems (ENB-TBNA), is increasingly favored. Airway management for these procedures has been successful using both tracheal tubes (TTs) and supraglottic airways (SGAs). Unlike an SGA, a TT lies below the vocal cords, which limits access to proximal (level 2) lymph nodes/lesions. Additionally, its longer length (32cm vs. 23cm) and smaller internal diameter (8-8.5mm vs. 11-12mm) subjectively impacts bronchoscope maneuverability, which may limit scope/biopsy target apposition. As such, SGA versus TT use may impact procedural diagnostic yield. However, no study has yet attempted to answer this question. Thus, the purpose of this study was to answer the question: Does airway type (TT vs. SGA) affect TBNA diagnostic yield?

METHODS: After IRB approval, charts of patients who underwent EBUS- or EBN-TBNA under general anesthesia between 2009 and 2014 were reviewed. Patients hospitalized within 24 hours before the index procedure, those already intubated, and those undergoing other planned procedures during the same anesthetic were excluded. Patient, procedure, and anesthetic characteristics, diagnostic yield, and complications were extracted and analyzed. Intergroup comparisons were performed using unpaired t and Fisher’s exact tests. P-values < 0.05 were considered significant. RESULTS: From 580 encounters, 437 records were analyzed after exclusions. TTs and SGAs were used in 46% and 54% of cases, respectively. Group age, gender, ASA physical status, body mass index, a priori selected co-morbidities, home CPAP and oxygen use, and anesthetic and procedure type were well-balanced. Diagnostic yield (TT=92%, SGA=94%; p=0.58), home discharge, procedure and post-procedure complication, and 30-day re-hospitalization and all-cause mortality rates were similar. SGA use was associated with less frequent paralytic drug (PD) use (5% vs. 86%; p<0.0001) and a shorter recovery time (117min vs. 135 min; p=0.007) at an airway conversion rate of 3% (vs. TT=0%; p=0.016). CONCLUSIONS: In this retrospective study, airway type did not appear to impact TBNA diagnostic yield. SGA use favors less frequent PD use, which may impart a shorter recovery time. Sampling level and airway type interactions are yet to be analyzed.
"FREE & EASY" OPPORTUNISTIC SCREENING FOR OSTEOPOROSIS AT ABDOMINAL CT USING ONLY THE SAGITTAL RECONSTRUCTION

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Support: Shapiro Summer Research Program; Wisconsin Academy of Rural Medicine (WARM); Department of Radiology, University of Wisconsin School of Medicine and Public Health

BACKGROUND: Opportunistic screening at abdominal computed tomography (CT) has been proposed using axial/transverse lumbar level 1 (L1) trabecular attenuation and by fracture assessment on the sagittal series. Retrospective sagittal series fracture assessment has also shown that vertebral fractures can go unreported on both CT and clinical assessment. OBJECTIVE: We sought to combine this dual evaluation of trabecular attenuation and vertebral fracture assessment on the sagittal reconstruction alone to improve efficiency. METHODS: Routine contrast-enhanced abdominal CT scans for any indication from 571 consecutive adults age 60 years or older from a single center over a 3-month period were retrospectively analyzed. L1 trabecular attenuation was measured using a 100 mm2 region-of-interest on both the transverse and sagittal series for comparison. The sagittal reconstruction was also analyzed for moderate-severe vertebral compression fractures using the Genant visual semi-quantitative method. Definite or probable osteoporosis by CT was defined by a moderate-severe fracture and/or sagittal L1 trabecular attenuation ≤110 Hounsfield Units (HU) (>90% specific for osteoporosis). Correlation was made with central dual-energy X-ray absorptiometry (DXA) (hip and L-spine) performed within four years of CT. RESULTS: The absolute mean difference in L1 trabecular attenuation between transverse and sagittal reconstructions was 6.7 (±5.7) HU, or 6.2%. At the 110 HU cut-off, the transverse and sagittal HU measurements were in agreement in 89.4% of cases. A total of 243 (42.3%) patients had likely osteoporosis by CT criteria, of which only 48 (17.6%) had previous DXA screening. Only 17 (35.4%) of these 48 patients had osteoporotic T-scores at central DXA (≤-2.5); most of the remaining cases are presumably DXA false-negatives. CONCLUSIONS: Assessment of the sagittal reconstruction alone at routine abdominal CT for both vertebral fractures and trabecular bone mineral density provides for a rapid and effective opportunistic screen for osteoporosis. This approach may be advantageous to DXA for initial evaluation. Future studies analyzing the cost-effectiveness of opportunistic osteoporosis screening at routine abdominal CT could further demonstrate its clinical utility.
MERKEL CELL CARCINOMA: THE UNIVERSITY OF WISCONSIN EXPERIENCE

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BACKGROUND: Merkel cell carcinoma (MCC) is an aggressive cutaneous malignancy with relatively poor outcomes. It has a 5-year overall survival rate of 30-64%. MCC was first characterized in 1972 as "trabecular carcinoma of the skin". The malignancy was subsequently renamed after the presumed cells of origin when further investigation suggested that the cancer originated in the neuroendocrine Merkel cells within the basal layer of the epidermis. Merkel cells have more recently been noted to lack proliferative capacity, and it is now suspected that MCC does not develop from differentiated Merkel cells but rather from cutaneous progenitor cells. The incidence of MCC has risen since it was first described in the 1980s due to both improved diagnosis and increased exposure to known risk factors such as UV exposure and chronic immunosuppression. Given the rarity of this disease, and its relatively recent recognition, the optimal treatment remains uncertain. While most groups recommended maximal safe surgical excision, the effectiveness of adjuvant therapies, the cases in which they should be utilized, and the optimal regimens remains unclear. OBJECTIVE: We sought to add to the published literature by reporting on patients treated at our tertiary care referral center for MCC over the last 30 years.

METHODS: A total of 87 histologically confirmed MCC patients were analyzed retrospectively at the University of Wisconsin Hospital and Clinics, from 1984 to 2014. We examined patient, tumor, and treatment characteristics via review of patient medical records. Overall survival was calculated, patient characteristics were reported, and statistical analyses were performed assessing outcomes and associated prognostic factors.

RESULTS: The median and mean follow-up of patients included in this analysis were 17 and 38 months, respectively (range of 0-210 months). Two and five-year overall survival rates were 52.7% and 32.0% respectively. Recurrence was documented in 31.0% of patients. Within this group of patients, 85.0% experienced locoregional recurrences while 48.1% had distant metastases, with 33.3% having both. Patients with a history of immunosuppression exhibited significantly worse survival (HR=1.92, p=0.019) when compared to immunocompetent individuals. Anatomically, head and neck was the most common location of primary lesions (N=49) followed by extremities (N=31). Comparatively, head and neck primaries predicted significantly poorer overall survival (HR=2.03, p=0.015) in comparison to all other analyzed sites. Nodal involvement (HR=2.56, p<0.001) was also a negative prognostic factor associated with poor overall survival while in our cohort primary tumor size did not predict for nodal involvement (p=0.775).

CONCLUSIONS: This study highlights the role of various factors in determining prognosis in the setting of Merkel cell carcinoma. Here, a history of immunosuppression, nodal involvement, and head/neck primary predicted for decreased overall survival. These findings may be leveraged to guide clinical management of MCC and predictors of clinical outcome.
RADIATION DOSE SAVINGS OF MRA-PE EXAMS

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Support: Shapiro Summer Research Program; Department of Radiology, University of Wisconsin School of Medicine and Public Health

BACKGROUND: An estimated 650,000-900,000 people are diagnosed with pulmonary embolism (PE) each year. Currently, the imaging gold-standard for the diagnosis of PE is computed tomographic angiography (CTA). These scans typically subject patients to 1-10 mSv of radiation, but it is not understood how exposure to these medical doses of radiation affect a patient’s long-term risk of developing cancer. Magnetic resonance angiography (MRA) has been found to possess similar negative predictive values (NPV) compared to CTA and has the benefit of not using radiation. OBJECTIVE: The aim of this study was to show that MRA and CTA exams are no different in their ability to exclude PE and that MRA exams have a significant radiation dose savings, which impacts a patient’s lifetime cancer risk.

METHODS: The electronic medical records (EMRs) for 567 patients that had a MRA performed between 2007-2012 as well as 567 matched patients that had a CTA performed were reviewed and information was collected. For patients with a negative exam for PE, follow up information was reviewed to assess if the patient had a venous thromboembolism (VTE) at intervals of 3, 6 and 12 months post-exam. This data was used to determine the NPV for MRA in excluding PE. For CTA patients in whom the dose-length product (DLP) was not recorded, body cavity sizes were determined. The DLP avoided was calculated using patient age, sex, and body cavity size. This was used to calculate the number of cancers avoided per million. RESULTS: The technical diagnostic rates of MRA-PE and CTA-PE exams were found to be 97.0% and 99.6% respectively. The NPV of MRA-PE exams for VTE was 98.85% (99.8-97.8, 95% C.I) at 3 months, 98.7% (97.7-99.7; 95%CI) at 6 months and 98.0% (97.0-99.0; 95% CI) at 12 months. The estimated DLP for 115 of the CTA-PE patients was 397.52 mGy*cm for males and 364.51 mGy*cm for females. The increase in lifetime cancer risk for these 115 CTA-PE patients was reported and was found to vary with age and gender. An unexpected finding was that 8 MRA-PE patients had a VTE between 1 and 2 years post-exam. CONCLUSIONS: MRA-PE and CTA-PE techniques were found to be similar in their ability to provide diagnostic exams. The NPV of MRA-PE was similar to those reported for CTA-PE exams for the exclusion of PE after 12 months of follow up. Therefore, MRA-PE exams can be used safely to exclude PE. MRA can be beneficial for younger patients and females to avoid medical radiation exposure. The finding of VTEs in 8 patients 1-2 years post-exam suggests that the gold-standard of 1 year as a follow-up time for assessing outcomes in the literature may not be long enough. The use of MRI can have a beneficial effect on reducing the long-term consequences of medical radiation.
A COMPARISON OF SINGLE SHOT ADDUCTOR CANAL BLOCK VERSUS FEMORAL NERVE CATHETER FOR TOTAL KNEE ARTHROPLASTY

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BACKGROUND: Total knee arthroplasty (TKA) is an evolving procedure associated with variable, intense postoperative pain. Continuous femoral nerve catheters (FNC), the current gold standard for postoperative TKA pain, may reduce quadriceps muscle strength and are associated with postoperative falls. Recent studies provide evidence that continuous adductor canal blocks (ACB) following TKA spare quadriceps motor strength and provide similar self-rated pain scores. OBJECTIVE: The aim of this study was to retrospectively compare single-injection adductor canal block (ACB) to continuous femoral nerve catheter (FNC) in a multimodal pain protocol for TKA. METHODS: After IRB approval, a total of 148 continuous patients were reviewed in the ACB group and 149 continuous in the FNB group. Patients who developed medical complications unrelated to anesthesia technique were excluded. Perioperative inpatient and physical therapy notes were reviewed. Statistical difference between groups was defined as a P value of less than 0.05. RESULTS: Baseline patient demographics showed no statistically significant differences between comparison groups. Similarly, there was no statistical difference between groups for mean perioperative opioid usage or self-reported pain scores at any time frame. Physical therapy data suggested a difference in rehabilitation capabilities between the ACB and FNC groups on both postoperative days one and two. Most notably, our data established a difference in the mean hospital length of stay with a time of 2.67 days (±0.56) for the adductor group compared to 3.01 days (±0.57) in the femoral group (p<0.0001). CONCLUSIONS: In conclusion, this study demonstrates that single-injection adductor canal blocks compared to continuous femoral nerve catheters in TKA patients may be superior for postoperative ambulation, knee flexion, and LOS while providing similar pain control and opioid requirements. Femoral nerve catheters, associated with additional costs, management, and risk of fall, did not appear to offer any outcome benefits to multimodal analgesia protocols. Based on the results of the study, we conclude that TKA pain management protocols should consider utilizing single-injection adductor canal blocks for total knee arthroplasties.
FABRICATION OF HIGH FIDELITY SIMULATED BREAST SKIN: A COMPARISON OF THREE SILICONE ELASTOMERS

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Mentor(s): Carla Pugh, MD, PhD

Support: Shapiro Summer Research Program; Department of Surgery; NIH R01EB011524 Grant; University of Wisconsin School of Medicine and Public Health

BACKGROUND: The clinical breast examination (CBE) poses a unique teaching challenge. Simulation technology provides a readily available learning platform for training CBE skills. However, current commercial simulators have a homogenous appearance and consistency that lack realism crucial to achieve competency. OBJECTIVE: The study aim was to assess the visual and tactile realism of three silicone breast skins for improvement of the skin for a CBE simulator. METHODS: Study participants (N=42) included a convenience sample of clinicians: nurses (N=23), medical students (N=9), pharmacy staff (N=6) and physicians (N=3). Participants performed CBEs on three breast models prepared from the same mold but using different silicone materials (Smooth-On, Inc., Easton, PA). Material A was a single layer of SomaFoma 15, material B was a single layer of EcoFlex 30, and material C was three layers, two made with Dragon Skin 10 and a middle layer containing 200% Slacker. On day one, the breast skins were filled with a hard breast positive, and on day two, a soft silicone insert (Nearly Me Technologies, LLC, Waco, TX). Participants completed a survey to assess the realism of the shape, softness and elasticity of the breast and nipple (4-point Likert scale: 0 = Not at all realistic; 3 = Highly realistic) and to rank the models on visual appearance, tactile characteristics and overall realism. Repeated measures ANOVA tested differences in realism. A Chi-Square was performed on the rank questions of visual, realistic feel and overall preference. RESULTS: All forty-two participants (90.4% female) performed CBEs on all three materials. SomaFoma was rated as much more realistic than EcoFlex and Dragon skin for all measures with the exception of the shape of the nipple, p>.05 (Table 1). SomaFoma was ranked higher on visual appearance, tactile characteristics and overall realism compared to EcoFlex and Dragon skin (p<.001). These results were independent of the breast insert under the skin (p>0.05). CONCLUSION: This study was successful at collecting discriminating information about silicone materials used to fabricate CBE simulator skins. Overall, participants preferred the skin comprised of SomaFoma. Review of participant comments suggests that SomaFoma’s superiority may result from the idealistic youthful appearance and overall heat retention at room temperature. Further work is needed to assess the role of how psychosocial factors effect evaluations of simulator realism.
DISEASE MANAGEMENT & FINANCIAL IMPLICATIONS OF ADDITION OF A HEALTH COACH/NUTRITIONIST IN 2 FAMILY MEDICINE CLINICS

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Mentor(s): Dennis J. Baumgardner, MD

Support: Department of Family Medicine Summer Student Research and Clinical Assistantship Program, University of Wisconsin School of Medicine and Public Health; Aurora Health Care

BACKGROUND: More than 80% of healthcare spending is attributed to chronic disease. Maintenance of chronic disease depends on medication adherence and lifestyle changes, and the majority of patients have not met their disease maintenance goals. Self-management support in the form of health coaching has been shown to improve clinical outcomes for patients with chronic disease. Since clinicians' time is limited, other personnel can serve as health coaches to work with patients on lifestyle changes.

OBJECTIVE: This study will examine the impact of a dual-trained Nutritionist/Health Coach on patients' clinical outcomes, and justify that the model is economically beneficial for patients in the Aurora Accountable Care Network (AACN).

METHODS: Patients diagnosed with diabetes, hypertension, hyperlipidemia, metabolic syndrome, or obesity will be referred to the Nutritionist/Health Coach by clinicians in two family medicine clinics. A retrospective chart review will allow comparison of clinical outcomes one year before and after the initial intervention for all patients, and comparison of billing data two years before and after for AACN patients only.

RESULTS: This study is ongoing; so far, 12 patients are enrolled and preliminary data indicate that chronic disease is fairly well-controlled, although all patients are obese (BMI>30).

CONCLUSIONS: Current limitations of the study include low enrollment and variable follow-up. Additionally, encounters with the Nutritionist/Health Coach must be paid for out-of-pocket, which creates bias towards those who can afford it and are highly motivated. The study is still in progress, but potential impact is promising.
LIFE COURSE PREDICTORS OF ASTHMA RISK IN A LARGE CLINICAL POPULATION AGE, SEX, AND BMI

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Support: Department of Family Medicine Summer Student Research and Clinical Assistantship Program, University of Wisconsin School of Medicine and Public Health

BACKGROUND: Current literature indicates the existence of a significant association between asthma prevalence and body mass index (BMI), with a dose-dependency between BMI and asthma control. These associations are modified by sex, possibly due to interactions between sex hormones and immune factors or underlying inflammation linked to both asthma and obesity. Studies indicate a stronger association in pediatric males and adult females. Studies to date have focused on exclusively pediatric or adult populations drawn from relatively small, epidemiological studies. OBJECTIVE: This cross-sectional study examined the effect of sex on the asthma-obesity association across childhood, adolescence, and adulthood – the life course of asthma – in a large clinical population. METHODS: We examined cross-sectional data in the University of Wisconsin Electronic Health Record Public Health Information Exchange (UW eHealth – PHINEX) database for 298,847 patients with at least two encounters at the UW Departments of Family Medicine, Internal Medicine, and Pediatrics clinics from 2007-2012. Prevalence of asthma and uncontrolled asthma were calculated after stratification by age group, sex, and BMI category. RESULTS: 40,011 patients had asthma (prevalence 13.4%), and 6554 had uncontrolled asthma (16.4% of patients with asthma). Asthma prevalence was higher in obese pediatric males (25.7% [95% CI 23.7, 27.7]) compared to obese pediatric females (19.2% [17.2, 21.2]) and higher in obese adult females of reproductive age (22.6% [21.8, 23.4]) compared to obese males of the same age (15.4% [14.6, 16.2]). Odds ratios of the association between obesity and asthma were similar (~1.5) for pediatric males and females but were significantly greater for adult pre-, peri-, and post-menopausal females (respectively 1.8 [1.7,1.9]; 2.1 [1.9,2.2]; 2.0 [1.8, 2.1]) than for males of corresponding age (respectively 1.4 [1.2, 1.5]; 1.5 [1.3, 1.7]; 1.4 [1.2, 1.5]). Similar but statistically non-significant patterns were observed for uncontrolled asthma. CONCLUSIONS: These data suggest an effect of age and sex on the association between asthma and obesity in a large, clinical data set supporting previous data implicating an effect of female sex hormones and obesity on asthma prevalence.
REVIEW OF THE ARTERIOVENOUS MALFORMATION STEREOTACTIC
RADIOSURGERY EXPERIENCE AT THE UNIVERSITY OF WISCONSIN

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Mentor(s): Edward Bender, PhD; Steven Howard, MD, PhD

Support: Shapiro Summer Research Program; Department of Human Oncology, University of Wisconsin School of Medicine and Public Health

BACKGROUND: Stereotactic radiosurgery (SRS) is a well-established, minimally invasive treatment option for patients diagnosed with cerebral arteriovenous malformations (AVMs). However, there are few reports on the long-term therapeutic effects and toxicities of treatment using linear accelerator (linac)-based radiosurgery. OBJECTIVE: To analyze the treatment parameters, toxicity, and outcomes of patients who received linac-based SRS for cerebral AVMs at the University of Wisconsin. METHODS: Patients receiving SRS for cerebral AVMs between 2000 and 2012 were analyzed retrospectively. Treatment parameters were collected from the Pinnacle treatment planning system. Acute and long-term toxicities were recorded according to Common Terminology Criteria for Adverse Events version 4.0. RESULTS: A total of 46 patients were analyzed with a median age of 36 years and median follow up of 4.4 years. Patient distribution by Spetzler-Martin grade was 22.7% grade II, 43.2% grade III, and 34.1% grade IV. The mean presenting nidus size was 2.6 cm and 87% resided in eloquent locations. The median prescription volume was 1.07 cc treated to a median prescription dose of 17 Gy (range 15-21) prescribed to the 65% isodose line (range 50-80). The median time to obliteration was 2.5 years, with 29% of patients achieving radiographic obliteration. Three patients experienced new-onset seizures post-SRS. Nine patients (19.6%) experienced new neurological deficits (≤ grade II) post-SRS, of which 3 persisted. There were 8 post-SRS hemorrhages (median grade II), one of which was fatal. One possible secondary malignancy was observed. Univariate analysis revealed neurological deficits were related to the 12 Gy volume, minimum planning target volume dose, prescription isodose line, prescription volume, and maximum dimension of the prescription volume. CONCLUSIONS: Significant hemorrhage and radiation injuries can be appreciated with long-term observation. Future work may focus on relating post-SRS bleeds to treatment parameters as well as conducting an imaging review for toxicities and recurrence. The single fraction cases in this study could be compared to outcomes and toxicities of fractionated cases. Additionally, 7 patients in this study received subsequent radiosurgeries on which additional analysis could be performed.
ANTITUMOR ACTIVITY OF INDOLE-3-CARBINOL AND 3,3'-DIINDOLYL METHANE IN COLORECTAL CANCER

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Support: Shapiro Summer Research Program; Kennedy Lab National Institutes of Health R01 Grant, Department of Surgery, University of Wisconsin School of Medicine and Public Health

BACKGROUND: Indole-3-carbinol (I3C) is a metabolite of glucobrassicin, a phytochemical found in cruciferous vegetables, and 3,3'-Diindolylmethane (DIM) is its major gastric acid condensate. There is evidence that diets high in cruciferous vegetables can lower risk for certain types of GI tumors. Both I3C and DIM have been found to modulate cell fate in a range of cancers. OBJECTIVE: We hypothesize that I3C and DIM will induce colon cancer cell death in vitro, and that dietary I3C will be chemoprotective against colorectal tumorigenesis in a mouse model. METHODS: DLD-1 Duke’s type C colorectal adenocarcinoma cells were propagated. Cells were treated with I3C or DIM. The in vitro cell viability and apoptosis assays were conducted with CellTiter-Fluor and Caspase-Glo 3/7 (Promega Madison, WI). The in vivo murine protocol consisted of C57BL/6 wild type mice. A two-stage initiation-promotion protocol using azoxymethane (AOM) and dextran sodium sulfate (DSS) was employed as a model of colorectal tumorigenesis. During and after AOM/DSS, mice were fed with either base diet or diet enriched with I3C. 16 weeks after AOM/DSS discontinuation, mice were sacrificed, and colon tumor incidence and multiplicity were assessed at necropsy. Statistical analysis was performed with MSTAT and Excel for Macintosh. RESULTS: We found a dose and time-dependent decrease in DLD-1 cell viability following both I3C (19% decrease from control p<0.05) and DIM (67% decrease from control p<0.001) treatment. This decrease seemed to be mediated by apoptosis, as both I3C (164% increase from control p<0.05) and DIM (900% increase from control p<0.001) induced apoptotic activity in vitro. In wild type mice, an I3C-enriched diet attenuated the effects of the tumorigenic protocol as evidenced by a decrease in both tumor incidence (8% in I3C diet VS 89% in base diet p<0.001) and tumor multiplicity (3.73 ave tumor/base diet mouse VS 0.125 ave tumor/I3C diet mouse p<0.05). CONCLUSIONS: I3C induces colon cancer cell death via apoptosis and DIM has a similar magnified effect. Dietary I3C is chemoprotective from colorectal tumorigenesis in vivo. Continued in vitro studies are planned to investigate the pathway that mediates the effects of I3C and DIM on colon cancer cells in vitro. Current In vivo work is focusing on real-time reversal of colon tumorigenesis with dietary I3C established via colonoscopy. The role of I3C and its metabolites as chemopreventives in the large bowel demands further study.
3-DIMENSIONAL HIGH RESOLUTION MANOMETRY OF THE UPPER ESOPHAGEAL SPHINCTER

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Support: Shapiro Summer Research Program; NIH grant R33DC0111130, Department of Surgery, University of Wisconsin School of Medicine and Public Health

BACKGROUND: High-resolution manometry (HRM) has proven useful in identifying disordered swallowing patterns, especially in quantifying pharyngeal and upper esophageal sphincter (UES) physiology. HRM is limited, however, by circumferential averaging of pressures on each sensor, resulting in limited pressure information from the asymmetrical pharyngeal anatomy. OBJECTIVE: This study applied 3-Dimensional HRM to investigate asymmetrical pressure patterns within the UES during swallowing and non-swallowing tasks. METHODS: UES pressure patterns at rest, during the valsalva maneuver, and during water swallowing were collected from 8 healthy subjects using a 3-Dimensional HRM catheter. RESULTS: ANOVA revealed a significant main effect of circumferential direction on pressure while at rest (p<0.001) and approached significance during the valsalva maneuver (p=0.057); pressure was greater in the anterior and posterior portions of the UES versus lateral positions. An effect of sensor level on coefficient of variation of pressure approached significance (p=0.059). During swallowing, circumferential direction had a significant main effect on pressure immediately before UES pressure dropped (p=0.001), while the UES was open (p=0.01), and at UES closure (p<0.001). There was also a significant main effect of sensor level on pressure immediately before UES pressure dropped (p=0.32) and at UES closure (p<0.001). Anterior and posterior pressures were again greater than lateral pressures. CONCLUSION: These results confirm that UES pressures measured by traditional HRM are composed of significantly differing pressure patterns, with the majority of the total pressure governed by the anterior and posterior regions. Improved understanding of UES pressure in a 3-Dimensional space will lead to more sophisticated treatments of pharyngeal and UES dysfunction.
MEMORY T CELL INFILTRATION IN HEPATIC COLORECTAL ADENOCARCINOMA METASTASES

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**Support:** Shapiro Summer Research Program; Department of Surgery NIH T35 DK062709 grant, University of Wisconsin School of Medicine and Public Health

**BACKGROUND:** Previous studies in primary colorectal adenocarcinoma have suggested that intratumoral infiltration by memory T cells may be strongly protective against the likelihood of metastatic disease dissemination. The prevalence and prognostic significance of memory T cell infiltration within metastatic foci is unknown. We hypothesized that memory T cell infiltration within resected hepatic colorectal metastases would be associated with favorable oncological characteristics. **METHOD:** Frozen samples from resected hepatic colorectal adenocarcinoma metastases were obtained from a prospectively maintained and institutionally-approved tumor bank. Thawed samples were fixed and analyzed by hematoxylin/eosin staining and by immunochemical analysis for expression of CD3 and CD45RO. CD3 (T cell) and CD45RO (memory T cell) expression was quantified under low power magnification by two blinded observers using a two-tiered low versus medium/high grading system. Clinicopathological and survival data were obtained from a prospectively-maintained institutional database. The approximate risk of disease recurrence was stratified using the Memorial Sloan-Kettering Cancer Center Clinical Risk Score (CRS). Comparison of categorical variables was performed using chi-square analysis, and differences in Kaplan-Meier estimates of overall and recurrence-free survival were compared using the log-rank test. **RESULTS:** Samples from ten resected tumors were obtained for this preliminary analysis. Eight tumors exhibited medium/high CD3 expression and 6 tumors exhibited medium/high CD45RO expression. The prevalence of T cell infiltration was somewhat higher among patients with an MSKCC Clinical Risk Score (CRS) ≥2 (100%) than patients with a CRS < 2 (33%) (p=0.07). The prevalence of memory T cell infiltration was higher among patients with a CRS ≥2 (86%) than patients with a CRS < 2 (0%) (p=0.03). T cell and memory T cell infiltration were not associated with differences in overall or recurrence-free survival. **CONCLUSION:** There is a high prevalence of memory T cell infiltration within resected hepatic colorectal adenocarcinoma metastases. Contrary to our hypothesis, intratumoral memory T cell infiltration alone is not obviously associated with differences in survival outcome, and its prevalence may be paradoxically higher in conditions of adverse tumor characteristics. Ongoing studies will explore the hypothesis that intrametastatic memory T cell infiltration may exert a protective influence that mitigates the prognostic impact of adverse tumor characteristics.
THE USE OF INTRAOPERATIVE TRIGGERED ELECTROMYOGRAPHY TO DETECT MISPLACED PEDICLE SCREWS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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BACKGROUND: Insertion of instruments or implants into the spine carries a risk of injury to neural tissue. Triggered electromyography is an intraoperative neuromonitoring technique that involves electrical stimulation of a tool or screw and subsequent measurement of muscle action potentials from myotomes innervated by nerve roots near the stimulated instrument. **OBJECTIVE:** To determine the ability of triggered electromyography to detect misplaced pedicle screws. **METHODS:** Articles were searched in U.S. National Library of Medicine, the Web of Science Core Collection database, and the Cochrane Central Register of Controlled Trials. Meta-analysis of pedicle screw studies was done on a per-screw basis to determine the ability to detect misplaced pedicle screws. Sensitivity, specificity, and receiver operating characteristic area under the curve (AUC) were calculated overall and in subgroups. **RESULTS:** Twenty-six citations were included in the systematic review. Eighteen pedicle screw studies were analyzed in the meta-analysis, with a total of 2,932 patients and 15,065 screws. The overall sensitivity of triggered electromyography in detecting misplaced pedicle screws was 0.78 and the specificity was 0.94. Overall receiver operating characteristic area under the curve (AUC) was 0.96. A triggered electromyography threshold of 10-12mA (AUC 0.99) and a pulse duration of 300μS (AUC 0.97) provided the most accurate testing parameters for detection of misplaced screws. Screws were the most accurate conductor (AUC 0.98). **CONCLUSIONS:** Triggered electromyography has a very high specificity but only fair sensitivity for detecting misplaced pedicle screws.
A COMPARISON OF EXPLICIT CRITERIA FOR DETERMINING APPROPRIATENESS OF ANTIBIOTIC PRESCRIBING IN NURSING HOMES

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BACKGROUND: Antibiotics are the most frequently prescribed medications in long-term care facilities (LTCFs). Many cases have been found to be inappropriate, often due to difficulty in diagnosis. Explicit criteria were developed to assist in making clinical decisions. The McGeer definitions were developed in 1991 to be used as surveillance definitions and the Loeb Minimum Criteria (LMC) were developed in 2001 as a diagnostic tool. Both criteria are commonly used to assess appropriateness in prescribing events, but to our knowledge the level of agreement between these two sets of criteria is unknown. OBJECTIVE: To examine the level of agreement between the McGeer definitions and the Loeb Minimum Criteria to assess appropriateness of antibiotic prescribing events. METHODS: A comparative analysis of the McGeer and Loeb criteria was performed using data abstracted from health records from five nursing homes (NH) in the Madison area. Antibiotic prescribing events were only analyzed for suspected urinary tract infections (UTI), respiratory tract infections (RTI) and skin/soft tissue infections (SSTI). Antibiotic courses initiated in the hospital and emergency department (ED) were excluded from further analysis. Each prescribing event was assessed for appropriateness separately using both McGeer and Loeb criteria. The overall level of agreement between the two sets of criteria was assessed using kappa statistics, stratified by indication for antibiotic initiation (UTI vs. RTI vs. SSTI). RESULTS: Of the 1108 antibiotic courses initiated in the 16-month period, 504 were initiated at the NH and prescribed for UTI, RTI or SSTI. Of the evaluable cases, 32.9% met McGeer definitions for infection and 36.9% met Loeb Minimum Criteria (LMC), with a kappa value of 0.346 representing the level of agreement. Of all the NH cases, 49.8% were found to meet either criteria and thus were determined to be appropriate. SSTI prescribing events had the highest proportion of appropriateness, with 67.9% meeting either McGeer or LMC. UTI events had the highest level of agreement (k=0.555) between the sets of criteria. CONCLUSIONS: Documentation supporting the appropriateness of antibiotic prescribing in NHs is frequently absent, regardless of explicit criteria employed. The overall level of agreement between the McGeer and Loeb criteria is low evidenced by low kappa coefficients. Determining which set of criteria has more utility to optimize and monitor quality of antibiotic prescribing in NHs requires additional study.
BACKGROUND: There is limited research on Sports-Related Concussions (SRC) in young athletes. The Child SCAT3 is a newly developed sideline assessment tool that measures symptoms, cognitive function, and balance in pre-adolescents (age 5-13). Its psychometric properties have not been established.

OBJECTIVE: To collect normative baseline Child SCAT3 data for young athletes ages 5-13 years.

METHODS: Eligible participants were any male or female, ages 5-13, participating in an organized sport (basketball, soccer, baseball, swimming). Participants were excluded if they were non-English speakers, had a lower leg injury within the past two months, or been treated for SRC within the past month. Testing was performed on-site at various sporting event locations in summer 2014. The Child SCAT3 assesses: Maddock’s score (MS, 0-4); number (CSI, 0-20) and severity (CSS, 0-60) of symptoms reported by the child and parent separately; orientation (OR, 0-4); immediate memory (IM, 0-15); concentration (CON, 0-6); balance on hard surface and foam (BESS-HS, 0-10; BESS-F, 0-10); tandem gait (TG, seconds); coordination (COR, 0-1); delayed recall (DR, 0-5). Summary statistics and t-tests were calculated for each test component.

RESULTS: A total of 478 athletes (244 males, 234 females, 196 5-9 year olds, 282 10-13 year olds, mean age ± SD = 9.89±1.94 years) were enrolled and completed testing. Component scores (mean ± SD) were: MS=3.65±0.66, Child CSI=9.18±5.27, Child CSS=13.50±9.71, Adult CSI=7.90±5.73, Adult CSS=10.25±7.94, OR=3.24±1.05, IM=13.46±1.88, CON=3.98±1.29, BESS-HS=0.96±1.33, BESS-F=3.32±2.41, TG=16.37±5.92, COR=0.91±0.28, DR=3.62±1.28. There were no differences in any composite test score based on previous history of SRC. Males and younger children (5-9yo) on average had higher symptom scores, lower cognitive scores, and more balance errors than females and older children (10-13yo) respectively (p<0.05). Over one-third of children did not know the date. Fifty six children could not correctly name all days of the week backward (84% were 5-9yo). Only 18% of 5-9yo could correctly repeat more than four digits backwards.

CONCLUSIONS: This study reports normative baseline Child SCAT3 values in a cohort of pre-adolescent athletes. There were significant differences in symptom, cognitive, and balance scores based on gender and age but not previous SRC. These normative values may help health care providers better interpret Child SCAT3 scores of concussed young athletes.
A PERIPHERAL NERVE WINDOW FOR CHRONIC IMAGING OF THE SCIATIC NERVE IN RATS

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Mentor(s): Samuel Poore, MD, PhD

Support: Shapiro Summer Research Program; Department of Surgery, Division of Plastic & Reconstructive Surgery, University of Wisconsin School of Medicine and Public Health

BACKGROUND: In vivo imaging is a useful tool to visualize the anatomy and physiology of biological systems, allowing the study of systems in a natural setting with minimal tissue disturbance. Chronic, indwelling in vivo imaging devices are being successfully used to study the brain, spinal cord, and mammary tissue in animal models. However, due to the lack of bone anchoring and difficulty accessing the deep nerve tissue, there are no current devices to chronically image biological processes in the peripheral nervous system under both non-pathological and pathological conditions (e.g. nerve regeneration). OBJECTIVE: The objective of this study was to develop a chronic and stable peripheral nerve window (PNW) for non-invasive imaging of the rat sciatic nerve for an extended duration.

METHODS: PNW Design – The PNW consists of a top device made of acrylonitrile butadiene styrene (ABS), which was printed on a 3-dimensional printer, attached to a quartz glass window. The top device allows the PNW to be sutured directly into tissue overlying the nerve. Underlying the nerve was a base of polydimethylsiloxane (PDMS), which was also 3D printed with a groove for the sciatic nerve to rest in. Surgical Procedure – Rats were anesthetized and the biceps femoris separated from the tensor fascia latae (TFL) to expose the sciatic nerve. The nerve was elevated above the muscle, and the biceps femoris and TFL were sutured together. A base of PDMS was passed underneath the nerve to hold it in a subcutaneous plane. The PNW was placed directly over the elevated nerve and sutured to the skin, which allowed visualization of the nerve through the window. Imaging Procedure – Bright field images, fluorescent images, and videos of the sciatic nerve were obtained three times a week using an upright fluorescent stereoscope. Vasculature was fluorescently labeled using a fluorescein isothiocyanate labeled dextran injection into the tail vein. RESULTS: Using the PNW we successfully imaged the sciatic nerve and vasculature for two weeks. Both the fluorescent and the bright-field images clearly demonstrated stable anatomy of the sciatic nerve, robust vasculature with “real-time” movement and passage of red-blood cells through individual capillaries and the clear visualization of the accompanying collagenous and muscular components. CONCLUSIONS: The peripheral nerve window is a unique device allowing for chronic in-vivo imaging of the sciatic nerve in rats, and has implications for the study of pathological processes such as nerve regeneration following injury. The unique design of the device will easily facilitate the integration of micro-electrode neural interfaces and/or microfluidic channels while allowing simultaneous real-time imaging of the nerve.
INDEPENDENT PREDICTORS OF POSTOPERATIVE ILEUS DEVELOPMENT

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Support: Department of Surgery NIH T35 DK062709 grant, University of Wisconsin School of Medicine and Public Health

BACKGROUND: Postoperative ileus has a significant impact on patient wellbeing, and with a 15% incidence in colectomy patients, costs US hospitals more than 750 million dollars a year. While some causative mechanisms have been identified, little is known about what places patients at risk for ileus.

OBJECTIVE: We aimed to identify patient, clinical, and surgical factors that independently affect the development of prolonged postoperative ileus.

METHODS: Patients who underwent elective surgery between 2011 and 2012 were identified from the colectomy-specific ACS-NSQIP database. We performed descriptive statistics and evaluated demographics, comorbidities, health indicators, preoperative treatments, and operative characteristics as independent risk factors for ileus using multivariate analyses. All analyses were performed with SPSS version 22. A p-value < 0.05 was considered significant for the purposes of this study.

RESULTS: We included 9734 patients in this analysis. Of the patients in this study, 1364 (14%) were found to have a postoperative ileus. Patients who developed an ileus were more likely to develop an postoperative complication (26.4% vs 9.9%, p < 0.001). In addition, patients who suffer post-operative ileus are significantly more likely to be readmitted (20% vs 13%, p < 0.001) and more likely to require reoperation (37% vs 13%, p < 0.001) compared with patients without ileus. Independent risk factors for ileus included demographic and preoperative factors including older patient age (OR 1.95, 95% CI 1.58-2.42), male gender (OR 1.41, 95% CI 1.24-1.60), obesity (OR 1.32, 95% CI 1.12-1.56), preoperative chemotherapy (OR 1.53, 95% CI 1.21-1.94), preoperative ascites (OR 1.86, 95% CI 1.07-3.22), preoperative sepsis (OR 1.74, 95% CI 1.32-2.29), and smoking (OR 1.20, 95% CI 1.02-1.41). Intraoperative and perioperative factors included lack of oral antibiotics (OR 1.29, 95% CI 1.10-1.50), lack of mechanical bowel preparation (OR 1.15, 95% CI 1.01-1.32), open approach (OR 2.04, 95% CI 1.77-2.36), and long operation times (OR 1.63, 95% CI 1.36-1.96).

CONCLUSION: We identified a number of modifiable risk factors for development of ileus including smoking, weight loss, preoperative oral antibiotics, mechanical bowel preparation, and surgical approach. Preoperative modification of risk factors for ileus may not only improve patients’ quality of life, but may also influence outcomes such as postoperative complications, readmission, and reoperation.
PREDICTORS FOR A SURGICAL APPROACH TO SUBSTERNAL GOITER

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Support: Shapiro Summer Research Program ; Department of Surgery, University of Wisconsin School of Medicine and Public Health

BACKGROUND: The thoracic approach to substernal goiters (SSG) is associated with greater morbidity. Accordingly, predicting which patients will require a sternotomy is imperative for pre-operative planning.

OBJECTIVE: There are two objectives of this study. The first is to compare the pre-operative and post-operative characteristics for three groups of patients: those with SSG requiring a sternotomy, those with SSG not requiring a sternotomy, and patients with large goiters but not substernal. The second is to identify predictors for sternotomy as a surgical approach for the removal of SSG.

METHODS: A retrospective review of the Endocrine Surgery Database at UW Hospital and Clinics was performed. Patients were included if they had large (>100g) thyroids or any mention of a substernal component during their pre-operative workup. Between 1995 and 2013, 220 patients met these criteria. Comparisons were made between patients who had a SSG and those whose thyroid glands were contained entirely within the neck, or a cervical goiter (CG). Further comparisons were made between those with a SSG who required sternotomy to excise their thyroid and those who underwent cervical incision only.

RESULTS: Of the 220 patients, 127 (58%) patients had SSG, of whom 7 (5.5%) required sternotomy. On bivariate analysis, there were no differences in gender, BMI, preoperative symptomatology, postoperative complications or length of stay for patient who had SSG vs CG. Patients with SSG were older (62 + 15 vs 51 + 17 years, p<0.001), more likely to undergo preoperative CT scanning (69% vs. 31%, p<0.001), and less likely to have preoperative hyperthyroidism (10% vs. 29%, p<0.001). Patients who underwent a sternotomy showed no difference in terms of gender, age, BMI, preoperative hyperthyroidism, or postoperative complications than those with SSG who underwent cervical incision thyroidectomy. All patients who underwent sternotomy underwent preoperative CT scanning, and they were more likely to have preoperative symptoms of chest pressure and voice complaints. Sternotomy took an average of 2 hours longer than a cervical incision, was associated with significantly more blood loss (600 + 408 vs. 190 + 118, p=0.04), and a longer length of stay (3.1 + 0.9 vs. 1.8 + 1.6 days, p=0.03) than cervical thyroidectomy.

CONCLUSIONS: Patients who required sternotomy were more likely to present complaining of chest pressure and voice complaints, which can indicate that sternotomy may be required. SSG rarely required sternotomy, and although sternotomy is more complex an operation for thyroidectomy, post-operative complaints were similar to those patients with SSG excised through cervical incision alone.
IMPROVING IRON DEFICIENCY SCREENING IN PEDIATRIC PRIMARY CARE

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Mentor(s): Pamela J. Kling, MD

Support: Shapiro Summer Research Program; UW Cardiovascular Research Center, University of Wisconsin School of Medicine and Public Health

BACKGROUND: In 2010, the American Academy of Pediatrics (AAP) recommended universal screening for anemia at one year of age. This contrasts with previous AAP statements supporting risk factor-based screening. This new recommendation stems from research revealing long-term neurocognitive dysfunction in infants with untreated iron deficiency anemia (IDA). Since the statement, there have been a series of educational efforts at the University of Wisconsin (UW), including two pediatric grand rounds and one pediatric quality improvement (QI) retreat. These efforts all focused on the importance of complying with the AAP recommendation. The Department of Family Medicine (DFM) did not undertake any educational efforts. Women, Infants, and Children (WIC) requires anemia screening, but access to results is restricted.

OBJECTIVE: To measure IDA screening rates and subsequently identify barriers to and facilitators of IDA screening in university-based ambulatory practices. To investigate the hypothesis that implementation of a “Best Practice Alert” (BPA) within the UW electronic medical record (EMR) would improve screening rates substantially, but that screening rates will still require bolstering using other means.

METHODS: The UW IRB approved this QI project. We determined the IDA screening rate for children with a well-child visit (WCV) aged nine to thirteen months in 2013 using the EMR servicing UW Pediatric and DFM clinics. In early 2014, a BPA was incorporated into the EMR for children between one and three years of age. This alert suggests that the provider screen the patient for anemia. After the alert was incorporated, screening rates were again determined. Analyses used Chi Square tests.

RESULTS: Overall screening rates before the BPA were 48.2%. Before the BPA, screening rates were 42.9% in DFM clinics and 51.2% in Pediatric clinics (p<0.05). Overall screening after the BPA improved to 72.7% (p<0.0001). After the BPA, screening rates were 62.4% in DFM clinics and 78.6% in Pediatric clinics (p<0.05). Pre/post-BPA rates more than doubled in Pediatric clinics (p<0.0001) and in DFM clinics (p<0.0001).

CONCLUSIONS: Guideline compliance in Pediatric clinics was higher than in DFM clinics, perhaps due to efforts set forth by the AAP, departmental educational efforts, and the QI retreat. The BPA more than doubled compliance, but post-BPA compliance was still only 72.7%. Any additional screening by WIC was not accounted for in the study. Further work is needed to improve screening endorsement in providers. Access to WIC data could improve our reported screening rates.
CONCUSSION INCREASES LOWER EXTREMITY MUSCULOSKELETAL INJURY RISK AFTER RETURN-TO-PLAY AMONG COLLEGIATE ATHLETES

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Support: Shapiro Summer Research Program; Department of Orthopedics and Rehabilitation, University of Wisconsin School of Medicine and Public Health

BACKGROUND: Previous studies have identified abnormalities in brain and motor functioning after concussion that persist well beyond a period of observed clinical recovery. Recent work suggests subtle deficits in neurocognition may be associated with impaired neuromuscular control. Thus, current return-to-play guidelines, which are based on resolution of standard clinical symptoms and signs, may put an athlete at increased risk of lower extremity musculoskeletal injury. OBJECTIVE: To determine the risk of lower extremity musculoskeletal injury during the 90-day period following return-to-play from concussion in a cohort of NCAA Division I collegiate athletes. METHODS: 87 cases of concussion among 75 athletes (58 men; 17 women) participating in NCAA Division I football, soccer, hockey, softball, basketball, wrestling, and volleyball at a single institution from 2011-2014 were included. The 90-day period following return-to-play for each case of concussion was reviewed for time-loss from acute lower extremity musculoskeletal injury, defined as acute fractures, muscle strains/tears, or ligament sprains/rupture of the hip, groin, thigh, knee, shin, ankle, and foot. Each 90-day period following return-to-play was matched to the same 90-day period in up to 3 controls. Control athletes without a history of concussion in the previous year were matched to concussed athletes by: 1) sport team/gender, 2) games played, and 3) position. A total of 189 control (142 men; 47 women) 90-day periods were reviewed for time-loss injury. Conditional logistic regression was used to assess the association between concussion and subsequent risk of acute lower extremity musculoskeletal injury. RESULTS: The incidence of acute lower extremity musculoskeletal injury was greater among concussed athletes (15/87; 17%) as compared to matched controls (16/189; 8%). The odds of sustaining an acute lower extremity musculoskeletal injury during the 90-day period following return-to-play were 2.66 times higher in concussed athletes than controls during the same 90-day period (OR: 2.66; 95% CI= 1.12, 6.28; p=0.026). CONCLUSIONS: Concussed athletes are at an increased risk of acute lower extremity musculoskeletal injury during the 90-day period following return-to-play.
TRENDS IN MALIGNANT MELANOMA INCIDENCE, SURVIVAL, AND MORTALITY IN WISCONSIN, 1968-2011

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Mentor(s): Mark Albertini, MD; Patrick Remington, MD, MPH

Support: Shapiro Summer Research Program; Department of Medicine, University of Wisconsin School of Medicine and Public Health

BACKGROUND: According to the Centers for Disease Control and Prevention, skin cancer is the most common form of cancer in the US. Malignant melanoma is the least common but deadliest of the three most common skin cancers and is associated with exposure to ultraviolet light and genetic factors that control characteristics such as lighter skin color, many large nevi, blue eye color, and red or blonde hair color. Alarmingly, despite decreased incidence rates of most other types of cancer, melanoma incidence and mortality rates have increased rapidly in recent decades. OBJECTIVE: To assess trends in malignant melanoma incidence, survival, and mortality in Wisconsin. METHODS: Incidence data for Wisconsin were obtained from the Wisconsin Cancer Reporting System Bureau of Health Information using Wisconsin Interactive Statistics on Health, while incidence data for the US were obtained from the Surveillance, Epidemiology, and End Results (SEER) system. The mortality to incidence ratio \[1 - \text{mortality/incidence}\] was used as a proxy to estimate relative 5-year survival in Wisconsin, while observed 5-year survival rates for the US were obtained from the Surveillance, Epidemiology, and End Results (SEER) system. The mortality to incidence ratio \[1 - \text{mortality/incidence}\] was used as a proxy to estimate relative 5-year survival in Wisconsin, while observed 5-year survival rates for the US were obtained from the Surveillance, Epidemiology, and End Results (SEER) system. The mortality to incidence ratio \[1 - \text{mortality/incidence}\] was used as a proxy to estimate relative 5-year survival in Wisconsin, while observed 5-year survival rates for the US were obtained from the Surveillance, Epidemiology, and End Results (SEER) system. RESULTS: During the past decade, malignant melanoma incidence rates increased 57% in Wisconsin (from 12.1 to 19.0 cases per 100,000); versus a 33% increase (from 20.9 to 27.7 cases per 100,000) in the US during that same time period. The greatest Wisconsin increase in incidence was 45-64 years (females) and 65 years of age or older (males). Overall 5-year survival in Wisconsin rose 10% (from 77% to 85%) and was unchanged at 82% in the US. Wisconsin overall mortality rates were unchanged at 2.8 deaths per 100,000; compared to a 10% increase in the US (from 3.1 to 3.4 deaths per 100,000). Wisconsin mortality rates improved for females age 45-64 and for males age 25-44. CONCLUSIONS: Despite improvements in malignant melanoma survival rates, increases in incidence represent a major public health challenge for physicians and policy makers.
PROMOTING WALKING IN SAUK COUNTY, WISCONSIN

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BACKGROUND: Physical inactivity is a major problem in the United States. Community leaders in Sauk County, Wisconsin developed a community health improvement plan with a goal to promote walking clubs—an evidence-based intervention—to improve physical activity levels in the County. OBJECTIVE: The primary objective of this study was to assess physical activity behaviors and attitudes of patients and physicians toward walking clubs and social networking to promote physical activity. METHODS: This cross-sectional study was performed during the summer of 2014 at the Sauk Prairie Clinic in Sauk City, Wisconsin. Surveys were developed using validated questions developed by the CDC to assess patients’ (n=210) and physicians’ (n=16) physical activity knowledge, attitudes, and behaviors. RESULTS: Overall, 48% of patients and 12% of physicians did not meet physical activity standards set by the CDC. Among patients, those who were overweight were less likely to participate in a PA club (11%), compared with those who were normal (20%) or underweight (32%) (p<0.04). However, 86% of patients did not want to join a walking club. Results also suggest that physical activity patterns are affected by the people in the patient’s social network. CONCLUSIONS: Although interventions to promote walking in clubs are efficacious at increasing physical activity, their use is uncommon. If Sauk County is to be successful in promoting physical activity through walking clubs, their use will need to be promoted in the community and clinical settings.
OMISSION OF PHYSICAL THERAPY RECOMMENDATIONS FOR PATIENTS TRANSITIONING FROM THE HOSPITAL TO SUB-ACUTE CARE

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BACKGROUND: While hospital care is delivered in a multidisciplinary fashion, hospital discharge communication typically involves only the physician members of the care team. The discharge summary/orders is the primary form of discharge communication for patients transitioning from the hospital setting to sub-acute care facilities. However, sub-acute care nurses in focus groups report that physical therapy (PT) recommendations are routinely omitted in the discharge summary/orders, yet these recommendations are critical for the high-risk patients (i.e., older adults, stroke and hip fracture patients) who require intensive rehabilitation. Additionally, they report that these omissions contribute to patient care delays, safety issues, and an increased rehospitalization risk. Although sub-acute care nurses perceive poor hospital discharge communication as a problem, it is not known how often PT recommendations are omitted from the discharge summary/orders. OBJECTIVE: Our objective was to quantitatively assess the communication of PT recommendations in hospital discharge summaries/orders, targeting (1) patient safety restrictions or precautions (e.g., fall risk), (2) level of assistance with sitting to standing (e.g., up with two), and (3) medical assistive devices (e.g., walker). METHODS: Retrospective medical record abstraction comparing recommendations made by the inpatient physical therapists in the PT consultation note to orders included in hospital discharge summary/orders for all hospitalized adult patients (n=613, average age 71) with primary diagnoses of stroke or hip fracture who received a PT consultation and were discharged to a sub-acute care facility from 2006-2008 from one large academic hospital. RESULTS: Overall, PT recommendations were completely omitted in 53% (322/611) and partially omitted in 47% (286/611) of patients; alarmingly, less than 1% (3/611) of patients had no omissions. Recommendations for patient safety restrictions or precautions were completely omitted in 54% (316/584) of patients. Recommendations for level of assistance with sitting to standing were completely omitted in almost 100% (535/537) while recommendations for medical assistive devices were completely omitted in 77% (409/532) of patients. CONCLUSION: PT recommendations made during a hospital stay for high-risk patients are routinely omitted from hospital discharge communications to sub-acute care facilities. Interventions to improve this communication are needed.
PROGNOSTIC FACTORS FOR NON-DIAGNOSTIC RENAL MASS BIOPSY

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Support: Shapiro Summer Research Program; Department of Urology, University of Wisconsin School of Medicine and Public Health

BACKGROUND: Percutaneous renal mass biopsy (RMB) may be used to guide treatment decisions, but approximately 15% of RMB yield non-diagnostic results and do not benefit the patient. The objective of this study is to identify patient and tumor characteristics that are associated with obtaining non-diagnostic RMB. OBJECTIVE: Prebiopsy anatomic and clinical factors can be used to identify patients at highest risk for non-diagnostic RMB. METHODS: After IRB approval, data were reviewed for all patients treated with RMB at the University of Wisconsin Hospital from 2000 to 2014 for whom prebiopsy imaging available. Univariable and multivariable logistic regression was performed to identify predictors of non-diagnostic RMB. Variables considered in the analysis included: imaging modality, type of biopsy, laterality, proximity to adjacent organs, tumor diameter, presence of radiologic enhancement, fat, calcification, necrosis, or cystic features, position within the kidney, body mass index, and skin to tumor distance. RESULTS: Of 565 biopsies performed on 515 patients, 83 (14.7%) were non-diagnostic after pathologic analysis. Median tumor size was 2.75cm (IQR 2.05-4.25) with 72.7% of the lesions <4cm. Cystic features were observed in 14.7% of patients and the non-diagnostic rate for cystic masses was 39.8%. Radiologic enhancement >20 HU was seen in 84.8% of lesions and median skin-to-tumor distance was 10cm (IQR 8.5-11). Independent predictors of non-diagnostic RMB as determined by multivariable logistic regression analyses were cystic features (OR 4.42, 95% CI 2.38-8.21, p < 0.0001), left-sidedness (OR 1.75, 95% CI 1.02-2.98, p = 0.04), tumor diameter ≤4cm (OR 2.66, 95% CI 1.27-5.55, p = 0.01), radiographic enhancement (OR 2.84, 95% CI 1.26-6.41, p = 0.01), and skin-to-tumor distance ≥13cm (OR 2.40, 95% CI 1.15-5.01, p = 0.02). CONCLUSIONS: Five predictors of non-diagnostic findings from RMB have been identified including: cystic features, left-sidedness, tumor diameter, radiologic enhancement ≤20 HU, and skin-to-tumor distance ≥14cm. These criteria can be used to identify patients with a significant risk for a non-diagnostic biopsy result and improve patient selection for RMB.
PREDICTIVE CATEGORIZATION OF HOT SPOTTERS IN THE EMERGENCY DEPARTMENT

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Support: Shapiro Summer Research Program; Department of Medicine, University of Wisconsin School of Medicine and Public Health

BACKGROUND: Hot spotters are frequent users of the ED that come to the Emergency Room over 7 times per year, and are admitted to the hospital over 50% of the time. These patients represent an interesting demographic, as they are extremely taxing on the healthcare system, but also potentially predictable. The ability to predict whether or not a person is more likely to become a hot spotter will allow for preemptive resource allocation towards such patients, ideally leading to fewer ED visits and hospital stays.

OBJECTIVE: Hot spotters are a demographic of ED patients who have 7 or more ED visits per year, AND are admitted to the hospital in over 50% of these visits. We are attempting to create a statistical model that can predict if a given group of patients will become hot spotters in the future.

METHODS: Patient demographic data of ED visits at UW Hospital from 2008-2011 was compiled and grouped into categories of age, sex, marital status, insurance status, method of arrival, chief complaint, and ICD-9 Code. Statistical analysis was performed on the data to discover if trends exist amongst the patients that went on to become hot spotters. This analysis is currently ongoing, with results yet to come. Once a model is created based on the results, patient data from 2012-2013 will be arranged and categorized in an identical manner to the 2008-2011 data. The model will be applied to this data to see if accurate predication of hot spotters occurs.

RESULTS: Patient data from 2008-2011 was organized and categorized based on sex, age, marital status, insurance status, method of arrival, chief complaint, and ICD-9 Code. The compiled spreadsheet was sent over to statisticians for modeling. Results are pending.

Conclusions: Predicting whether or not a patient will become a hot spotter (uses ED over 7 times a year and is admitted in over 50% of these visits) will allow for the allocation of greater resources towards these patients at a preventative stage, reducing the number of costly ED visits and hospital admission down the line. A lack of significant statistical findings would also be interesting, as it would indicate the inability to predict whether or not a certain group of patients will become hot spotters in the future.
A REVIEW OF INTERVENTIONAL STUDIES DURING THE CHOLERA EPIDEMIC IN HAITI

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Mentor(s): Marvin Birnbaum, MD, PhD

BACKGROUND: In October 2010, the Haitian Ministry of Public Health and Population (MSPP) reported a cholera epidemic caused by contamination of the Artibonite River. Prior to the outbreak, cholera had never been documented in Haiti; as of January 2014, 698,893 cases and 8,540 deaths have been reported by MSPP. Following the outbreak, the local and international community launched an extensive response. Statistics on caseloads and efforts by local and international partners are readily available. Yet without agreed upon frameworks guiding responses and subsequent reporting mechanisms, reports generally do not contain sufficient levels of detail to draw conclusions for future interventions. In contrast, interventional studies examine responses more systematically and may be useful in facilitating comparisons and applying lessons to future outbreaks. OBJECTIVE: To examine publicly available documents relating to the 2010 cholera outbreak in Haiti and subsequent responses, in order to answer the following questions: 1. What information is publicly available on interventional studies conducted during the epidemic, and what was the impact(s) of these interventions? 2. Can comparisons be made between the interventions and what lessons can be learned from comparing interventions? METHODS: A PubMed literature review was conducted using the search parameters ‘Haiti’ and ‘cholera’. Papers were categorized as interventional studies, epidemiological studies, or other. Interventional studies were then compared based on approach, geographic location, target population and impact data. RESULTS: The PubMed literature review yielded 171 papers, 12 (7%) of which were interventional studies. An expanded review of WHO, CRED, USAID Development Experience Clearinghouse and National Library of Medicine’s Disaster Literature databases yielded no additional interventional studies. Of the 12 interventional studies, only two (17%) included any impact data. Neither was able to assess the impact on reducing incidence or mortality related to cholera. Additionally, the unstructured formats and differing levels of detail provided prohibited comparisons between interventions. CONCLUSION: Guidelines for future interventional disaster studies are proposed to provide useful structured information to contribute to the science of disaster health. However, without a repository housing previous and ongoing research to guide quality improvement efforts, responding organizations must continue to rely on individual experience, leading to a predominance of ‘eminence-based’ rather than ‘evidence-based’ interventions.
ACTIVATING AND INHIBITORY KIRs AND KIR-LIGANDS INFLUENCE LYMPHOMA RITUXIMAB RESPONSE

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Support: Shapiro Summer Research Program; NIH Grant R01 CA166105; Hyundai Hope on Wheels Grant; Midwest Athletes Against Childhood; University of Wisconsin-Madison Carbone Cancer Center; ECOG; Public Health Service Grants CA21115, CA23318, CA66636, CA21076, CA14958 and from the National Cancer Institute, National Institutes of Health and the Department of Health and Human Services.

BACKGROUND: Immunotherapeutic response in cancer patients may vary dependent upon patients’ genotype. NK cells are a major contributor to tumor directed immunotherapeutic responses. The highly polymorphic killer-cell immunoglobulin-like receptors (KIR) that interact with class-I HLA (KIR-L) are major modulators of these NK cell responses. OBJECTIVE: We investigated the role of KIR/KIR-L interactions in patients from a recent Eastern Cooperative Oncology Group clinical trial that sought to optimize rituximab administration in patients with low tumor burden follicular lymphoma. In this trial patients responding to induction rituximab were randomly assigned to receiving maintenance rituximab every 13 weeks or only when showing progressive disease. METHODS: DNA was analyzed to assess KIR and KIR-L genotype and its influence on patient response to rituximab. The contributions of inhibitory KIR/KIR-L interactions (matched vs. mismatched), activating KIR/KIR-L interactions, and KIR haplotype on patient clinical response to treatment were assessed. RESULTS: In contrast to what has been reported previously, we did not see an association between overall KIR/KIR-L matched vs. mismatched, nor an overall impact of KIR haplotype on response to rituximab. We did find associations between certain KIRs, their ligands and patient outcome. Interestingly, we found that inhibitory KIR/KIR-L mismatch was associated with improved progression-free survival in KIR haplotype A patients only. Independent of KIR genotype, KIR-L HLA-C2+ patients had decreased progression-free survival, and HLA-Bw4+ patients had increased tumor shrinkage and improved progression-free survival, but only in the maintenance rituximab arm. Additionally, the presence of activating KIRs, 2DS1 and 3DS1, confer worse tumor shrinkage when their ligands were present, supporting a role for NK cell hyposensitization. CONCLUSIONS: As most NK cells express an array of both inhibitory and activating KIRs their activation must reflect a balance of both activating and inhibitory signals. These clinical data suggest that there are simultaneous inhibitory and activating KIR and KIR-L interactions in vivo. They support the hypothesis that NK cells are involved in the clinical response to rituximab and that KIR/KIR-L interactions influence tumor shrinkage and progression-free survival. Furthermore, they suggest that certain KIRs and KIR-Ls may have differential potency in influencing this clinical response.
ANATOMIC RELOCALIZATION OF PROSTATE CANCER IN ACTIVE SURVEILLANCE PATIENTS IS ASSOCIATED WITH PATHOLOGIC FAILURE

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Support: Shapiro Summer Research Program; Wisconsin Academy of Rural Medicine (WARM); Department of Urology, University of Wisconsin School of Medicine and Public Health

BACKGROUND: Prostate cancer (PC) is the most common cancer among US males, but a notable percentage of these cancers are clinically insignificant. To avoid unnecessary treatment, active surveillance (AS) protocols have been developed. However, more extensive disease is an area of concern in the management of these patients. It is therefore important to identify factors that predict or are associated with more extensive disease. OBJECTIVE: To determine clinicopathologic factors that predict AS failure.

METHODS: Criteria for AS included stage T1c, Gleason score <7, <3 positive cores, and less than 50% involvement of a single core. Patients on follow-up that exceeded these criteria were considered failures and offered therapy. Patient characteristics at diagnosis included rebiopsy time, age, PSA, PSA density (PSAD), BMI, follow-up PSAD, history of negative biopsy, and biopsy core relocalization. Relocalization was defined as cancer in a different location within the prostate on repeat biopsy. Cox regression models were used to assess AS failure among groups.

RESULTS: Of 106 men undergoing PC evaluation at UW Hospital Clinics who met AS criteria, 71 underwent transrectal ultrasound (TRUS) validation biopsy within one year of diagnosis. Fourteen of these patients demonstrated relocalization of PC following validation biopsy. Of those who had relocalization, 11(79%) went on to fail AS, while only 9 of 57(16%) who did not demonstrate relocalization failed AS (p<0.001). Biopsy relocalization (HR 20.46, 95% CI 5.85-71.52; p<0.001) and PSAD (HR 1.14, 95% CI 1.003-1.28; p=0.45) at diagnosis were significantly associated with AS failure.

CONCLUSIONS: Anatomic relocalization of PC following validation biopsy and increased PSAD are associated with AS failure. Many of these failures likely represent understaging at the time of initial biopsy.
LOW PARATHYROID HORMONE LEVELS AFTER TOTAL THYROIDECTOMY: INCIDENCE AND TIME TO RESOLUTION

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Support: Department of Surgery NIH T35DK062709 grant, University of Wisconsin School of Medicine and Public Health

BACKGROUND: Parathyroid hormone (PTH) levels are often measured after thyroid surgery and can be used to detect patients at risk for postoperative hypoparathyroidism. OBJECTIVE: To elucidate the time course of parathyroid gland function recovery and to determine the incidence of permanent hypoparathyroidism. METHODS: Patients who underwent a total or completion thyroidectomy from 1/2006 to 12/2013 were identified from a retrospective review of a prospectively collected institutional database. Low PTH was defined as a PTH measurement <10 pg/mL immediately after surgery. Recovery of parathyroid gland function was defined as PTH ≥10 pg/mL and no need for therapeutic calcium or activated vitamin D (calcitriol) supplementation to prevent hypocalcemic symptoms. Patients were considered to be permanently hypoparathyroid if they had not recovered within 1 year. Multivariate logistic regression modeling was performed to identify independent risk factors for a low postoperative PTH and for permanent hypoparathyroidism. RESULTS: Of 1054 total thyroidectomy patients, 189 (18%) had postoperative PTH <10 pg/mL. Of those 189 patients, 132 (70%) showed resolution within 2 months of surgery. At 1 year, 20 patients were considered to have permanent hypoparathyroidism due to the need for ongoing supplementation. Surprisingly, 50% of those patients had recovery of PTH levels to ≥10 pg/mL yet still required supplementation to avoid symptoms. The permanently hypoparathyroid group represents 11% of patients with initial postoperative PTH <10 pg/mL and 2% of the entire cohort. On multivariate analysis, independent risk factors for low postoperative PTH included parathyroid autotransplantation (OR = 2.6; 95% CI, 1.8-3.8) and the presence of parathyroid tissue on final pathology report (OR = 2.2; 95% CI, 1.5-3.3). The only independent risk factor for permanent hypoparathyroidism was parathyroid tissue on pathology report (OR = 3.6, 95% CI, 1.1-11.5). Interestingly, age, gender, neck dissection, thyroiditis, and malignancy were not independently associated with low postoperative PTH or permanent hypoparathyroidism. CONCLUSIONS: Low PTH is a common occurrence after thyroid surgery, but the vast majority of patients showed parathyroid gland function recovery within 2 months of surgery. Notably, 5% of patients with low postoperative PTH resolved 6-12 months after surgery, suggesting that 12 months may be the most appropriate time point for defining hypoparathyroidism as permanent.
FUNCTIONAL OUTCOMES OF MEDIAL PATELLOFEMORAL LIGAMENT REPAIR FOR PATIENTS WITH RECURRENT PATELLAR INSTABILITY

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Support: Shapiro Summer Research Program; Department of Orthopedics and Rehabilitation, University of Wisconsin School of Medicine and Public Health

BACKGROUND: Dislocation and subluxation of the patella are common knee injuries that can result in recurrent patellar instability (RPI). The medial patellofemoral ligament (MPFL) is commonly injured as it restrains against excessive lateral patellar displacement. RPI may also occur from injury without dislocation, attenuating the MPFL. Patients with RPI may pursue surgical options, such as MPFL repair, if non-operative treatments are ineffective. MPFL repair involves direct repair of ligament with sutures and/or anchoring devices in the mid-substance or at either bony attachment. MPFL repair may be done in isolation or with more extensive patellar realignment procedures. However, few studies have adequately assessed the outcomes of isolated MPFL repair for recurrent patellar instability (RPI) and to determine specific factors associated with successful outcomes.

OBJECTIVE: Our purpose was to evaluate the results of isolated MPFL repair for recurrent patellar instability (RPI) and to determine specific factors associated with successful outcomes.

METHODS: A new database was created, compiling data for patients with RPI that had a MPFL repair performed by Dr. Scerpella. Following IRB approval, pertinent clinical information was acquired from electronic medical records. Pre-op X-rays and MRI scans were analyzed for pertinent radiographic measurements (i.e. patella height). Several patients had completed pre- and post-operative functional outcome assessments for clinical purposes, and these results were obtained from other database. A student’s t-test was performed to compare pre and post-op functional outcome scores.

RESULTS: 17 patients underwent MPFL repair and provided at least 6 months of follow-up data (Mean 11.82 months). No patient reported a post-op RPI event and most (94.1%) had improved patellar stability with no apprehension on physical examination. 6 patients with functional outcome testing showed improvement, particularly in SF-12 PCS scores, a measure of physical health status (Mean pre: 38.31 and post: 52.51; p<0.05). The small sample size precluded correlation of outcomes with other factors such as radiographic measurements, gender, and BMI.

CONCLUSIONS: This review provides preliminary evidence of improvement following isolated MPFL repair for RPI. Additional subjects and longer follow-up are required to make definitive conclusions. A prospective study, assessing similar outcomes and including a patellar-specific tool (Kujala score) has been initiated. More definitive analyses, assessing outcomes and potentially influential predictors of outcomes, will be completed when sufficient data has been collected.
THE INFLUENCE OF PERI-MENARCHEAL PHYSICAL ACTIVITY ON STRENGTH AND LEAN MASS ACQUISITION IN ADOLESCENT FEMALES

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Support: Shapiro Summer Research Program; Department of Orthopedics and Rehabilitation, University of Wisconsin School of Medicine and Public Health; Orthopedic Research and Education Foundation; SUNY Upstate Medical University; the National Institute of Arthritis, Musculoskeletal and Skin Diseases (R03AR047613; R01AR054145)

BACKGROUND: Studies have correlated height, body mass, sex, and chronological age with strength throughout puberty, but these factors explain only 40-70% of variance in strength scores of children, leaving considerable variance unexplained. As a modifiable factor, physical activity (PA) represents an effective strategy to improve many health outcomes, and has been demonstrated to correlate with lean mass accrual during childhood and late adolescence. It is unique to the literature to investigate the relationship between PA, strength, and lean mass acquisition within the context of the peri-menarcheal maturational window; this time frame represents a crucial period for bone accrual, which is closely associated with lean mass development. Thus, the aim of the present study was to evaluate the influence of peri-menarcheal PA on development of strength and lean mass. METHODS: Subjects from an ongoing longitudinal study (1997-present) were selected for the current analysis. Subjects underwent annual whole body and regional DXA scans, as well as semi-annual anthropometry, strength (grip strength, sit-up repetitions), maturation, and self-reported physical activity (PA) tracking (h/wk of organized PA). Subjects were included if DXA scans were assessed ~1 year pre-menarche (PRE) and post-menarcheal (POST) scans ~2 years after PRE, with complete PA data 6-12 months prior to PRE and between scans. Regression analyses were performed to evaluate the explanatory value of PA 6-12 months prior in predicting PRE outcomes, and the role of PA interDXA in predicting PRE to POST outcomes. Analyses accounted statistically for PRE muscle trait, POST gynecological age, and change in standing height between scans. RESULTS: 80 subjects were included in the analyses. Mean interDXA interval was 2.1 years (1.8 to 2.4). Mean gynecologic age at PRE was -1.1 years (-1.5 to -0.5) and at POST was 1.0 years (0.5 to 1.8). PA 6-12 months prior to baseline measures predicted PRE lean mass for arms (p=0.018), legs (p=0.013), and whole body (p=0.005), and PRE sit-up repetitions (p=0.006). InterDXA PA predicted POST lean mass for arms (p=0.06), legs (p=0.086), and whole body (p=0.032). CONCLUSIONS: PA significantly influenced lean mass accrual in a dose-dependent fashion both prior to PRE and across the peri-menarcheal window. Additionally, PA prior to PRE was found to significantly influence PRE strength, but peri-menarcheal activity did not predict strength development across this period. These preliminary findings suggest that the peri-menarcheal window presents an important period for lean mass acquisition in females, and modifiable behaviors like physical activity can significantly modulate this critical stage of growth.
CLINICAL SIGNIFICANCE OF RENIN-ANGIOTENSIN SYSTEM INHIBITION ON NON-MUSCLE INVASIVE BLADDER CANCER

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BACKGROUND: It has been suggested in a prior report (Ann Surg Oncol, 2012) that inhibition of the renin-angiotensin system (RAS) may affect recurrence of non-muscle invasive bladder cancer (NMIBC).

OBJECTIVES: We sought to validate in our dataset if inhibiting the RAS with ACE-inhibitors (ACE-I) and angiotensin receptor blockers (ARBs) provided a clinical benefit on recurrence and progression of NMIBC. METHODS: An institutional bladder cancer database identified 422 patients treated with transurethral resection (TUR) for NMIBC. Three hundred forty patients met inclusion criteria and were taking ACE-I/ARBs at the time of their first TUR. Progression was defined as stage T2. Cox proportional hazards models were used to evaluate associations with recurrence-free (RFS) and progression-free survival (PFS).

RESULTS: Median follow-up was 3 years (IQR 1.3-6.1). Median patient age was 69.6. A total of 200 (59%) patients had a recurrence and 14 (4.1%) had stage progression. The number of patients receiving either an ACE-I or ARB was 143. On univariate analysis, factors associated with improved RFS included presence of cis (p=0.040), bacillus Calmette-Guerin (BCG) therapy (p=0.003), and ACE-I/ARB therapy (p=0.009). Multivariate analysis demonstrated that patients treated with BCG therapy (HR 0.68, 95% CI 0.47-0.87; p=0.002) or ACE-I/ARB therapy (HR 0.61, 95% CI 0.45-0.84; p=0.005), were less likely to experience tumor recurrence. The 5-year RFS rate was 45.6% for patients treated with ACE-I/ARBs and 28.1% for patients not treated with ACE-I/ARBs (p=0.009). Subgroup analysis was performed evaluating patients on BCG therapy alone (n=85) and patients on BCG and ACE-I/ARB therapy (n=52) on NMIBC pathology (Ta, T1, cis). Univariate Cox proportional regression revealed that patients treated with BCG and ACE-I/ARB therapy (HR 0.46, 95% CI 0.21-0.99; p=0.046) had better RFS compared to patients treated with BCG alone for stage Ta. CONCLUSION: The inhibition of RAS is associated with improved RFS. The reduction in recurrence from BCG therapy was improved when combined with RAS inhibitor administration and thus warrants a prospective randomized trial.
CITESC ZILNIC: RESEARCH TO SUPPORT A PHYSICIAN-INITIATED EARLY CHILDHOOD READING PROGRAM IN CLUJ COUNTY, ROMANIA

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BACKGROUND: Literacy is an important health issue beginning in infancy because of its role in physiological brain development and future social ramifications. Family physicians can play a key role in encouraging parents to read aloud to their children. However, screening for pre-reading skills and the promotion of early literacy are not currently integrated in Romanian medical practice. **OBJECTIVE:** This research explored the feasibility of beginning Citesc Zilnic (CZ, “Read Everyday”) a proposed early childhood literacy program to be promoted by family physicians in Romania. **METHODS:** This mixed method study included a phone survey with 115 family physicians from Cluj County, Romania and ethnographic interviews with 15 of these survey respondents in greater depth. Survey items addressed demographics, attitudes toward literacy, current practices and previous experiences in literacy education. Interview data were analyzed with thematic analysis. **RESULTS:** Of 171 physicians contacted for the phone survey, 115 were willing to be surveyed. Only one respondent claimed to have had any training in literacy promotion. Literacy was considered a significant issue in Romania by 96% of respondents and 98% considered literacy to be related to children’s developmental health. However, only 8% always said they discussed pre-reading and early literacy with families. Nonetheless, 67% of responding physicians expressed interest in participating in the implementation of an early literacy program like CZ in their practices. Thematic data analysis of interviews revealed that, with adjustments to local cultural and economic conditions, the majority of Romanian family physician respondents would welcome an early literacy program. **CONCLUSIONS:** Most family physician interviewees considered early literacy an important issue of preventive medicine and believed it should be addressed in the medical office. However, many felt that they lacked the background knowledge and training to effectively promote pre-reading skills and early childhood literacy. A few respondents, on the other hand, while seeing the issue as important, did not see it as being appropriately within the scope of their practice. Lack of time and bureaucratic demands were common themes impeding potential plans for early literacy promotion, yet the majority of respondents were interested in participating in such a program. These data were used to create training and promotional materials for CZ’s pilot program.
QUALITY IMPROVEMENT AT DHULIKHEL HOSPITAL AND THE KIRNETAR OUTREACH CENTER IN NEPAL

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BACKGROUND: Quality improvement (QI) includes many systematic and continuous actions that aim to measurably improve health services and health outcomes. The use of QI in Nepal is the aim of a collaboration between the Global Health Institute and Dhulikhel Hospital. The Dhulikhel Hospital is a community-based health institution that aims to improve health care delivery in resource-limited settings. At the rural outreach centers there is limited staff and resources, so this initiative aims to streamline utilization in order to increase efficiency and quality of care provided. METHODS: A waiting time study and patient satisfaction survey were created to establish baseline quality indicators for current and future QI efforts. Interns at the Dhulikhel Hospital conducted the a patient flow observation study with time and motion measures. The study also included patient perspectives obtained through survey questions and intern impressions of the doctor’s attitudes and behaviors using a 5-point Likert scale. At the Kirnetar Outreach Center a patient satisfaction survey was created using staff and patient input that were obtained using an affinity diagram exercise and interviews. The survey was translated into Nepali and conducted by eighth grade students from the local KPS School. RESULTS: A total of 12 patients took part of the waiting time study at Dhulikhel Hospital. They traveled to Dhulikhel from 7 different cities and their travel times ranged from 15 minutes to 22 hours. The average time spent at the hospital as an outpatient (or before admission) was 140 minutes. The average waiting time was 65 minutes per patient. Discussions were started with hospital administration to redesign space utilization in the new OPD building and reevaluate allocation of human resources. There were a total of 25 patients surveyed at the Kirnetar Outreach Center. The results of the survey showed areas where patients were satisfied with the care, but there were several areas with room for improvement. Only 64% of patients followed the queue during their visit. Patients were least satisfied with the wait time overall and at the pharmacy as well as how the hospital staff considered their financial situation. Based on the results, signs, and checklists were utilized to improve the number of patients that followed the queue and also to improve pharmacy work flow and financial consideration. CONCLUSIONS: The results will serve as a benchmark for future improvement work and help to elucidate areas for improvement. Due to the dedication of the staff at the Dhulikhel Hospital and Kirnetar Outreach Center the outlook of QI is very promising and improvements can be quantitatively measured by the quality indicators established by this research.
UPREGULATION OF CALCIUM INSENSITIVE NEDD4.2L E3-LIGASE SPLICE VARIANTS IN DISEASED HUMAN HEART LEFT VENTRICLE

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Mentor(s): John Kyle, PhD; Jonathan Makielski, MD

Support: Shapiro Summer Research Program; Department of Medicine, University of Wisconsin School of Medicine and Public Health

BACKGROUND: Nedd4.2L is an E3 ubiquitin ligase that has been shown to associate with Nav1.5, the cardiac sodium channel, and regulate its cell surface expression, and thereby regulates excitability. Two major isoforms are typically considered functionally relevant, but not much is known about their expression in heart. OBJECTIVE: This study aims to measure relative expression of mRNA transcripts of two major isoforms, Nedd4.2L-C+ and Nedd4.2L-C-, in tissue from the left ventricle of 4 failing and 4 normal hearts. METHODS: Specimens were obtained after surgical explantation for transplantation. Total RNA was extracted, and relative expression of mRNA transcripts of both Nedd4.2L isoforms were determined using qPCR, using isoform specific primers alongside GAPDH primers. RESULTS: Both isoforms were expressed in normal hearts, with 1.4 fold more expression of Nedd4.2L-C+ compared to Nedd4.2L-C-. Interestingly, a 1.6 fold increase in expression of nedd4.2LC- compared to Nedd42.LC+ was noted in failing heats. There was a notable decrease in Nedd4.2L-C+ expression in failing hearts relative to normal human hearts. Also, a significant (3 fold) increase in Nedd4.2L-C- expression is seen in failing hearts relative to normal human hearts. CONCLUSIONS: The increased expression of Nedd4.2L-C- seen in failing hearts could account for the marked decrease in peak I_{Na} seen in heart failure.

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AORTIC PULSE WAVE VELOCITY MEASURED WITH 4D-FLOW MRI IN PATIENTS WITH PORTAL HYPERTENSION

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Mentor(s): Christopher Francois, MD; Scott Reeder, MD, PhD

Support: Shapiro Summer Research Program; Department of Radiology, University of Wisconsin School of Medicine and Public Health

BACKGROUND: Portal hypertension is one of the major complications of cirrhosis and results from the increased hepatic resistance to portal venous and hepatic arterial blood flow. Although it is known that the changing hemodynamics result from a vascular hyporeactivity to vasoconstrictor agents, it is unclear how these changes specifically affect the aorta. Recently, a rat model of chronic portal hypertension demonstrated a wound-like inflammatory and fibrotic response of the aorta leading to aortic stiffening. Hemodynamic changes can be measured with MRI using a technique known as pulse wave velocity (PWV) and is a biomarker of vascular stiffening.

OBJECTIVE: The aim of this study was to determine whether pulse wave velocity measured with MRI can be used to detect hemodynamic changes in the descending aorta in patients with portal hypertension compared to healthy volunteers.

METHODS: Flow-sensitive four-dimensional (4D flow) MRI was acquired in patients with clinically diagnosed portal hypertension (n=11) and healthy volunteers (n=12). Computation fluid dynamics software (EnSight) was used to reconstruct an angiogram from the data. EnSight enabled placement of an aortic centerline where 40 analysis planes were automatically placed with equidistant separation. The flow waveform from each analysis plane along the supraceliac aorta was exported and loaded into Matlab where PWV was analyzed using several methods including time-to-peak (TTP), time-to-upstroke (TTU), time-to-foot (TTF), and cross-correlation (XCOR). PWV was compared between the two groups.

RESULTS: Mean aortic PWV was not statistically different in patients with portal hypertension compared to healthy volunteers (TTP: P = 0.64, TTU: P = 0.87, TTF: 0.64, XCOR: P = 0.87).

CONCLUSIONS: We have used 4D flow MRI to measure aortic PWV in cirrhotic patients. This technique is non-invasive and provides vessel velocimetry over a wide volumetric coverage with high spatial resolution. 4D flow MRI, therefore, enables analysis of complex vascular hemodynamics in systemic disease states such portal hypertension. We speculate that the lack of an age-matched control group in this study may have led to this result and larger populations may be needed to identify significant changes in PWV.
STUDY OF G1248R HCM-CAUSING MUTATION IN CARDIAC MYOSIN BINDING PROTEIN-C

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Mentor(s): J. Carter Ralphe, MD

Support: Shapiro Summer Research Program; UW Cardiovascular Research Center, University of Wisconsin School of Medicine and Public Health

BACKGROUND: Hypertrophic cardiomyopathy (HCM), is an inherited cardiac disease occurring in 1 in 500 individuals. Mutations in the MYBPC3 gene, encoding cardiac myosin binding protein-C (cMyBP-C) are prevalent causes of HCM. The mechanisms through which missense mutations in MYBPC3, prevalent causes of childhood onset HCM remain understudied and poorly understood. OBJECTIVE: To assess the contractile performance and define the molecular mechanism underlying the G1248R cMyBP-C mutation reported to cause pediatric onset HCM. METHODS: We used adenoviral gene transfer to express wild type and G1248R cMyBP-C in unremodeled, murine engineered cardiac tissue (mECT) constructs lacking endogenous mouse cMyBP-C. Contractile performance of mECTs were assessed using a standard force transducer and perfusion system. Subsequently, RNA and protein were extracted from mECT and qRT-PCR and Western blotting performed to quantify cMyBP-C expression levels. Additional mECT were subjected to immunohistochemical analysis to verify cMyBP-C incorporation into the sarcomere. RESULTS: Quantitative PCR and western blot analysis showed expression of protein and RNA from G1248R cMyBP-C was equivalent to wild type murine cardiomyocytes. Histological staining of cMyBP-C in relation to other sarcomeric proteins revealed that mutated G1248R cMyBP-C incorporates normally into the sarcomere, with the classical doublet pattern seen. Assessment of contractile function revealed that the G1248R mutation does not alter mECT contractile function under basal conditions. Following beta 1 receptor stimulation, however, mECT expressing G1248R cMyBP-C failed to accelerate relaxation kinetics. CONCLUSION: Immunohistochemical data suggests that misincorporation of G1248R cMyBP-C does not play a role in the pathophysiology of this mutation as was previously hypothesized. The failure of G1248R mECT to accelerate relaxation kinetics following beta adrenergic stimulation suggests that normal cMyBP-C phosphorylation or contractile response to phosphorylation may be disrupted in the G1248R mutation. This finding warrants further study to explore the effect of phosphorylation on the pathology of the G1248 HCM causing mutation.
PROTEASE ACTIVATED RECEPTOR-3 EXPRESSION IS DECREASED IN HUMAN BENIGN PROSTATIC HYPERPLASIA

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Support: Shapiro Summer Research Program, University of Wisconsin School of Medicine and Public Health; National Institutes of Health: DK093690 (WAR), CA123199 (WAR) T32GM07356 (TMN), and F30DK093173 (TMN)

BACKGROUND: While the cause of abnormal prostate growth in benign prostatic hyperplasia (BPH) remains incompletely understood, it is likely that growth factors secreted by the stroma promote epithelial growth. Protease activated receptors (PARs) are G-protein coupled receptors with diverse biologic functions, that have been shown to enhance prostate cell proliferation, and induce production of fibroblast growth factors. While PAR-1 and PAR-2 have been studied in BPH, PAR-3 expression has not been previously evaluated in the prostate. Therefore, we investigated expression of PAR-3 in human BPH.

METHODS: We performed multiplexed immunohistochemistry to detect PAR-3 in normal prostate tissue (96 cores from 52 patients) and BPH (n = 48 cores from 24 patients) on a tissue microarray. We used a multispectral imaging platform for automated scanning, tissue, cell and compartment segmentation and marker quantification. RESULTS: In the epithelium of BPH cores, we observed a decrease in nuclear PAR-3 expression (-40%, P < 0.0001) and cytoplasmic expression (-41%, P < 0.0001). In the stroma, we found that PAR-3 expression was also decreased in BPH in the nucleus (-35%, P < 0.0001) and cytoplasm (-15%, P = 0.01), relative to normal prostate tissue. CONCLUSIONS: In contrast to other reports about PAR-1 and PAR-2 expression in BPH, we found nuclear and cytoplasmic PAR-3 expression is decreased in the stroma and epithelium of BPH. To our knowledge, this is the first characterization of PAR-3 expression in BPH.
TREATING SPINAL CORD INJURIES WITH NERVE GRAFTS AND SUTURES
RELEASEING NEUROTROPHIN-3

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Mentor(s): Amgad Hanna, MD

Support: Shapiro Summer Research Program; Department of Neurological Surgery, University of Wisconsin School of Medicine and Public Health

BACKGROUND: After a spinal cord injury (SCI), axons fail to regenerate causing permanent paralysis due to an immediate mechanical impairment of the axon and a persisting anatomical gap. One way to aid in axon regeneration is to implant a peripheral nerve graft (PNG), which provides a scaffold to bridge the anatomical gap, allowing axons to regenerate and promote functional recovery. To further promote axon regeneration, delivery of cytokines to the site of injury may act synergistically with a PNG. The cytokine Neurotrophin 3 (NT-3) promotes axon sprouting and growth. A standard surgical suture with a calcium phosphate coating was used to stabilize, control, and deliver NT-3 within its therapeutic range.

OBJECTIVE: A protein delivery system was developed and implemented to evaluate the potential synergistic effects of a PNG coupled with sustained release of NT-3 to promote functional recovery following a SCI.

METHODS: Rats underwent complete spinal cord injury at T10 creating a 3 mm long defect. A control group received no further intervention. In groups receiving intervention, two PNGs were placed in the injury site. One PNG group received injected NT-3 treatment, one received suture treatment with NT-3-loaded sutures, and one received no additional protein therapy. Rats were sacrificed after 8 weeks. Functional recovery was assessed using the Basso Beattie Bresnahan (BBB) locomotor rating scale. An axon tracer cholera toxin-B (CTB) was injected into both sciatic nerves to evaluate axon regeneration through the PNGs. To quantify the total number of axons in the grafts, neurofilaments were labeled on transverse sections of the PNGs.

RESULTS: Functionally, the rats with PNGs + NT-3 loaded suture (2.83±0.39) and the rats treated only with PNGs (2.04±0.48) had significantly higher BBB scores compared to the controls (0.55±0.22) on day 56 postoperatively. Positive CTB labeling was noted in nearly all invention groups. Neurofilament labeling on transverse sections of the graft revealed that the rats treated with the NT-3 loaded sutures had significantly more axons per graft (1244±50) than the group of rats with only PNGs (543±168).

CONCLUSIONS: It appears as though the NT-3 loaded sutures are aiding the growth of axons into the graft but they are not extending through the graft. Future studies will be performed to promote axon extension through the graft by breaking down scar tissue at the graft spinal cord interface.
ETHICAL AND LEGAL ISSUES IN REFUSAL OF TREATMENT FOR SEVERE COMBINED IMMUNODEFICIENCY

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BACKGROUND: Several years ago at UW Hospital, an infant “Anna” with a form of Severe Combined Immunodeficiency (SCID), a fatal condition without treatment, was given a potentially curative hematopoietic stem cell transplant over the objections of her parents and other members of their Amish community. This treatment was mandated in a court hearing after the family was reported for medical neglect in refusing treatments for the infant. The courts have historically been involved with minor organ transplants as there are often issues regarding parental conflict of interest, especially when siblings are being considered as a potential donor. However, this court ruling is unique in that it represents what we believe to be the first court-ordered transplant over parental objections. This project centers on exploring the complex ethical and legal issues surrounding Anna’s case.

OBJECTIVES: To address the following in an academic article (case report and ethics discussion): 1. Was it in Anna’s interests to receive treatment? 2. Should Anna’s brother have been tested to see if he was a good HLA-match? 3. If he had been a suitable match, should the brother have been a donor over parental objections? 4. How long should post-transplant supportive care gone on against parental objections? 5. What legal background exists around parental refusals of treatment, child neglect-reporting, and minor transplantation? 6. Whether, retrospectively, Anna’s case should have been handled differently, especially given that this case worsened already strained relations between many medical providers and the state Amish community.

METHODS: This project consisted largely of literature review, interviews of physicians involved with Anna’s case, meetings with UW legal and IRB staff, and writing and editing a manuscript for publication.

RESULTS: We are in the final stages of editing a manuscript to be submitted for publication. In short, we conclude that while the report that while many of the decisions made in Anna’s case were justifiable, a decision to use the brother as a donor against parent wishes (if he had been a match) would have been questionable, and that the parental desire to limit treatments should have been followed earlier than it was in this case.

CONCLUSIONS: The questions raised by this case have implications that extend to other cases. Given the high incidence of rare genetic disorders within communities like the Wisconsin Amish, ideally a system would be found that would enable medical treatments for infants born with curable conditions while enlisting the support of Amish families. We conclude with some ideas about mechanisms to enable that in the future.
SEX DIFFERENCES IN PREDICTORS OF LONGITUDINAL CHANGES IN CAROTID ARTERY STIFFNESS

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Support: Shapiro Summer Research Program; Department of Medicine, Division of Cardiovascular Medicine, University of Wisconsin School of Medicine and Public Health; University of Wisconsin Cardiovascular Research Center; Contracts HC95159-HC95169; Grants HL07936 and HL 094760 from the NHLBI; Grant ES015915 from the NIEHS; Grants RR024156 and RR025005 from the NCRR; Contract RD831697 from the US EPA (note: this abstract has not been formally reviewed by the EPA)

BACKGROUND: Sex differences in predictors of longitudinal changes in carotid arterial stiffness have not been described previously in a multi-ethnic cohort. OBJECTIVE: To identify and describe sex differences in predictors of longitudinal progression of carotid arterial stiffness. METHODS: Carotid artery distensibility coefficient (DC) and Young’s Elastic Modulus (YEM) were measured using B-mode ultrasound in 2650 MESA (Multi-Ethnic Study of Atherosclerosis) participants at baseline and after a mean of 9.4 years. Participants were 45-84 years old and free of cardiovascular disease at baseline. Sex-specific predictors of change in DC (10-3 mmHg-1) and YEM (mmHg) were evaluated using multivariable linear regression models. RESULTS: The 1236 men (46.6%) were 60.0 (standard deviation 9.3) years; 40% were White, 22% Black, 16% Chinese, and 22% Hispanic. The 1414 (53.4%) women were 59.8 (9.4) years old with a similar race distribution. Despite similar rates of change in DC and YEM, predictors of changes in distensibility markers differed by sex. In men, Chinese (β=-0.267, p=0.002) and Black (β=-0.210, p=0.003) race/ethnicity, baseline systolic blood pressure (β=-0.004, p=0.012) and treated diabetes mellitus (β=-0.206, p=0.047) were associated with more rapidly decreasing DC (accelerated stiffening). Starting antihypertensive medication was associated with improved DC (β=0.155, p=0.027), whereas stopping antihypertensives was associated with higher more rapid stiffening (increased YEM, β=362.8, p=0.046). In women, higher education level was associated with slower stiffening (DC β=0.170, p=0.041; YEM β=400.6, p<0.001). Baseline use of lipid-lowering medication also predicted slower stiffening (YEM β=209.3, p=0.034), whereas baseline use of antihypertensive medications (YEM β=195.4, p=0.011) and systolic blood pressure (DC β=-0.003, p=0.023; YEM β=3.6, p=0.041) predicted increasing stiffening in women. Menopausal status did not affect changes in DC or YEM. CONCLUSIONS: Longitudinal changes in carotid artery stiffness parameters are associated with systolic blood pressure and antihypertensive therapy in both sexes; however, race/ethnicity (in men) and level of education (in women) appear to have different contributions between the sexes. These observations have implications for the pathophysiology and prevention of age-related arterial stiffening.
**IMPROVING PREDICTIVE VALUE OF TRAUMA SCORING THROUGH INTEGRATION OF ASA-PS WITH ISS**

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**Support:** Shapiro Summer Research Program; Department of Surgery, University of Wisconsin School of Medicine and Public Health

**BACKGROUND:** Many methods exist for predicting mortality among adult trauma patients; however, most systems ignore patient co-morbidity, a significant predictor of outcome. The American Society of Anesthesiologists Physical Status (ASA-PS), a well-validated and easy-to-use scale, is an assessment of pre-operative status that has been shown to accurately predict post-operative mortality. **OBJECTIVE:** Using ASA-PS as a marker of cumulative patient comorbidity severity we sought to test whether we could improve the predictive power of the Injury Severity Score (ISS), the most commonly utilized trauma grading system, with respect to mortality, major complication, and discharge disposition. **METHODS:** A retrospective review of a prospectively collected and internally validated database at an academic Level I trauma center was performed for consecutive adult admissions between 2009-2013. Abbreviated Injury Scale (AIS) was measured by region (head/neck, face, thorax, abdomen, extremities, general) and severity of injury (1 to 6). ISS was measured by summing the squares of the three most injured regions. ASA-PS scores were assigned based on patient comorbidities and then integrated with the ISS in various permutations, including adjustments of ASA-PS for patient age >70 and using individual AIS components of ISS. We assessed these various models for predictive ability with a primary outcome of mortality and secondary outcomes of major complications per National Trauma Data Bank definitions as well as discharge disposition using receiver operating characteristic (ROC) analysis. **RESULTS:** All of the ISS/ASA-PS hybrid formulas outperformed ISS in predictive power for mortality, major complication, and discharge disposition. The best overall permutation, \((\text{AIS1})^2 + (\text{AIS2})^2 + \text{(Age-Modified ASA-PS)}^2\), yielded an ROC of 0.888 for mortality as compared to ISS with an ROC=0.853 (p<0.001). Similar differences were seen for discharge disposition (Hybrid ROC=0.743; ISS ROC=0.639, p<0.001) and major complication (Hybrid ROC=0.761; ISS ROC=0.719, p<0.001). **CONCLUSIONS:** Incorporating ASA-PS into calculations of trauma scoring is both simple and more predictive of mortality, major complication, and discharge disposition than the traditional ISS metric. Replacing ISS with this new method, which takes patient age and comorbid condition into account through adaptation of ASA-PS improves prognostication of outcomes and enables care providers to prioritize resources for injured patients.
DETERMINATION OF THE CLINICAL PHENOTYPE ASSOCIATED WITH FMR1 EXPANSIONS IN A POPULATION-BASED SAMPLE

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Support: Shapiro Summer Research Program; Waisman IDDRC Core Grant (M.R. Mailick, PI, P30 HD03352); Centers for Disease Control and Prevention through the Association of University Centers on Disability (M.R. Mailick, PI)

BACKGROUND: Fragile X syndrome (FXS), the most common inherited form of intellectual disability, is caused by expansion of a trinucleotide CGG repeat in the FMR1 gene. Individuals with FXS have >200 CGG repeats. Those with the FMR1 premutation (55-200 CGG repeats; PM) have an increased risk of having a child with FXS and are more likely to develop a variety of health conditions. Research on the phenotype of the FMR1 gray zone (defined here as 41-54 CGG repeats; GZ) is very limited. GZ alleles also exhibit instability when passed to subsequent generations. OBJECTIVE: This study focuses on features associated with the FMR1 GZ and PM and patterns of instability of CGG repeats across generations. METHODS: Data were obtained from the Marshfield Clinic Personalized Medicine Research Project (PMRP), an ongoing population cohort study with stored DNA linked to comprehensive medical records. 19,996 DNA samples were assayed for FMR1 CGG repeat length. Family pedigrees were constructed. 20 families with FMR1 PM or GZ carriers in 2 or more consecutive generations were chosen (n=63 individuals). Control families (<40 CGG repeats) with the exact same genealogic structure matched for age in each generation were included for comparison. Pedigrees were annotated with ICD-9 codes in the following domains: reproductive, psychiatric, cognitive, musculoskeletal/motor, neurologic, thyroid, autonomic, pain, gastrointestinal, obesity. Mean family differences were summarized by taking the differences between number of ICD-9 codes between cases and their matched controls and calculating the mean difference for each family pair. RESULTS: Of the 63 individuals with FMR1 expansions, there were 38 GZ (41-54 CGG repeats) and 25 PM (57-125 CGG repeats). 3 females carried two GZ alleles. 43 CGG expansion transmissions were observed, with most (n=24) being stably transmitted. Expansion occurred in 16 transmissions, 4 of which were GZ expansions. Contraction occurred in 3 transmissions, with the largest from 51 to 46 CGG repeats. The number of ICD-9 codes in the cognitive domain was significantly higher in case families than controls (p=0.04) and case families were more likely to have ≥1 neurologic (p=0.0003) and ≥1 autonomic (p=0.05) symptom. CONCLUSIONS: Findings support the hypotheses that FMR1 GZ and PM alleles often exhibit instability when being passed to subsequent generations and carriers are at an increased risk of certain health conditions.
ASSESSMENT OF SWAB AND BIOPSY SAMPLING METHODS FOR VOCAL FOLD MICROBIOTA STUDIES

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Support: Department of Surgery NIH T32 Training Grant DC009401, University of Wisconsin School of Medicine and Public Health

BACKGROUND: The microbiota is comprised of bacteria, fungi, and archaea that reside on epithelial surfaces throughout the body. Shifts in normal microbial communities have now been linked to disease in numerous body sites. We sought to compare two sampling methods for microbiota study in healthy vocal folds -- swabbing and biopsies. Biopsy of true vocal folds is problematic because it can lead to scarring and dysphonia and therefore this methodology cannot be used to evaluate healthy vocal folds in humans. Swabbing has been used to assess microbial communities in other areas of the body because it is less invasive and does not disrupt the normal epithelium. If swabbing of vocal folds reveals similar microbial communities to samples taken by biopsy, swabbing could be used as an alternative to biopsy. Additionally, the microbial communities of false vocal folds could be used as proxies for true vocal folds for analysis of the microbiota, but the similarity between these two niches is unknown.

OBJECTIVE: Our objectives were to compare the microbial communities of samples taken by swabbing to those taken by biopsy and to compare microbiota of true and false vocal folds. METHODS: We used 6 pigs in our comparison of the microbial communities in vocal folds. True and false vocal fold mucosal samples were collected using sterile Catch-All swabs and biopsy. Total DNA was extracted and the V3-V5 region of the 16S rRNA gene was amplified. Resulting amplicons were sequenced using 454 pyrosequencing.

RESULTS: Analysis of data from all six pigs suggests that microbial communities are unique in relative composition for individual pigs, though all communities were dominated by bacteria in the phyla Actinobacteria, Bacteroidetes, Firmicutes, Fusobacteria, and Proteobacteria. Principal coordinates analysis of the communities from showed that swabbing and biopsy resulted in similar community structure. An inconsistent relationship was measured for the microbiota between the true and false vocal folds.

CONCLUSIONS: The microbiota of swabbed and biopsied samples were similar suggesting that swabbing could be used as a reliable alternative to biopsy. Swabbing will allow for greater assessment of microbial communities in healthy individuals since it is much less traumatic to the epithelium and does not cause scarring. Further research is necessary to determine the relationship between true and false vocal fold microbiota.
BACKGROUND: This is a continuing multicenter, prospective, observational study funded by the Veterans Administration (VA) evaluating roles of Traumatic Brain Injury (TBI) and psychiatric comorbidities in the development of Psychogenic Non-Epileptic Seizures (PNES) and Epileptic Seizures (ES) in veterans. While PNES and ES have similar clinical presentation, studies from civilian population suggest that PNES are thought to be neuro-psychiatric in origin, often associated with Post-Traumatic Stress Disorder (PTSD). These studies also indicate mild TBI as a risk factor for developing PNES. While the misdiagnosis of PNES occurs both in civilian and veteran populations, veterans experience a greater delay in receiving a correct diagnosis. During this lag period, majority of these veterans endure long-term use of anti-epileptic drugs (AEDs) and their side effects, resulting in an impaired quality of life. Additionally, the VA incurs significant costs from the unnecessary use of AEDs. Therefore, it is ethically and financially imperative that studies be conducted to assess and evaluate the possible etiology of PNES within the veteran population.

OBJECTIVE: This study evaluates the roles of TBI and psychiatric co-morbidities in the development of PNES and ES in the veteran population. Correctly identifying the cause and development of PNES can lead to the creation and implementation of effective interventions to ultimately improve the lives of many Veterans.

METHODS: Participants are selected from a pool of veterans who have been admitted to the local VA Epilepsy Center of Excellence (ECoE) for long-term continuous video-EEG monitoring for evaluation of their seizures. Study activities are completed during the participant’s stay at the Epilepsy Monitoring Unit (EMU). Activities consist of a broad range of neuro-psychological tests, in addition to subjective questionnaires and tests. Participants also undergo a Structured Clinical Interview for DSM IV (SCID) conducted by the site psychologist. The differential diagnosis provided by the attending clinician is also collected. Only the PNES-diagnosed patients will be followed up 9-12 months post EMU discharge for seizure status update.

RESULTS: Because of the ongoing nature of the study, preliminary results have not yet been assessed. However, in an effort to assess potential biases in the study, the EMU diagnosis was used to examine if there were differences in the diagnosis between those who consented vs. those who did not. Out of the 63 EMU patients from March 25, 2013 to August 1, 2014, 8 were excluded because ineligibility or inability to participate because of external factors. From the 55 eligible patients, 42 consented (76.4%), while 13 did not (23.6%). Within the consent group (n=42), 36% (n=15) were diagnosed with ES, 26% (n=11) PNES, 2% (n=1) other non-ES, and 36% (n=15) inconclusive. The non-consent group (n=13) consisted of 39% (n=4) diagnosed with ES, 23% (n=3) PNES, and 38% (n=5) inconclusive. The diagnosis of ES vs. PNES was independent of whether or not the patient agreed to participate in the study (p=0.368, x2= 0.80907, df=1).

CONCLUSIONS: These results decrease the likelihood of any sampling bias in the recruitment of study participants. It also suggests that the potential diagnosis of PNES was not a factor for EMU patients in deciding whether or not to participate in the study.
ANESTHESIA TECHNIQUE ON POSTOPERATIVE ANALGESIA IN TOTAL HIP ARTHROPLASTY PATIENTS

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BACKGROUND: There is currently no research on the results of combined spinal epidural versus epidural alone following total hip arthroplasty. By analyzing the results of different anesthesia techniques used when total hip arthroplasty is being performed, we could possibly find a more advantageous anesthesia technique. If there were a superior anesthesia technique, it would show up in improved clinical outcomes and postoperative variables such as pain, nausea, and physical therapy. OBJECTIVE: The aim was this study was to evaluate four anesthesia/analgesia modalities commonly utilized during total hip arthroplasty. METHODS: Following IRB approval, a chart review of 453 patients who had undergone total hip arthroplasty from August 2010 to March 2012 was performed. The anesthesia modalities evaluated included general anesthesia, epidural anesthesia with overnight epidural analgesia, combined spinal-epidural anesthesia with overnight epidural and combined spinal-epidural anesthesia without overnight epidural. Total opioid administration, self-rated postoperative pain, post anesthesia care unit time, hospital time, and physical therapy participation were recorded. RESULTS: The use of combined spinal and epidural anaesthesia (CSE) overnight (O/N) versus CSE without an overnight epidural catheter was associated with a significant reduction in opioid analgesic administration. CSE O/N compared to epidural resulted in similar postoperative pain and opioid administration. However, CSE O/N was associated with a decreased incidence of conversion to GA relative to the epidural group. CONCLUSIONS: There may be a number of anesthesia strategies that result in improved perioperative outcomes in patients presenting for THA. In the intraoperative setting, the provision of neuraxial anesthesia appears to result in an improved experience. The provision of a CSE (effectively a spinal), predictably was associated with a decreased incidence of conversion to GA. The insertion of an epidural catheter allows the CSE to be dosed prior to entry into the OR without worrying about with less opioids administered and better analgesic delivery. CSE O/N in our study was shown to be a better treatment option compared to CSE without an overnight epidural catheter. CSE O/N and Epidural groups were essentially the same in all comparative outcomes. GA had significantly lower postoperative outcomes compared to regional anesthetic techniques. If GA is clearly the inferior group in regards to postoperative outcomes, then having one of the regional anesthetic groups have a higher conversion rate over to GA would be an unwanted consequence. Through this reasoning, with a significantly lower conversion rate lower rate to GA, CSE O/N would be the best choice for anesthetic technique in hip replacements. If CSE O/N is to be consistently used as the anesthetic technique for total hip arthroplasty further investigation with randomized, blinded, and controlled trials should be done.
ANTITUMOR EFFECTS OF ANTI-CD40+CpG COMBINED WITH IMMUNOCYTOKINE AND CHECKPOINT BLOCKADE MONOCLONAL ANTIBODIES

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BACKGROUND: The treatment of cancer has seen significant improvements over the past decade, largely because of therapies that target patients' own immune systems to stimulate immune responses against malignant cells. An important goal in cancer immunotherapy is the development of novel combinations of therapeutic agents that improve treatment outcomes, often accomplished by targeting the different antitumor mechanisms of different classes of immune cells. In this project, we exploit the over-expression of disialoganglioside GD2 on the surface of neuroblastoma and melanoma cancer cells by using a genetically-engineered immunocytokine called hu14.18-IL2 IC. The hu14.18-IL2 immunocytokine binds to GD2 and enhances antibody-dependent cell-mediated cytotoxicity, mainly by NK (natural killer) cells. We also sought to activate T cells through use of anti-CTLA-4 (cytotoxic T-lymphocyte-associated protein 4), an antagonistic mAb that blocks inhibitory signals that prevent full T cell activation. The final arm of this project focused on macrophage activation using an agonistic anti-CD40 (cluster of differentiation 40) mAb and TLR9 (toll-like receptor 9) agonist CpG-ODN 1826 (an oligodeoxyribonucleotide consisting of numerous sites with adjacent cytosine-guanine nucleotides). The combination of anti-CD40+CpG is a potent activator of macrophages. However, when anti-CD40+CpG therapy is combined with hu14.18-IL2 and anti-CTLA-4, synergistic antitumor effects mediated by NK cells, cytotoxic T cells, and macrophages are observed in vitro and in vivo.

OBJECTIVE: The adaptive and innate immune systems can become activated by the combination of hu4.18-IL2 IC, anti-CTLA-4 mAb, anti-CD40 mAb, and CpG-ODN, resulting in tumor growth inhibition and possibly regression tumor-bearing mice.

METHODS: C57BL/6 mice were injected s.c. (subcutaneously) with syngeneic B78 mouse melanoma cells. Tumors were allowed to grow for several days. Anti-CD40 and anti-CTLA-4 were injected i.p. (intraperitoneally). Hu14.18-IL2 IC and CpG were injected i.t. (intratumorally). Tumors were measured using digital calipers for the entirety of experiments, and tumor volumes were then calculated.

RESULTS: Tumors in the combined treatment group grew more slowly than untreated tumors or tumors treated with single agents.

CONCLUSIONS: The combination of hu14.18-IL2, anti-CTLA-4, anti-CD40, and CpG results in significantly delayed tumor growth and possibly regression in treated mice, even when treatment is started at a late stage in tumor development.
TOBACCO USE AS A PREDICTOR OF POOR OUTCOMES OF CLOSTRIDIUM DIFFICILE INFECTION

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BACKGROUND: The epidemiology of hospital-acquired infections (HAIs) is a topic at the forefront of medical research in the United States. With roughly 100,000 patient deaths each year attributable to HAIs and a financial burden that has been estimated in the range of 30-45 billion dollars per year, the prevalence and severity of the problem can be described as little short of a national emergency. Among HAIs in the United States, one of the most common causative bacterial agents is Clostridium difficile. Infections involving C. difficile have received particular attention due to their high frequency, with over 250,000 cases diagnosed annually, and the substantial increase in their frequency over the past three decades while most types of HAIs are declining. Identifying the risk factors associated with severe cases of C. difficile is a major step toward reducing the risk of morbidity and mortality for vulnerable individuals diagnosed with this increasingly common and severe infection. As an easily identifiable behavior with known impact on immune function and gut microbiota, tobacco use has been shown to be associated with increased incidence of C. difficile, while its relationship with severe outcomes of C. difficile remains poorly understood. METHODS: We performed a retrospective chart review of 1037 patients from the University of Wisconsin Hospital and Clinics given the ICD-9 diagnosis of C. difficile at the University of Wisconsin Hospital and Clinics from July 15, 2009 to the April 22, 2014 for whom tobacco use information was recorded. A number of demographic and clinic variables were systematically extracted from the electronic medical records and data were analyzed through univariate and multivariate logistic regression, chi-squared analyses, as well as Kaplan-Meier and Cox proportional hazard survival regression, using STATA MP-11 (64-bit) software. RESULTS: A 2 day increase in median length of stay was observed for current smokers as compared to all other patients. Patients with greater degrees of cigarette smoke exposure were also observed to have a lower rate of cure within 14 days of beginning therapy for C. difficile, higher rates of readmission and recurrence, and higher rates of death before completion of therapy, as compared to their respective control groups, although these results were not statistically significant. Multivariate regression analyses shed light on the more statistically significant roles of other clinical factors, such as fever, high WBCCs, low systolic blood pressure readings, age, and chronic kidney disease, on outcomes of infection. CONCLUSIONS: The investigation of tobacco use as a predictor of poor outcomes highlights this characteristic as an easily accessible piece of patient information which may offer clinically useful insight into the risk of poor outcomes of C. difficile infection. Limitations of our study include the lack of tobacco use information for every patient within the potential sample, the lack of detailed tobacco use information such as length and extent of smoke exposure, and lack of follow-up on patients in our sample who received care outside of UW Hospital and Clinics. The potential clinical utility of considering patient tobacco in context of C. difficile diagnosis warrants further investigation of this association with a larger sample size, more detailed clinical information, and more quantitative tobacco use information.
A COMMUNITY HEALTH NEEDS ASSESSMENT OF A MEDICAL MISSION POPULATION IN IMO STATE, SOUTH-EASTERN NIGERIA

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BACKGROUND: Short-term medical missions (STMMs) are a common route for health professionals to extend their skills and services to resource-limited developing countries. Despite the growing number of medical missions, current public health data is limited on the health needs of the communities served. Many short-term medical missions lack continuity, follow-up care, and multi-interventional strategies that are needed to improve health of the communities. OBJECTIVE: The aim of this study is to assess the socioeconomic characteristics and health needs of a rural population in Owerri, Imo State, Nigeria served by Mezu International Foundation (MIF), a non-profit organization. This would enable STMMs to efficiently utilize their limited resources to address specific needs of the patient population and empower them to improve their health. METHODS: Pre and post-assessment surveys were created to assess the health needs of the patient population participating in the MIF medical mission. Out of over 2000 people, a random sample of 100 patients was interviewed with the surveys. The pre-assessment survey addressed 1) socioeconomic characteristics; 2) healthcare access; and 3) reasons for seeking medical care. The post-assessment survey examined: 1) diagnoses given, 2) patients' understanding of their health, 3) preventive care attitudes and 4) patients' comments on the mission. The pre-assessment surveys were taken during triage prior to medical exams and health counselling. The same patients were asked the post-assessment questions after their medical exams. RESULTS: Based on the pre-assessment survey, 58% of the patient population was low income and 42% was middle income status. The post-assessment revealed that the major contributors to poor health include eye diseases (89%), hypertension (64%), arthritis (47%), and chronic pain (24%). The patients’ comments reflected their gratitude (62%), the impact of the mission in their lives (49%), and their hopes for sustainability of the mission (35%). Patients had improved understanding of their health conditions and positive attitude to health after education was provided. CONCLUSION: The health problems in the medical mission population were associated with socio-economic risk factors. Proper assessment of health needs of the population and a focus on education during medical missions may encourage better health practices and help target the available resources to meet specific medical needs of the community.
QUANTIFYING THE INCREASE IN MEDICAL IMAGING UTILIZATION AND ITS EFFECT ON NEGATIVE LAPAROTOMY FOR APPENDICITIS

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BACKGROUND: Appendicitis is a common cause of abdominal pain in the emergency department, there being 250,000 appendectomies performed in the United States annually. Physical examination has limited accuracy for this diagnosis, so medical imaging is commonly used. OBJECTIVE: The use of computerized tomography (CT) has been shown to decrease the negative laparotomy rate for appendicitis. We aimed to quantify the use of CT, ultrasound (US), and magnetic resonance imagining (MRI) for the diagnosis of appendicitis at UW over the past 2 decades. METHODS: This is a retrospective study of patients admitted to UW Hospital since 1992 with an ICD-9-CM code for appendicitis. Once identified, data was abstracted from each patient’s chart including year of visit, gender, age, and type of imaging used (if any). The proportion of patients undergoing each imaging type was calculated by year. Regression analysis was performed by year to determine whether age, gender, or BMI affected the imaging choice. Statistical analysis was performed by a biostatistician using R statistical software. The years included were 1992, 1993, 1996, 1998, 2001, 2003, 2006, 2008, 2011, 2012, 2013, and 2014.

RESULTS: There were 2222 individuals admitted for appendicitis during the years evaluated in this study, including 967 women and 599 children. In general, the use of CT to diagnose appendicitis increased significantly over the study period (from 1.5% to 92.4%), while the diagnosis of appendicitis without imaging decreased substantially (from 91.2% to 3.4%). This trend was statistically significant for all subgroups (men, women, adults, children) to the p<0.0001 level. However, there was no statistically significant difference in the trend in use of CT to diagnose appendicitis when comparing men to women (p=0.8047) or adults to children (p=0.1004). Additionally, while men and children were less likely to have imaging performed, this trend was not statistically significant (by gender, p=0.5304; by age, p=0.6550). Though we did quantify the number of patients who had an US or MRI during the study period, there was no clinically or statistically significant increase in the utilization of these tests.

CONCLUSIONS: Use of CT increased substantially over the 22 year period in our study. This increase was seen regardless of patient age or gender. Conversely, this trend was not seen with US or MRI.
NEWBORN IRON DEFICIENCY IS ASSOCIATED WITH AN ALLERGIC CYTOKINE PROFILE

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BACKGROUND: Obese pregnancy and excessive weight gain are independently associated with both newborn iron deficiency (ID) and early asthma diagnosis. T helper type 1 (Th1) and type 2 (Th2) lymphocytes carry out distinct roles in immune function. Th1 cells produce primarily IFN-g and Th2 cells produce a variety of cytokines including IL-5. A Th2-skewed immune phenotype characterizes allergic asthma and may serve as a biomarker for future atopic disease. Th2 cells have significantly greater intracellular iron stores than Th1 cells, which may increase Th2 cell cytokine production relative to Th1 cytokine production in low iron conditions. Furthermore, previously published evidence links low umbilical tissue iron to childhood wheezing. This points to ID mediating the link between maternal obesity and atopic disease in offspring. OBJECTIVE: To test umbilical cord blood iron status and Th2/Th1 cytokine patterns in order to analyze whether newborn ID mediates the relationship between maternal obesity and cytokine biomarkers for atopic disease. METHODS: UW and Meriter Hospital IRBs approved this study. Eligible subjects included women delivering healthy term newborns via scheduled cesarean sections at Meriter Hospital. Subjects were categorized by maternal BMI at delivery (obese BMI ≥30, not obese BMI <30 kg/m2) and also by cord iron status (ID ferritin ≤25th percentile, not ID ferritin >25th percentile). Cord blood samples were tested for erythrocyte iron (hemoglobin), transport iron (transferrin), and storage iron (ferritin). Mononuclear cells were separated from whole blood and cultured for 24 hours with an allergic stimulus (phytohemagglutinin). Supernatant Th2/Th1 cytokine production was assayed. Statistical analysis included t-test and ANOVA. RESULTS: A total of 77 cord blood samples were processed from 47 obese and 30 non-obese pregnancies. Hemoglobin and transferrin values did not differ, but plasma ferritin was lower in the obese group (84.6±7.6 vs. 117.6±12.9 ng/mL, p<0.03). Supernatant IL-5 and IFN-g did not differ between obese and non-obese. ID showed higher mononuclear IL-5 (p<0.008) but similar IFN-g production. Th2/Th1 ratio, calculated as IL-5/IFN-g, did not differ in obese and non-obese but was higher in the ID group than non-ID group (0.081±0.014 vs. 0.031±0.004, p<0.001). CONCLUSIONS: Although obesity plays a part in depleting newborn iron, these data support that it is fetal storage iron status that controls the Th2 expression and imbalanced Th2/Th1 cytokine responses in mononuclear cells. Depleted storage iron at birth may be the factor that predisposes a child to allergic disease later in life by skewing immune cytokine response.
HESPERIDIN ACCELERATES HEALING OF SPLINTED CUTANEOUS EXCISIONAL WOUNDS IN MICE

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BACKGROUND: Every year in the United States, more than 6.5 million patients suffer from wound-related complications, and treatment is estimated to cost over $25 billion. After an injury, keratinocytes from the wounded edge must proliferate, migrate across the wound bed, and differentiate in order to restore normal barrier function. We are interested in discovering new methods by which to enhance proliferation, migration, and differentiation in order to improve the wound healing process. Hesperidin, a natural flavonoid found in citrus fruits and honey, has been shown to improve epidermal barrier function.

OBJECTIVE: In this study, we investigated the effects of hesperidin on the rate of wound healing in murine splinted cutaneous excisional wounds, a model shown to stimulate healing in human tissue.

METHODS: Six week old, male mice (n=14) were anesthetized, shaved, and two full-thickness 6 mm wounds were created on their backs under aseptic conditions. A 12 mm silicone stent was secured around each wound using cyanoacrylate glue and interrupted 5-0 nylon sutures in order to prevent healing by contraction and to promote healing by formation of granulation tissue. A sterile non-adherent dressing and transparent occlusive dressing were placed over the wound. Twenty-four hours after injury, hesperidin (10 μM) or vehicle (0.01% DMSO) was applied topically to each wound and was repeated daily. Digital photographs were taken of the wounds every day at each dressing change and treatment application. Wound closure was defined by gross visualization of resurfacing epithelia and calculated as a percent area of the original wound size. Wounds were quantified using ImageJ software (NIH) and expressed as a ratio of wound area to stent area, with scaling normalized to the inner diameter of the splint.

RESULTS: The wound sizes were similar in both groups at the beginning of treatment. Addition of hesperidin (10 μM) significantly accelerated the rate of wound closure compared to DMSO control on day 4 (% open, 44±3 vs 53±2 respectively, p<0.05) and on day 5 (% open, 23±3 vs 33±3 respectively, p<0.05). Wound closure for both groups was complete by day 8.

CONCLUSIONS: Hesperidin accelerates cutaneous wound closure in our in vivo model. Based on this novel finding, further studies should evaluate the mechanisms by which hesperidin accelerates the wound healing process, possibly leading to the development of new and effective therapeutics for wound healing in patients.
DO PATIENTS WITH EXTREME OBESITY HAVE WORSE OUTCOMES AFTER SURGERY FOR RENAL CELL CANCER?

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Support: Department of Surgery NIH T35 Training Grant DK062709, University of Wisconsin School of Medicine and Public Health

BACKGROUND: Obesity is a prominent health concern in the United States and plays an important role in health-care decision making. Surgery is technically challenging in patients with excessive body fat and many studies have suggested worse outcomes in patients with extreme obesity, especially when body mass index (BMI) is greater than 35 or 40. However, renal cell carcinoma (RCC) can have a high mortality rate and surgery is the primary treatment for localized disease. Few studies have objectively evaluated outcomes for RCC patients with extreme obesity who are treated surgically. OBJECTIVE: To evaluate outcomes for patients with extreme obesity who were treated surgically for RCC. METHODS: Patient and disease characteristics were reviewed for all RCC patients from 2000-2014 who were treated surgically at the University of Wisconsin Hospital. Patients who had concomitant IVC thrombectomy were excluded from analysis. Outcome measures included: overall survival (OS), cancer specific survival (CSS), complications within 90 days, hospital readmissions, transfusion rate, length of hospital stay and duration of anesthesia. Complications were classified using the Clavien-Dindo scale (≥IIIa=major complication). Charlson comorbidity (CCI) scores were calculated and tumor complexity was determined using the RENAL nephrometry system. Cox proportional hazards analysis or logistic regression was used to evaluate association of extreme obesity and common prognostic factors with outcome variables. RESULTS: A total of 738 patients were eligible for this study, including: 176 (24%) had a BMI ≥35 and 89 (12%) with BMI ≥40. In patients with BMI ≥35 or ≥40 there were no significant differences in OS, CSS, 90 day mortality, major complications rate, total complication rate, incidence of hospital readmission, or length of hospital stay. Both BMI ≥35 and ≥40 were associated with increased anesthesia time. Patients with BMI ≥35 or BMI ≥40 required an additional 40 or 50 minutes of anesthesia time respectively. TNM stage, CCI, and RENAL nephrometry score were predictive of OS and CSS. Age and CCI predicted increased risk of major complications, blood transfusion and longer hospital stay. Partial nephrectomy, CCI and RENAL nephrometry score predicted increased readmission risk. CONCLUSION: Extreme obesity is associated with longer anesthesia times, but no difference in cancer outcomes or complications in RCC patients treated surgically with BMI ≥35 or ≥40.