TRANSFORMING CURIOSITY INTO INQUIRY

10TH ANNUAL

Medical Student Research Forum

PROGRAM and ABSTRACTS

JANUARY 17, 2012

Support for the 10th Annual Medical Student Research Forum is provided by UW School of Medicine and Public Health, Office of Academic Affairs; Herman and Gwendolyn Shapiro Foundation; Wisconsin Medical Alumni Association
January 17, 2012

Health Sciences Learning Center

1:00–5:30 PM

1:00-1:15 PM
Welcome
Robert N. Golden, MD
Dean and Vice Chancellor for Medical Affairs

1:15-2:00 PM
2012 Shapiro Guest Lecture
Physician-Scientist: Is It for Me?

Bermans Iskandar, MD
Professor of Neurological Surgery
UW School of Medicine and Public Health

As Professor in the Department of Neurological Surgery and Director of
Pediatric Neurosurgery at American Family Children’s Hospital, Dr. Iskandar is
a physician-scientist role model: clinician, teacher, and researcher whose laboratory has been instrumental in
hypothesizing and proving a significant role for folic acid in regeneration and repair of the adult CNS after injury.

Dr. Iskandar is a graduate of California State University at Northridge and received his MD degree from the
University of Pennsylvania School of Medicine. He completed his residency, serving as Chief Resident, in the
Division of Neurosurgery at Duke University Medical Center. He joined the UW faculty in 1997.

Dr. Iskandar’s areas of clinical expertise include craniofacial repair, brachial plexus reconstruction, and
endoscopic surgery for tumors and congenital brain anomalies. He gained national recognition for pioneering
endoscopic intracranial surgical procedures and novel imaging techniques aimed at minimizing the radiation
exposure of children with hydrocephalus, as well as developing new technology to analyze the craniocebral
CSF flow in children with Chiari malformation and syringomyelia.

Over the past 14 years, Dr. Iskandar’s lab has been a magnet for students interested in the neurosciences.
He has mentored more than 50 high school, undergraduate and medical students through programs such
as NASA/Sharp, Medical Scholars, Shapiro Summer Research and the Research Honors Program. Their
productivity has been outstanding, resulting in some 36 papers, presentations or publications, and 12
awards, including the UW Hilldale Research Fellowship, Shapiro Excellence in Student Research Award, and
the American Academy of Neurological Surgeons Medical Student Research Fellowship.

In 2011 Dr. Iskandar was honored with a Dean’s Award for Excellence in Medical Student Research Mentorship.

2:15-4:00 PM
Student Research Podium Presentations (Concurrent Sessions)

4:00-5:30 PM
Student Research Poster Session and Reception

Listing of student podium and poster presentations and abstracts follow.

Abstracts are listed alphabetically by student last name.
Student Podium Presentations
Sessions run concurrently from 2:15 - 4:00 pm

SESSION A ..................Room 1306 HSLC
Jonathan Sohn
Thiocoraline Regulates Neuroendocrine Phenotype and Inhibits Proliferation in Carcinoid Tumor Cells

Bret Valentine
A Qualitative Investigation of a National Advanced Care Planning Health Policy

Steve Biro
Response of Type II Diabetes Mellitus to the Preoperative Liquid Diet as a Predictive Model for Diabetes Resolution in Bariatric Surgery Patients

Kristin Ebert
Step Rate Modification while Running

Daryl Fields
The Use of Ghrelin to Reduce Spinal Cord Injury Immunopathology

Alexis Guzmán
Evaluating the Effects of Statewide Smoking Regulations on Smoking Behaviors among Participants in the Survey of the Health of Wisconsin (SHOW)

Barrett Wagner
Serological Analyses in Children with Neuroblastoma: Clinical Associations

SESSION B ..................Room 1345 HSLC
Sarah Humphrey
Treatment of Pulmonary Emboli: Defining Clinical Parameters for Safe Outpatient Therapy

Sarah Kreul
A Phase III Skin Cancer Chemoprevention Study of DFMO in Subjects with a History of Non-Melanoma Skin Cancer (NMSC): Follow-up of NMSC Events Greater than 5 Years Post-Study Participation

Ben Landgraf
Evaluating Portal Venous Hemodynamics with 4D Flow: How Essential is the Temporal Dimension?

Cristina Merkhofer
Day of Surgery Associated with Length of Stay in Patients Undergoing Thoracic Surgery

Eleni Moraités
Utilization of Steroids for Dermatological Disorders in the Emergency Department

Dina Marie Pitta
The Impact of Prior Breast Augmentation on Short and Long Term Surgical Outcomes for Women Diagnosed with Breast Cancer

Parker Hoerz
Walkable Neighborhoods, Physical Activity, and Coronary Heart Disease Risk: Results from SHOW

Dominic Schomberg
Neurocatheter Convection Enhanced Delivery Performance in a Gel Model of the Brain

SESSION C ..................Room 1335 HSLC
Laurel Bessey
The Incidence of Thyroid Cancer by FNA Varies by Age and Gender

Levi Stodola
Characterizing Uptake and Retention of 18F-FDG in Mesenchymal Stem Cells to Facilitate Tracking In Vivo

Alicia Sprecher
Interdisciplinary Cancer Care Team Composition and Communication

Kevin Shepet
Hereditary Medullary Thyroid Cancer: Age-Appropriate Thyroidectomy Improves Disease-Free Survival

Ernesto Bogarin
Treatment of Spinal Cord Injury Using Peripheral Nerve Grafts and a Sustained Release of ChondroitinaseABC

E. Racquel Racadio
Improved Evaluation of African American Infant Mortality Statistics in Wisconsin: Determining Data Analysis Strategies for the Lifecourse Initiative for Healthy Families (LIHF)

Gauthami Soma
Early Graft Failure after Lower Extremity Arterial Bypass: Results from More than 200 Hospitals
1. **Algharabil, Jehad**  
   Na-K-Cl Cotransporter-mediated Intracellular Chloride Regulation in Brain Tumor Stem Cells

2. **Andreason, Molly**  
   Hormone-receptor Positive (HR+) Breast Cancer (BrCa) and Exogenous Hormone Use Among Wisconsin Women

3. **Bernardoni, Brittney**  
   Skeletal Effects of Fat Mass Loss in Obese Adolescents

4. **Borkenhagen, Jenna**  
   Reduced Contractile Reserve: A Therapeutic Target in Heart Failure with Preserved Ejection Fraction

5. **Carr, Jason**  
   Stenting for Malignant Obstruction in the Upper Urinary Tract

6. **Ciske, Ben**  
   Pressure Gradients Within and Across Intracranial Aneurysms Using MR Phase Contrast Velocity Data

7. **Ciske, Jennifer**  
   Preliminary Investigation Between Cognitive Test Performance and Cardiovascular and Dementia Risk Scores

8. **Dale, Andrea**  
   Micro RNA Analysis in Thyroid Cancer Stem Cells

9. **Destree, Craig**  
   Identifying Predictive Risk Factors for the Development of Hepatocellular Injury during Liver Transplantation

10. **Dreis, Michael**  
    Antibiotic Utilization in Long Term Care Facilities in Wisconsin

11. **Eppinger, Benjamin**  
    Urban and Rural Differences in Health-related Quality of Life and Healthcare Access

12. **Flanagan, Claire**  
    Molecular Significance of BRAF Mutations in Multiple Myeloma

13. **Flanders, Christian**  
    A Prospective Chart Review Analyzing Predictive Variables Associated with Blood Cultures in the ED

14. **Gamble, John**  
    Risk factors for Acquisition of Clostridium difficile Infection in Solid Organ Transplant Recipients

15. **Garvens, Bonnie**  
    The Effect of Prison Release on Disease Progression and Development of Viral Resistance in HIV+ Inmates

16. **Garvey, Thomas**  
    Improving Loss of Follow-up of Patients with Abnormal Cervical Cytology at Two Clinics

17. **Gorges, Logan**  
    Transgenerational Epigenetic Inheritance of Enhanced Spinal Cord Regeneration Following Spinal Cord Injury

18. **Greatens, Marcus**  
    Intratendinous Injection of Platelet-Rich Plasma into Lamb Extensor Carpi Radiialis Tendon

19. **Groth, Jeremy**  
    Intravenous Magnesium Sulfate is Ineffective at Alleviating Propofol Injection Pain: a Randomized, Double-blind, Placebo Controlled Trial

20. **Hahn, Luke**  
    Natural History of Nonalcoholic Hepatic Steatosis: Risk for Progression to NASH and Cirrhosis

21. **Harrison, John-Henry**  
    Evaluating the Effect of Brain Aneurysm Repair Modalities on Cognitive and Emotional Function

22. **Heier, Jake**  
    Wire-Guided Intubation through a Face Mask using the Seldinger Technique in an Urgent Difficult Airway

23. **Hemmy, Davida**  
    IRB Approval, What First Time Applicants Should Know Regarding IRB Processes Here and Abroad

    Ratio of Neutrophil to Lymphocyte Counts - Rapid and Simple Test to Predict Upstaging prior to Radical Cystectomy for Urothelial Carcinoma
25. Hsu, Shao-Pu P  
   *Irx4 is a Marker for Cardiac Ventricular Progenitor in Mouse Embryonic Stem Cells*

26. Hunt, S. Matthew  
   *Latino Lay Health Advisors: Background, Motivations, Challenges, and Strengths*

27. Kim, Chloe  
   *Evaluating the Masako Maneuver Using High-resolution Manometry and Electromyography*

28. Kopish, Kristin  
   *Physical Activity Levels and Health-Related Quality of Life in Young Female Athletes with Knee Injuries*

29. Kovacic, Karlo  
   *Multimodality Image Fusion to Guide Transendocardial Stem*

30. Lai, Ngan Betty  
   *Excessive Weight Gain After Total Thyroidectomy: Myth Or Reality?*

31. Lee, Gene  
   *Retrospective Review of Outcomes in Ulcerative Colitis Patients Intolerant of Mesalamine*

32. Lhost, Jennifer  
   *Evaluating Effectiveness of Disaster Medicine Training for Medical Students*

33. Luangrath, Mitchell  
   *Effect of Human Serum on Complement Activation by Ch14.18 mAb*

34. Mai, Stephanie  
   *Comparative Analysis of Existing Surgical Risk Assessment Tools to Predict Post-Operative Mortality Rates After Radical Cystectomy*

35. Manley, Nathan  
   *Early Evaluation of a Program to Integrate Antiretroviral Therapy into Zambian TB Clinics*

36. McLimore, Heather  
   *Effect of Multiple Risk Factors on Newborn Iron Status*

37. Miller, Andrew  
   *Platelet-Rich Plasma for the Treatment of Chronic Planter Fasciopathy in Adults: A Case Series*

38. Moore, Tyler  
   *The Impact of a Parent Child Preoperative Program in Perioperative Anxiety in Children*

39. Moreland, Anna  
   *Susceptibility of Enzyme-Treated Candida albicans Biofilms to Killing by Macrophages*

40. Nguyen, Anthony  
   *Interpersonal Trust, Race/Ethnicity, and Access to Healthcare*

41. Nussbaum, Christina  
   *Analysis of LIKE COLLEGE Study Recruitment*

42. Pankratz, Joshua  
   *Title Pending*

43. Patel, Priyesh  
   *Hesperetin Activates Notch1 Signaling, Induces Cell Differentiation, and Causes Apoptosis in Anaplastic Thyroid Cancer*

44. Peterson, Brad  
   *Performance Data to Predict Athletic Injury*

45. Polsinelli, Amanda  
   *Characterizing Frequent Fliers and Hotspotters in the Emergency Department*

46. Radtke, Andrew  
   *Presurgical fMRI and Morbidity Outcomes in Patients with Vascular Lesions*

47. Rice, Stephanie  
   *Angiosarcoma Outcomes and Prognostic Factors: The UW Experience*

48. Rozich, Noah  
   *Importance of Pre-op Platelet Count in Predicting Outcome for Resection of Hepatocellular Carcinoma*

49. Sonkarley, Price  
   *Evaluation of Three Patients with Cricopharyngeal Dysfunction: Can High-Resolution Manometry Help*
Predict Surgical Success?

50. Stein, Andrew
    Potential Role of Mesenchymal Stromal Cells in Pancreatic Islet Transplantation

51. Suhonen, Joshua
    Does Appendiceal Length Correlate with the Likelihood of Developing Acute Appendicitis?

52. Tipping, Matthew
    Clinicopathological Characterization of Glioblastoma

53. Tolly, Brian
    Ground Reaction Forces and Osteogenic Index of the Sport of Cyclocross

54. Weigert, Rachel
    Investigating the Relationship Between Fetal Iron Deficiency and Eosinophilia at 6 months-12 months

55. Weiker, Madelyn
    Identification of Clinical and Pathologic Factors Associated with Recurrence of Renal Cell Carcinoma

56. Wickre, Mark
    Identification of Epigenetic Regulators of Fetal Hemoglobin Expression

57. Zapolsky, Nathan
    Emergency Department On-Site: Integrating Doctors, PAs, and Nurses into Event Medical Care
**Na-K-Cl Cotransporter-mediated Intracellular Chloride Regulation in Brain Tumor Stem Cells**

**Authors:** Douglas B. Kintner; Jehad Algharabli; Dandan Sun, MD, PhD

**Department:** Department of Neurological Surgery, University of Wisconsin School of Medicine and Public Health

**Mentor:** Dandan Sun, MD, PhD

**Support:** Shapiro Summer Research Program; Department of Neurological Surgery

**BACKGROUND:** In this study, we investigated the expression and function of the Na(+)-K(+)-Cl(-) cotransporter isoform 1 (NKCC1) in brain tumor-derived stem-like cells (BTSCs). NKCC1 is essential for ion homeostasis and volume regulation. Recent studies have suggested the involvement of NKCC1 cotransporter in glioma growth and migration.

**METHODS:** We tested the immunohistochemical expression of NKCC1, as compared to astrocytes or human neural stem cells (HNSCs). To determine the role of the NKCC1 cotransporter in volume regulation in BTSCs, we measured regulatory volume increase (RVI) rates in BTSCs and HNSCs under hypertonic conditions.

**RESULTS:** We found that the immunohistochemical expression of NKCC1 was markedly increased in BTSCs, as compared to astrocytes or human neural stem cells (HNSCs). In addition, BTSCs maintain intracellular chloride ([Cl−]i) levels which are well above the electrochemical equilibrium for Cl- and decreased upon treatment with bumetanide, a specific NKCC1 blocker (68 ± 3 mM and 15 ± 6 mM, respectively). Consistent with the immunological staining, initial RVI rates were significantly faster in BTSCs (3.0 ± 0.1 percent volume change/min) compared to HNSCs (0.4 ± 0.2 percent volume change/min). RVI rates were bumetanide-sensitive, indicating RVI is mediated by the NKCC1 cotransporter in these cells. Under either hypotonic or low extracellular chloride conditions, [Cl−]i levels decreased in BTSCs. When tonicity or extracellular chloride was subsequently restored, the ability of BTSCs to replenish [Cl−]i was largely mediated by NKCC1. Finally, we investigated whether NKCC1 is involved in BTSC viability subsequent to apoptotic-mediated cell shrinkage. While bumetanide treatment alone did not affect cell viability, bumetanide treatment sensitized BTSCs to temozolomide-induced cell death by ~2.5 fold, reaching a mean cell death of ~50%.

**CONCLUSIONS:** Our findings strongly suggest that the NKCC1 cotransporter’s role in volume regulation affects BTSC viability and survival. Understanding the role ion transporters play in GBM progression and pathology can be beneficial for management and treatment of patients with GBMs.
Hormone-receptor Positive (HR+) Breast Cancer (BrCa) and Exogenous Hormone Use Among Wisconsin Women

Authors: Molly Andreason, BS, BA; Wendy Ledesma, MD, Kari Wisinski, MD., James Dean, BS; Amye Tevaarwerk, MD

Department: Department of Medicine, Division of Hematology/Oncology, University of Wisconsin School of Medicine and Public Health

Mentor: Amye Tevaarwerk, MD

Support: Shapiro Summer Research Program; Department of Medicine

BACKGROUND: Exogenous hormone use (EHU) is an established risk factor for developing breast cancer (BrCa), especially in postmenopausal women. A significant portion of current and future female BrCa is or will be associated with EHU. This study aimed to characterize the incidence of EHU among Wisconsin women diagnosed with BrCa, particularly those with a gene assay predictive of the risk of distant recurrence (Oncotype DX). We hypothesized that EHU among women with BrCa would be higher than the national average.

METHODS: Female HR+ BrCa cases diagnosed 2005-2010 within the UW system were analyzed in a retrospective chart review consisting of manual and electronic search (Oncotype subset), and compared to a dataset from the UW Cancer Registry on all female BrCa from 2005-2010, which was electronic review only (baseline population). EHU was defined as use of any exogenous estrogen or progesterone product prior to BrCa diagnosis, whether oral, transdermal, or vaginal for ≥12 months. Similar data from 2 other Wisconsin institutions are pending.

RESULTS: 154 women had a HR+ breast cancer and an Oncotype DX and 25/154 (16%) reported using exogenous hormones at diagnosis. 750/2800 (27%) women of the baseline population reported EHU at diagnosis. 67/154 (43%) of the Oncotype subset reported EHU sometime within their lifetime.

CONCLUSIONS: The incidence of oral EHU after menopause is around 15% nationwide. Within the Oncotype subset, post-menopausal EHU at or within 5 years of diagnosis for women 55 or older was 16% (11/68), which is similar to national use estimates. The incidence of all exogenous hormone use at diagnosis among our baseline population was significantly higher than this (27%), but this is for all ages. Within the Oncotype subset, incidence of all EHU for all ages at diagnosis was lower than the baseline population (16%).
Skeletal Effects of Fat Mass Loss in Obese Adolescents

Authors: Brittney Bernardoni, BS1; Aaron Carrel, MD2; Sijian Wang, PhD3; Tamara Scerpella, MD4

Department: 1University of Wisconsin School of Medicine and Public Health; 2Department of Pediatrics, University of Wisconsin School of Medicine and Public Health; 3Department of Biostatistics and Medical Informatics, University of Wisconsin School of Medicine and Public Health; 4Department of Orthopedics and Rehabilitation, University of Wisconsin School of Medicine and Public Health

Mentor: Tamara Scerpella, MD

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

BACKGROUND: Osteoporosis is an important public health concern for older men and women. Enhancement of peak bone mineral content (BMC) is protective for osteoporosis and nearly half BMC is accrued during puberty. As adolescent obesity rises, the effect of excess fat mass (FM) on bone acquisition has become an important area of research. Thus far, studies have shown conflicting evidence with FM being negatively positively and not correlated with total BMC. The effects of weight loss on BMC acquisition are unknown; thus the primary aim of this study was to examine the effects of FM loss on BMC acquisition in obese children.

METHODS: 55 obese children from a single middle school participated in a randomized controlled study evaluating the effects of a 9-month school-based exercise program. Non-bone lean mass (LM), FM, sub-head BMC, leg BMC, and lumbar spine BMC were assessed pre- and post-intervention using whole-body dual energy x-ray absorptiometry (DXA). Multiple linear regression analyses explored the effect of the intervention, FM change and LM change on change in BMC/ht at sub-head, spine, and leg regions. Variables were entered in a step-wise fashion as follows; intervention indicator, pre-test BMC/ht, gender, chronologic age, pre-test ht, change in ht, pre-test LM, change in LM, change in FM. The intervention indicator and pre-test BMC were forced into the model, regardless of significance; other variables were removed if p>0.05.

RESULTS: Significant variables for sub-head BMC/ht (R2 model=0.49) included; pre-test LM (p=0.006), change in ht (p=0.0003), and change in FM (p=0.006). Significant variables for change in spine BMC/ht (R2 model=0.35) included; pre-test LM (p=0.033) and change in FM (p=0.003). Significant variables for change in leg BMC/ht (R2 model=0.67) included; pre-test LM (p=0.003), change in ht (p=0.00005), and change in FM (p=0.001).

CONCLUSIONS: In this cohort of obese adolescents, change in FM was positively correlated with change in BMC at sub-head, spine, and leg regions. Thus, subjects who lost FM had a lesser BMC gain than those who gained FM. As large amounts of bone are gained during adolescent growth, this finding may have detrimental long-term skeletal health implications. This is especially concerning since a decrease in FM improves health and is a key target in many interventions. Future research is required to elucidate the relationship between FM and BMC change and to target interventions that decrease FM while maintaining or increasing BMC.
The Incidence of Thyroid Cancer by FNA Varies by Age and Gender

Authors: Laurel Bessey, BS; Ngan Betty Lai, BA; Nicholas Coorough, BS; Herbert Chen, MD, FACS; Rebecca Sippel, MD, FACS

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

Mentor: Rebecca Sippel, MD, FACS

Support: Department of Surgery NIH T35 Training Grant DK062709

BACKGROUND: Fine needle aspiration (FNA) is currently the standard diagnostic procedure used to evaluate thyroid nodules for malignancy. Factors such as age and gender may impact the risk of a thyroid nodule being malignant. The aim of this study was to determine the influence of age and gender on the rate of thyroid nodule malignancy by FNA.

METHODS: A database of 3,981 consecutive patients who underwent thyroid FNA between 2002 and 2009 at our institution was reviewed. Patients were grouped based on age and gender and the percentages of benign, indeterminate, and malignant biopsies were determined. Statistical analysis was performed using SPSS.

RESULTS: Our patient population included 2,766 women (mean age ± SD, 52 ± 15.2) and 964 men (mean age ± SD, 59 ± 13.8). 259 (6.5%) patients had a non-diagnostic FNA result. Of the 3,722 (93.5%) patients with diagnostic FNAs, 196 (5.3%) had malignant FNA cytology. Malignant FNAs were twice as frequent in patients age ≤45 vs. those >45 (8.1% vs. 4.0%, p<0.001). Overall, men had more indeterminate (10.2% vs. 6.3%, p<0.001) and malignant (6.7% vs. 4.8%, p=0.034) FNAs than women. This gender-based difference for malignant FNAs was greatest in patients over age 45 (6.0% vs. 3.2%, p=0.001). The incidence of malignant FNAs for women peaked in their 30s (10.4%) whereas the incidence of malignant FNAs for men peaked 10 years later in their 40s (12.1%). Both men and women had the lowest incidence of malignant FNAs in their 70s (2.3% and 1.9% respectively).

CONCLUSIONS: Our study shows that the typical 5% risk of thyroid nodule malignancy on FNA varies depending on patient age and gender. A patient’s age and gender should therefore be considered when counseling someone of their risk of thyroid cancer by FNA.
Response of Type II Diabetes Mellitus to the Preoperative Liquid Diet as a Predictive Model for Diabetes Resolution in Bariatric Surgery Patients

Authors: Steven M. Biro, BS, MS; Diane Olson, MS, RD, CDE; Michael J. Garren, MD; Jon C. Gould, MD

Department: Department of Surgery, University of Wisconsin School of Medicine and Public Health; UW Health Bariatric Surgery Program

Mentors: Jon C Gould, MD; Michael J. Garren, MD

Support: Department of Surgery NIH T35 Training Grant DK062709

BACKGROUND: The prevalence of obesity and type II diabetes mellitus (T2DM) is rapidly increasing. In morbidly obese individuals with T2DM, bariatric surgery offers a novel therapeutic endpoint – complete disease remission. In our bariatric surgery program, patients are placed on an 800 calorie/day, very low-calorie diet (VLCD) for 2 weeks prior to surgery. Some diabetic patients experience significant improvement in blood glucose control and reduced insulin requirements on this VLCD. We sought to define the relationship between diabetic response to the pre-op VLCD and T2DM resolution rates post-op in a select group of bariatric surgery patients with the most severe diabetes – those requiring injectable insulin.

METHODS: The study group was comprised of 51 insulin-dependent T2DM patients who underwent bariatric surgery at the UW Health Bariatric Surgery Program from August 2006 to February 2011. Subjects’ blood sugars and insulin requirements prior to initiating the VLCD were compared with those at 10 days on a VLCD. Patients with a > 50% reduction in total insulin dosage to maintain appropriate blood glucose control were considered ‘rapid responders’ to the pre-op VLCD. All others were considered ‘non-rapid responders’. Subjects were followed up to 1-year post-op to determine T2DM resolution rates (complete cessation of all antidiabetic medication).

RESULTS: Twenty-nine patients (57%) were considered ‘rapid responders’ to the pre-op VLCD [21 underwent laparoscopic gastric bypass (LRYGB) and 3 laparoscopic adjustable gastric band (LAGB)]. There were 22 ‘non-rapid responders’ (14 LRYGB and 7 LAGB). Rapid and non-rapid responders did not differ based on age, sex, pre-op body mass index, HbA1c, or duration of T2DM. T2DM resolution rates were significantly greater in the ‘rapid responder’ group vs. ‘non-rapid responder’ group at 3 months (8/29, 27.6% vs. 2/22, 9.1%; p=0.16), 6 mo. (11/25, 44% vs. 3/22, 13.6%; p=0.02), and 12 mo. (16/22, 72.7% vs. 1/17, 5.9%; p<0.01). Evaluating LRYGB patients alone for weight loss (% excess weight loss or %EWL), the ‘rapid responder’ group showed greater %EWL at 3 months (40.1% vs. 28.2%, p<0.01), 6 mo. (55.2% vs. 40.2%, p<0.01), and 12 mo. (67.7% vs. 47.3%, p<0.01).

CONCLUSIONS: Insulin-dependent T2DM bariatric surgery patients who display a rapid response (≥50% reduction in insulin requirements) to the pre-op VLCD are more likely to experience early resolution of T2DM post-op and greater weight loss.
Treatment of Spinal Cord Injury using Peripheral Nerve Grafts and a Sustained Release of ChondroitinaseABC

Authors: Ernesto A. Bogarin, BA; Daniel Hellenbrand, BS; Euhaa Hwang; Amgad Hanna, MD

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

Mentor: Amgad Hanna, MD

Support: Shapiro Summer Research Program; Department of Neurological Surgery

BACKGROUND: After spinal cord injury (SCI), axons in the central nervous system fail to regenerate, causing permanent paralysis. One of the primary reasons axonal regeneration is limited in the central nervous system (CNS) is due to the formation of the glial scar. One of the primary molecules in the glial scar that inhibit axonal growth is chondroitin sulfate proteoglycans (CSPGs). Degrad ing these CSPGs with chondroitinase ABC (chABC), an enzyme that digests glycosaminoglycan chains on CSPGs, has been shown to promote axonal regeneration and functional recovery after SCI. One limitation of chABC is that it loses its enzymatic activity at 37ºC in 2-3 days, while the CSPGs are upregulated for two weeks. An ideal application method would involve an in vivo mechanism that provides a sustained release of chABC directly to the injury site.

A way to support axonal growth through an injury site is to implant a peripheral nerve graft. When implanted into the CNS, this pre-degenerated peripheral nerve graft creates a permissible environment for axons to grow through by providing growth factors to the site and forming a scaffold through which new axons can grow.

The combination of a peripheral nerve graft and a sustained release of chABC will create a permissible environment for axons to grow through a spinal cord injury site and enhance functional recovery.

METHODS: Donor rats will have their sciatic nerve cut proximally, 7 days prior to transplant. The recipient rats undergo a laminectomy at T10 and a 3mm length of their spinal cord is transected. Two 3mm sciatic nerve grafts are placed into the spinal cord to bridge the gap. One group of rats will also receive a hydrogel tube containing microspheres that release chABC. The rats are kept alive for eight weeks to assess functional recovery. After eight weeks some rats will have BDA injected into the brainstem and conjugated CTB injected into both sciatic nerves. The rats are perfused two weeks after the injections and the spinal cord is sectioned for immunohistochemistry analysis.

RESULTS: Preliminary results show a trend in an increase in functional recovery in all treated groups by BBB testing compared to the control group.

CONCLUSIONS: The current preliminary results are promising and the addition of other experimental procedures like electrophysiology, growing factors and other sources of sustained release would help in the understanding of spinal cord injury and restoration.
Reduced Contractile Reserve: A Therapeutic Target in Heart Failure with Preserved Ejection Fraction

Authors: Jenna F. Borkenhagen; Holly S. Norman, PhD; Melissa Bailey, RDCS, RVT; Todd M. Forsythe; Nancy K. Sweitzer, MD, PhD

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

Mentors: Nancy K. Sweitzer, MD, PhD; Holly S. Norman, PhD; Melissa Bailey, RDCS, RVT; Todd M. Forsythe

Support: Shapiro Summer Research Program; UW Cardiovascular Research Center; NIH 1R21HL106103-01 (NKS); 1UL1RR025011 from the Clinical and Translational Science Award (CTSA) program of the National Center for Research Resources, NIH

BACKGROUND: Roughly half of all patients with heart failure have a normal ejection fraction (EF). This condition, named Heart Failure with preserved Ejection Fraction (HFpEF), is a multifactorial disease. The contributing factors and underlying physiology are poorly understood, making diagnosis and treatment a challenge. The chief complaint of many HFpEF patients is dyspnea on exertion, but diagnostic tests are typically performed at rest. There is a strong need for a sensitive and specific, non-invasive diagnostic test for HFpEF.

Dobutamine is a β-1 receptor agonist which increases contractility of the myocardium. Previous research demonstrated that dobutamine increases EF in control subjects but not in HFpEF patients. Thus, HFpEF patients appear to have abnormal contractile reserve. Our aim is to assess the potential of low-dose dobutamine to diagnose HFpEF. We hypothesize that EF will increase with low-dose dobutamine in patients with non-HFpEF causes of exertional dyspnea, but not in patients with HFpEF.

METHODS: Subjects are being recruited into four study groups: HFpEF, pulmonary disease, hypertension with left ventricular hypertrophy, and healthy controls. During study sessions, echocardiographic images and other data were acquired at baseline and repeated after two incremental doses of dobutamine.

Analysis of echocardiographic recordings was performed using TomTec software. Change in EF following dobutamine administration was the primary outcome variable. EF values were calculated using 4D analysis software to make end-systolic and end-diastolic traces. Left Ventricular (LV) torsion was calculated as the difference in maximum rotation between the base and apex.

RESULTS: Initial results show a smaller increase in EF with sequential administrations of dobutamine in a HFpEF subject compared to a pulmonary disease subject and a healthy control. Torsion of the LV endocardium increased with dobutamine in all three subjects. Torsion of the LV epicardium was smaller in magnitude and showed a less definitive trend.

STATUS & FUTURE INTENT: Subject study visits and data collection are currently in progress. Once all data is gathered, the role of contractile reserve and also ventricular-vascular coupling in HFpEF will be evaluated. Contractile reserve will be assessed using change in EF and LV torsion. Ventricular-vascular coupling will be assessed by incorporating tonometry data to calculate pulse wave velocities and characteristic impedance.
Stenting for Malignant Obstruction in the Upper Urinary Tract

Authors: Jason Carr, BS; Stephen Nakada, MD

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

Mentors: Stephen Nakada, MD; Kris Penniston, PhD

Support: Shapiro Summer Research Program; Department of Urology

BACKGROUND: Patients with malignant obstruction of the upper urinary tract require intervention to maintain kidney function and for symptomatic relief. The reported failure rate for the most common intervention, retrograde stenting, varies greatly (19-45%) with little agreement on factors which contribute to failure. This challenges physicians and patients when planning for treatment and discussing alternatives.

METHODS: We retrospectively reviewed records for patients who underwent retrograde ureteral stenting for malignant obstruction of the upper urinary tract at the University of Wisconsin Hospital and Clinics from 1999 to 2009. Patient demographics were extracted from 74 records on 80 obstructed ureters. Failure was defined as the need for an alternative procedure to alleviate unresolved symptoms or to maintain kidney function.

RESULTS: 21 of 80 (26.3%) stented ureters failed. The highest failure rate (n>=4) occurred in prostate (50%), transitional cell (38%) and cervical (38%) cancers. The lowest rates of failure (n>=4) occurred in those with lymphoma (20%) and ovarian (7%) cancers. Two factors we reviewed predicted failure with statistical significance: solitary kidney (p=0.016) and stent malfunction (p<<0.01). Stent change interval (p=0.12), pre-op serum creatinine (p=0.16), sepsis (p=0.18) and emergency department admission (p=0.13) showed marginal predictive value.

CONCLUSIONS: Our results affirm the difficulty reported by other groups in establishing a prognostic framework for this procedure. We found that type of cancer is helpful in predicting stent failure and that stent malfunction and solitary kidney are statistically significant predictors of stent failure in those with malignant ureteral obstruction.
**Pressure Gradients Within and Across Intracranial Aneurysms Using MR Phase Contrast Velocity Data**

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**Mentor:** Patrick Turski, MD, FACR

**Support:** Shapiro Summer Research Program; Department of Radiology; NIH R21EB009441-01 Functional MRA of the brain

**BACKGROUND:** The purpose of this research is to calculate pressure gradients within and across intracranial aneurysms using MR phase contrast velocity data (PC VIPR). The area of pulse wave transmission through aneurysms has not been fully explored. This research is the first part in the analysis of pressure wave transmission through intracranial aneurysms. Our hypothesis was that pressure pulsatility would be dampened by a large aneurysm, such that the pressure distal to the aneurysm would have less pulsatility than the pressure proximal to the aneurysm. We believe this is because the aneurysm will act as a balloon like capacitor dampening the pulse waves as they pass through. Furthermore, it has been suggested that following treatment of a large aneurysm, the subsequent restoration of pulsatile flow in a vascular bed without auto-regulation can lead to hemorrhage. Reliable, non-invasive methods to determine pulsatility in intracranial aneurysms are needed.

**METHODS:** Four aneurysms from 4-6 mm in diameter were included in this study. A PC-VIPR MRA sequence was used to obtain cardiac-gated velocity measurements of the whole brain. The data obtained from PC-VIPR was graphically processed to yield fluid velocity vector plots. Using fluid relationships we processed the data from pathological sub-volumes of the intracranial vasculature to yield dynamic pressures proximal, distal, and inside of the aneurysms. An extension of the pulsatility index was used. The pulsatility of the pressures is equal to the difference between the peak systolic and minimum diastolic pressures divided by the mean pressure during the cardiac cycle at each point proximal, distal, and inside the aneurysms.

**RESULTS:** In the 4 aneurysms, the maximum and minimum pressures gradients were calculated. The average pressure drop from proximal to distal was 3.87 mmHg and the average pressure drop from proximal to within the aneurysms was 4.07 mmHg which is not significant. The pulsatility decreased from proximal to distal and the overall pulsatility on the contralateral side was higher.

**CONCLUSIONS:** This study helped define the methods to be used to analyze the pressure gradients. Further studies will include phantom studies and the analysis of multiple different sized aneurysms. We would like to analyze the data from side wall aneurysms of 3-5, 6-10, 11-15, and 16-20 mm in diameter to determine the impact of aneurysm size on the pulsatility.
Preliminary Investigation Between Cognitive Test Performance and Cardiovascular and Dementia Risk Scores

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Support: Shapiro Summer Research Program; Department of Medicine

BACKGROUND: Many modifiable dementia risk factors are also cardiovascular risk factors. Thus, both cardiovascular and dementia risk assessments may serve as future tools for diagnosing and predicting the onset of dementia and Alzheimer’s disease (AD). To investigate the screening tool that best predicts cognitive performance, we analyzed cardiovascular and dementia risk scores and cognitive tests outcomes using SHARP Study baseline data.

METHODS: SHARP participants were 40-69 years old and had a parental history of AD (n=69). Pearson and Spearman correlations, and T-tests were calculated to evaluate relationships between risk scores and cognition as well as group differences in cognitive performance on baseline data. Cardiovascular risk profiles were derived from Reynolds Risk Score (RRS), Prospective Cardiovascular Münster (PROCAM) Coronary Risk Assessment, and Framingham Risk Score (FRS), and dementia risk was derived from Kivipelto Dementia Risk Assessment. The study population was stratified into APOE4 positive and APOE4 negative subpopulations for additional analysis.

RESULTS: The four significant (p<0.05) correlations between risk scores and cognitive tests in the non-stratified data were PROCAM and Trail Making Test B (TMTB) (r=0.262), FRS and Mental Control (r=-0.296), and RRS and Stroop Color-Word (SCW) (r=-0.287) and TMTB (r=0.259). The four significant correlations found in the APOE4 negative stratified data were FRS and Mini-Mental State Exam (MMSE) (r=-0.352) and SCW (r=-0.353), and RRS and MMSE (r=-0.358) and SCW (r=-0.365). The four significant correlations in the APOE4 positive stratified data were PROCAM and TMTB (r=0.414) and HVLT Delayed Recall Raw Score (r=-0.439) and HVLT Delayed Recall Percent Retained (r=-0.409), and RRS and TMTB (r=0.046). The APOE4 positive subgroup had higher Kivipelto Risk Scores than the APOE4 negative subgroup. This was the only significant group difference (p<0.001).

CONCLUSIONS: Our results parallel previous studies that found executive function is the cognitive domain that typically declines early in people at risk for AD. Based on our findings, it is plausible RRS is best capable of assessing general cognitive function and executive functioning in asymptomatic middle-aged adults (ages 40-69) with a parental history of AD, and that PROCAM is best capable of assessing memory and learning in those in this population with the APOE4 polymorphism. In our sample, neither the Framingham nor Kivipelto Risk Scores predicted cognitive function.
**Micro RNA Analysis in Thyroid Cancer Stem Cells**

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**Support:** Shapiro Summer Research Program, Department of Pathology and Laboratory Medicine

**BACKGROUND:** Changes in microRNA expression have been demonstrated to play a role in the progression of papillary thyroid cancer (PTC) and anaplastic thyroid cancer (ATC). It is also known that subpopulations of stem-like cells exist in thyroid cancers possessing tumorigenic properties. However, miRNA expression has not been evaluated in cancer stem-like cells (CSC) isolated from either cancer type. Therefore, we compared expression of two miRNA’s in PTC and ATC cell lines to normal thyroid cell lines and also compared the expression of the same two miRNA’s in subpopulations of PTC and ATC cell lines positive for the cancer stem cell marker CD133 to the CD133- subpopulation. The two miRNA’s, miR-200a and miR-221, have been demonstrated to be altered in PTC and ATC. We predict the expression of these two miRNA’s will be significantly different in CSC stem cell subpopulations compared to the non-CSC subpopulation and normal thyroid cells.

**METHODS:** CD133+ and CD133- subpopulations of PTC (cell lines BCPAP and TPC-1) and ATC (cell lines 8505 and FRO81-2) were separated using FACS. Expression of miRNA in PTC, ATC, and normal thyroid (cell line Nthy-ori-3-1) was analyzed using RT-PCR.

**RESULTS:** Expression of miR-200a was significantly higher, compared to the normal thyroid cell line in both PTC cell lines tested (p = 0.025), in one of the ATC cell lines, 8505, (p = 0.005), both CD133+ and CD133- subpopulations of the PTC cell line BCPAP (p = 0.05), and both CD133+ and CD133- subpopulations of the ATC cell line 8505 (p = 0.005), with n = 3 for all the cell lines tested. Expression of miR-221 was significantly higher, compared to the normal thyroid cell line in the BCPAP cell line (p = .005) and the 8505 cell line (p = 0.01). Expression of both miR-200a and miR-221 in the CD133+ subpopulations as compared to the CD133- subpopulations were not significant for either the BCPAP or 8505 cell lines.

**CONCLUSIONS:** Expression of miR-200a and miR-221 were significantly higher in PTC and ATC cell lines, compared to the normal thyroid cell line. Also, expression of miR-200a was significantly higher in the CD133+ subpopulations, compared to normal thyroid. However, no significant difference was observed for either miRNA levels between the CD133+ and CD133- subpopulations. These results suggest that differences in miRNA expression in CSC’s may play a role in thyroid cancer pathogenesis - the mechanisms of which may be elucidated by future research.
Identifying Predictive Risk Factors for the Development of Hepatocellular Injury during Liver Transplantation

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BACKGROUND: Ischemia reperfusion injury (IRI) is an unavoidable process that occurs during the liver transplantation. We have previously shown that the severity of hepatocellular damage due to IRI leads to inferior long-term patient and graft survival. The purpose of this study was to identify donor, recipient, and intraoperative risk factors that were predictive of increased hepatocellular damage occurring within the first week of transplantation.

METHODS: We performed a retrospective analysis of 507 deceased donor, liver transplants performed at our institution between 2002 and 2009. Data were acquired from individual chart reviews and from our prospectively collected liver transplant database. We identified donor, recipient, and intraoperative variables that could potentially impact the severity of hepatocellular injury. Using these variables, we performed an analysis of variance to determine if the variables correlated with peak serum alanine aminotransferase (ALT) levels within the first week after transplant. Significance was defined as p value ≤ 0.05.

RESULTS: Intraoperative vasopressor use was strongly associated with elevated ALT postoperatively (p≤0.02), specifically norepinephrine, vasopressin, and dopamine. Other significant intraoperative variables included portal vein anastomosis redo (0.001), implantation time (0.01), intraoperative time (<0.001), and use of a mesenteric venous jump graft (0.02). Significant preoperative variables included percentage of donor liver microsteatosis and macrosteatosis (0.02, <0.001), preoperative portal vein thrombosis (PVT) (0.04), donation after cardiac death (0.001), and donor height (0.03). Donor age (0.48) and cold ischemic time (CIT) (0.94) were not found to be significant.

CONCLUSIONS: The identification of risk factors for IRI will hopefully allow for more deliberate decision-making before, during, and after surgery. Combination of these risk factors may have additive deleterious effects on hepatocellular injury. Avoidance of these known risk factors when possible may have a positive impact on limiting hepatocellular injury and improving liver transplant outcomes.
Antibiotic Utilization in Long Term Care Facilities in Wisconsin

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Support: Shapiro Summer Research Program; Department of Medicine

BACKGROUND: Antibiotic use is a major driver of antibiotic resistance, and improving antibiotic use is considered a major public health priority. Epidemiological studies have repeatedly documented high rates of antibiotic resistance in nursing homes. The extent and overall patterns of antibiotic use in nursing homes remain poorly understood. A recently completed cohort study on antibiotic resistance in Wisconsin nursing homes provided us with an opportunity to better characterize antibiotic use in regional nursing homes.

METHODS: A prospective cohort study was performed on 6 Wisconsin nursing homes. 449 nursing home resident charts were reviewed for antibiotic utilization to determine antibiotic starts (AS) per 1,000 resident-days and days of therapy (DOT) per 1,000-resident days stratified by facility and antibiotic class.

RESULTS: 65.3% of residents received antibiotics, receiving between 1 and 13 antibiotic starts. Antibiotic consumption by class and across facilities varied considerably based on the utilization metric employed. For example, fluoroquinolone use represented 36% of the total number of antibiotic starts in the study facilities but only 25% of the days of therapy. The difference in the overall consumption of antibiotics by facility ranged by 48% (4.22 to 6.27) when measured by AS per 1,000 resident days but 335% (34 to 114) when measured by DOT per 1,000 resident-days. The antibiotic consumption was concentrated within a small group of residents, with residents receiving 5 or more AS accounting for 28% of all AS and 22% of all DOT. There was marked variation between facilities.

CONCLUSIONS: Residents of Wisconsin nursing homes are commonly exposed to antibiotics. The extent to which patterns (both in choice of agents and intensity of exposure) of antibiotic use contribute to the generation of antibiotic resistance requires further exploration. However, the marked variation in antibiotic utilization seen in our cohort suggests that there is substantial room for improvements in antibiotic use.
Step Rate Modification while Running

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**BACKGROUND:** Running with an increased step rate has been shown to reduce the joint loading at the hip and knee. Because excessive joint loading is a risk factor for running-related injuries, using an increased step rate as a treatment for injuries related to joint loading may be beneficial. However, the amount of training necessary to change step rate is unclear. The aim of this study was to identify if subjects were able to reproduce an increased step rate five weeks after an initial training session. This study will be used to support a randomized controlled trial investigating if increasing step rate is an effective treatment for runners with anterior knee pain.

**METHODS:** Ten injury-free, recreational runners (4 females, 6 males; age 33.0 ± 14.9 years) took part in this study. Subjects ran on an instrumented treadmill at their self-selected speed and step rate while ground reaction forces were recorded. Subjects were then taught to run at a step rate 8% above their preferred using a 15-minute, standardized training protocol, which included periods with and without the metronome. Subjects returned for a one-week follow-up session, where they were retrained using the standardized protocol if they were unable to reproduce the modified step rate. Four weeks later, subjects attempted to independently reproduce the modified step rate. Step rates were calculated from the ground reaction forces and compared to the desired rate. Successful training for the step rate group was defined by being within 3% of the desired step rate, which is the natural variability of a runner's step rate.

**RESULTS:** Subjects were able to successfully reproduce the modified step rate five weeks after initial training. Subjects were, on average, within 2.82% of the desired step rate.

**CONCLUSIONS:** A maximum of two 15-minute training sessions is sufficient for subjects to independently reproduce a modified step rate of 8% above their preferred step rate, five weeks after an initial training session. Therefore, increasing a runner’s step rate can be achieved with a simple procedure, resulting in a reduction of the biomechanical demands of running. The simplicity of this gait retraining makes it a feasible method to use in a study investigating the effects of cadence modification in runners with anterior knee pain.
Urban and Rural Differences in Health-related Quality of Life and Healthcare Access

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Support: Shapiro Summer Research Program; Survey of the Health of Wisconsin (SHOW), Department of Population Health Sciences; National Institutes of Health; Wisconsin Partnership Program; UW Institute for Clinical and Translational Research; Discretionary funds, Department of Population Health Sciences

BACKGROUND: Previous studies have found statistically significant differences in Health-related Quality of Life (HRQOL) between urban and rural residents in clinical populations. We aimed to determine if there are differences in HRQOL and access to health care for rural and urban residents in the general Wisconsin population and whether healthcare access influences HRQOL scores.

METHODS: Data for this study was collected from 1570 Wisconsin residents as part of the 2008-2010 annual surveys conducted as part of the Survey of the Health of Wisconsin (SHOW). HRQOL was measured using the SF-12 Health Survey. Geographic residence was classified using Rural Urban Commuting Codes as Urban, Suburban or Rural. Access to Healthcare was defined using 5 questions: (1) did the participant have health insurance for the previous 12 months; (2) had they failed to fill a prescription due to cost; (3) if the participant’s usual source of care was a doctor’s office; (4) whether the patient had received a flu shot in the last yr; and (5) being “Very Satisfied” when asked how satisfied they were with the healthcare they received.

RESULTS: Unadjusted HRQOL scores showed no statistical difference between urban and rural residents. No statistically significant healthcare access differences were seen between Urban and Rural residents, except rural residents were nearly twice as likely to be very satisfied with their healthcare (OR: 1.7, 1.0-2.9). In our model, after adjusting for age, sex, race, education and income, only “Failing to get meds due to cost” was shown to have a statistically significant impact on both physical (-4.8; p<0.001) and mental (-2.8; p=0.01) component HRQOL scores.

CONCLUSIONS: Differences between urban and rural residents in HRQOL scores seen previously in clinical populations were not observed in Wisconsin. The lack of differences in health care access between urban and rural residents may in part be do to the large network of tertiary care clinics spread across the state as well as other policies and programs being implemented across the state to support access to care in rural communities.
The Use of Ghrelin to Reduce Spinal Cord Injury Immunopathology

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Support: Shapiro Summer Research Program; Department of Neurological Surgery

BACKGROUND: Spinal cord injury can be induced by many different mechanisms ranging from infection to blunt force trauma. Regardless, immunopathology is a trademark of all spinal cord injury which works to further damage neurons and their supportive glia during and after the initiating injury has been removed. By targeting the central immune cell of the CNS, microglia, we believe that we can reduce immunopathology and help promote functional recovery following spinal cord injury. We will be studying the effects of the gastric derived hormone, ghrelin, on suppressing CNS immunopathology. Ghrelin has already been shown to be effective in other models of SCI but we are seeking to develop a better understanding of how and under what situations does ghrelin impact the microglia mediated immune response.

METHODS: Cultures of microglia were stimulated with LPS, TMEV (virus mimic) and IFN-gamma. The groups were subsequently treated with either ghrelin or ghrelin and its associated inhibitor, GHRP-6. The timing of treatment was either at the same time of stimulation or 24 hours following. The production of pro-inflammatory and anti-inflammatory cytokines was assessed using PCR analysis.

RESULTS: Our in-vitro study has shown that ghrelin can significantly reduce levels of pro-inflammatory cytokines (IL-6, TNG-a, IL-1b) while promoting production of anti-inflammatory cytokines (IL-10) within TMEV and LPS stimulated microglia. Timing of drug administration did not have an effect on ghrelin’s ability to modify cytokine expression. Ghrelin’s ability to reduce pro-inflammatory cytokines and promote anti-inflammatory cytokines was partially hindered with introduction of GHRP-6. Ghrelin did not have a significant impact on cytokine production within IFN-gamma treated samples regardless of timing or GHRP-6 administration.

CONCLUSIONS: We have shown for the first time that ghrelin’s inhibition of microglia activation is stimulus dependent and timing independent. This has provided a better understanding of the therapeutic significance of ghrelin as well as the timing/stimulus variability in microglia activation. We plan to pursue these findings further with in-vivo mice models of multiple sclerosis.
Molecular Significance of BRAF Mutations in Multiple Myeloma

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BACKGROUND: Despite therapeutic advances in studying multiple myeloma (MM), it has a low median survival of 3 years. This is in part due to a limited understanding of its pathogenesis. Recently, however, there have been major advances in understanding its genetic basis. Some of the most significant mutations identified have been in the BRAF gene family, especially V600E and G469A. BRAF inhibitors against V600E are already used for other types of cancer, so we postulated that these therapies may extend to G469A. The Asimakopoulos lab has developed a κ-Myc murine model that is the first integrated mouse model for MM. Thus, the goal is to ultimately use retrovirally-mediated gene delivery of V600E and G469A into κ-Myc mice and to compare mutants at the molecular level.

METHODS: BRAF mutants were cloned into pMSCV PIG retroviral vectors using sticky-end PCR. The vector was generated using restriction digests and treatment with calf intestinal alkaline phosphatase to prevent vector religation. The vector was ligated to the BRAF inserts, transformed via heat shock into competent E.coli, and expanded in culture. The plasmid constructs were subsequently isolated and purified, then evaluated for appropriate gene orientation by gel electrophoresis. Next, the plasmids were sequenced and compared to wild-type BRAF using Mesquite software. Mutants were transfected into GPT-293T cells containing env using calcium-phosphate precipitation and harvested on sucrose columns.

RESULTS: Clinically relevant BRAF alleles were cloned into a retroviral vector using a primer-driven PCR approach. Additionally, an HA-tag was successfully introduced using the same approach. The accurate introduction of the tag in frame with the coding sequence of BRAF was confirmed via sequencing. Next, the constructs were packaged into an avian enveloped infectious retrovirus, which were designed to be capable of being taken up by mammalian cells bearing the avian retroviral receptor, TVB. The packaged virus has since been successfully expressed in human myeloma cell line RPMI 8226.

CONCLUSIONS: Mutant BRAF was expressed in a lineage and disease-specific context. The results and novel reagents generated will lead to further insights into the molecular mechanisms of MM. The in vitro system will allow for transcriptomic comparison between cell line clones expressing wild-type BRAF compared to G469A and V600E. Ultimately, the mutants will be studied in vivo in the κ-Myc murine model for MM.
A Prospective Chart Review Analyzing Predictive Variables Associated with Blood Cultures in the ED

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Support: Shapiro Summer Research Program; Department of Medicine, Division of Emergency Medicine

BACKGROUND: The purpose of this study is to undertake a detailed study of the use of blood cultures in the ED and to identify predictors of bacteremia. We hypothesize that most cultures are unnecessary to patient care and can be safely eliminated. Blood cultures are a commonly ordered test. However, the general indications for blood cultures are poorly defined and culture yields are remarkably low. The true positive rate is usually low (2-8%) with few clinical useful results. There are often equal false positive to true positive rates. The low yield and false positives have significant financial costs.

METHODS: This is a retrospective chart review taking place at an teaching hospital with an annual census of approximately 40-45,000. All patients for whom a blood culture was performed in 2009-2010 were eligible for inclusion. A detailed chart review was performed on consecutive patients from 10/1-12/31/2010. Demographic, clinical and laboratory data were abstracted for each patient. All variables were then used to derive a clinical prediction model for culture positivity.

RESULTS: There were 2872 blood cultures in 2009 (7% of patients), 3375 in 2010 (8%). Detailed information was obtained on 600 patients. There were 90 positive culture results (15%). Of these 28 were contaminants. 361 patients had a focal infection and a local source culture was done in 257 (of which 151 were positive). 44 (50%) patients with positive blood cultures had local infections and of these 30 had focal cultures with positive results. 21 were concordant, but 9 were discordant and of these the blood culture was a contaminant in 7. Variables contained in the predictor model were temperature, total WBC, neutrophil %, platelet count, and presence of a focal infection. Using a probability of >2.5%, the sensitivity was 94%, while reducing the number of cultures by 25%.

CONCLUSIONS: Using an evidence-based approach to guide the use of blood cultures can lead to significant cost savings. We have developed a prediction rule for predicting a true positive blood culture. Having a focal infection is an independent and important predictor of bacteremia. However, results of blood culture results are concordant with focal culture result and when discordant overwhelmingly contamination. Even in those patients with a >2.5% probability of bacteremia, by our model, blood cultures could be forgone in those with focal infections.
Risk Factors for Acquisition of *Clostridium difficile* Infection in Solid Organ Transplant Recipients

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**Support:** Shapiro Summer Research Program; Department of Medicine, Division of Infectious Diseases

**BACKGROUND:** *Clostridium difficile* infection (CDI) is a major health concern in solid organ transplant (SOT) recipients, affecting up to 16% of kidney and 7% of liver recipients. Risk factors for CDI, including antibiotic and healthcare exposure, are common among transplant recipients. However, it is unknown if there are other risk factors for development of CDI unique to SOT recipients. We performed a case-control study to determine risk factors for CDI in SOT recipients.

**METHODS:** We undertook a case-control study of kidney and liver transplant recipients with and without CDI over a 14-year period at a single center. Subjects were matched based on year of transplant, organ type, and duration of follow-up. Data including hospitalization, antibiotic exposure, co-morbidities, and concomitant infections were collected for cases and controls. Data analysis was done using logistic regression.

**RESULTS:** We identified 106 kidney and 63 liver transplant recipients with at least one episode of CDI, and 208 kidney and 115 liver transplant recipients without CDI. There were 315 (64%) men and 177 (36%) women with a mean age of 51.7 (SD 11.7, range 20-78). Immunosuppression included steroids (99%), calcineurin inhibitors (91%) and antimetabolites (84%), with some patients on monoclonal antibodies (50%), and polyclonal antibody therapy (18%). Univariate analysis identified the following risk factors: hemodialysis, active malignancy, colitis, prior ICU care within 30 days of CDI diagnosis, surgical procedure within 30 days of CDI diagnosis, antibiotic exposure (concomitant, exposure within 30 days of diagnosis, and total exposure), and liver/biliary/pancreatic surgery.

**CONCLUSIONS:** This study supports previously identified risk factors for CDI, such as antibiotic exposure and colitis. It also identifies a number of other independent risk factors for CDI found in SOT recipients, including active malignancy and recent liver, biliary, or pancreatic surgery. These findings can be used to better understand a patient’s risk for developing CDI following SOT.
The Effect of Prison Release on Disease Progression and Development of Viral Resistance in HIV+ Inmates

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BACKGROUND: While many HIV+ prisoners are diagnosed and initiate antiretroviral therapy (ART) during their incarceration, several studies have demonstrated that treatment interruptions are common when inmates transition into the community. Such interruptions allow for the progression of infection, as evidenced by increased viral load and decreased CD4+ cell counts. Development of drug resistance in this context has not yet been described. This study investigated the effect of prisoners' release on disease progression and resistance.

METHODS: We retrospectively analyzed clinical and laboratory data from 2001-2010 for 134 patients who received HIV care prior to release from prison and after re-incarceration (after a median duration of 17.3 months in the community). To investigate the effect of release from prison on HIV control and viral resistance, we compared HIV viral load, CD4+ cell count, and HIV resistance (genotype) prior to release and after re-incarceration.

RESULTS: HIV genotype data obtained at the time of re-incarceration were available for 38 inmates. Antiretroviral resistance mutations were detected in 23 (60%) of these cases upon re-entry into prison-based care. 10 inmates had HIV genotype testing done prior to release and at re-incarceration, of which 8 (80%) had novel resistance mutations. 9 of these 10 cases required a change to the antiretroviral regimen due to treatment failure with resistance. New mutations detected included L63P (7 cases), K103N (7 cases) and M184V (5 cases). For these 38 inmates, mean CD4+ counts decreased from 468 cells/µL prior to release to 391 after re-incarceration. Viral loads increased from a mean of 34,381 to 50,043 copies/mL. 12/38 patients (32%) had undetectable viral loads prior to release; after re-incarceration, this decreased to 5/38 patients (13%). 24/38 (63%) reported receiving HIV care in the community prior to reincarceration.

CONCLUSIONS: A significant number of HIV+ prisoners are reincarcerated with novel resistance mutations and suboptimal virologic control. Recent incarceration should be viewed as a risk factor for poor engagement in HIV care, inferior treatment outcomes, and increased resistance. Interventions are needed to optimize virologic control within the prison system as well as improve continuity of HIV care and drug adherence among former prisoners.
Improving Loss of Follow-up of Patients with Abnormal Cervical Cytology at Two Clinics

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BACKGROUND: Management of cervical cytology abnormalities requires tracking and testing of patients over many years. In a residency clinic, this follow-up may span the tenure of one or more resident physicians. Implementation of a spreadsheet to track and manage abnormal cervical pathology results may improve provider communication and patient adherence with recommended follow-up.

METHODS: We identified all patients from two family medicine residency clinics (Verona and Wausau) with a first abnormal cervical pathology result from November 2005 to November 2007 (Control group, Verona: 67 patients; Wausau: 53 patients) and from November 2008 to May 2010 (Experimental group, Verona: 104 patients; Wausau: 69 patients). The Experimental group was followed using a spreadsheet that listed a patient’s abnormal result, the next recommended step, and the due date for this step. This spreadsheet was reviewed monthly, and patients with overdue monitoring were identified and reminded of the need for evaluation by telephone and/or letter. All patients were evaluated for adequate follow-up. Each step was scored as “appropriate” or “inappropriate” based on American Society for Colposcopy and Cervical Pathology guidelines, and “inappropriate” steps were reviewed to see if the need for follow-up was adequately communicated to patients.

RESULTS: After implementing a tracking system, the number of follow-up steps that were performed appropriately increased by 5.9% at the Verona clinic (p-value = 0.29, two-tailed), and 0.8% at the Wausau clinic (p-value = 1, two-tailed). The number of steps with adequate provider communication increased by 9.7% at the Verona clinic (p-value = 0.0082, two-tailed), and by 2.9% at the Wausau clinic (p-value = 0.66, two-tailed).

CONCLUSIONS: Use of a tracking system improved adherence to cervical cytology monitoring guidelines and provider communication of the recommended follow-up to patients, but these improvements were significant only in the communication of recommended follow-up at the Verona clinic.
Transgenerational Epigenetic Inheritance of Enhanced Spinal Cord Regeneration Following Spinal Cord Injury

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Support: Shapiro Summer Research Program; Department of Neurological Surgery.

BACKGROUND: The adult central nervous system (CNS) has little ability to heal and regenerate axons following injury. This effect is related to extrinsic inhibitory signals and an intrinsic failure to express genes required for effective neuron outgrowth. Epigenetic factors such as DNA methylation may contribute to such change in gene expression. We have shown that DNA methylation mediates folate-induced axonal regeneration in the injured CNS. We hypothesize that the effect of folate on CNS regeneration may transfer to offspring not directly exposed.

METHODS: Spinal Cord Regeneration Model (SCRM) Surgery: Sprague-Dawley rats were subjected to surgery. The cervical cord was exposed through a laminectomy. Using a pair of forceps, a 0.5 mm deep injury was made in both columns. A sciatic nerve segment harvested from the hindlimb was placed at the injury site. Two weeks later, a tracer was placed at the free end of the nerve graft. Twenty-four hours later, the animal was anesthetized. The L5 dorsal root ganglia (DRG) were removed bilaterally, postfixed, incubated in sucrose and frozen in OCT. Sections were cut at 12-µm with a cryostat. The spine was separated from the skull and laminae were removed to allow harvesting of the spinal cord for biochemical studies. Sections were examined under a microscope and the number of fluorescently-labeled cells were counted.

RESULTS: A mating pair of Sprague-Dawley rats was treated with intraperitoneal doses of folic acid starting 14 days before mating and given daily until the pups were weaned at day 21. Subsequently, non-sibling matings of offspring were bred to create F1-F3 generations with no additional folate treatment. Another mating pair given daily IP water injections was used to breed a control colony. Males from F1-F3 underwent injury and placement of a nerve graft at the injury site according to the SCRM method. This peripheral graft provides a permissive environment for axonal growth. Animals whose family lineage received IP folic acid showed rates of regeneration 3.6 times higher than control animals in each respective generation (F1-F3).

CONCLUSIONS: Folate supplementation produces progeny with enhanced spinal axon regenerative ability after injury. This effect is seen with oral and IP administration, is transgenerational and correlates closely with methylation changes to the germline. These findings have widespread implications in disease occurrence and therapy in the CNS as well as other systems.
Intratendinous Injection of Platelet-Rich Plasma into Lamb Extensor Carpi Radialis Tendon

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

Mentor: John Wilson, MD, MS

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

BACKGROUND: Platelet-rich plasma (PRP) is used to treat tendinopathy. The feasibility, distribution, and tissue-modifying effects of intratendinous PRP injection have not been studied. The objectives of this study are to determine: (1) the feasibility of intratendinous injections of PRP, (2) the distribution of PRP after intratendinous injection, and (3) whether intratendinous injection alters tissue morphology.

METHODS: Tendons received a methylene blue-containing PRP injection (PRP/MB; n=6), methylene blue only injection (MB; n=6), or a control needlestick (n=6). A single bolus injection with 0.25 mL of injectant was performed using a 22 gauge needle, inserted proximally at a 45 degree angle. Pre- and post-injection weights were obtained to determine the volume of retained injectant. Histological evaluation was performed to determine the distribution of injectant and whether tendon morphology was altered.

RESULTS: The injection groups increased in weight following the injection; the PRP/MB group increased by an average 0.22± 0.03 g (62.7% injectant volume retained), and the MB group increased by an average 0.23±0.10 g (52.4% injectant volume retained). The difference between injection groups was not significant (p=0.78). The control group did not significantly change in weight (0.05±0.07 g, p=0.12).

The mean proximodistal penetration of injectant in the PRP/MB group was 2.91±0.32 cm with a mean tendon cross-sectional penetration of 0.21±0.06 cm. The MB group showed a mean proximodistal spread of 2.77±0.40 cm with a mean cross-sectional penetration of 0.27±0.04 cm. The proximodistal spread was not different between groups (p=0.80) although the cross-sectional spread was greater in the MB group (p=0.02).

Injected tendons exhibited disruption to normal tendon morphology while control tendons retained normal tendon morphology.

CONCLUSIONS: Intratendinous PRP injections are technically possible, and the injectant remains within the tendon after injection. Solutions injected into tendon primarily distribute longitudinally within the tendon, with minimal cross-sectional spread. Injected tendons demonstrate disruption of normal tendon morphology compared to control tendons. Further study is warranted to examine effects of intratendinous injection into tendons and other tissue.
Intravenous Magnesium Sulfate is Ineffective at Alleviating Propofol Injection Pain: a Randomized, Double-blind, Placebo Controlled Trial

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

Mentor: Kristopher Schroeder, MD

Support: Shapiro Summer Research Program; Department of Anesthesiology

BACKGROUND: Propofol is commonly used for the induction of general anesthesia and sedation during monitored anesthesia care. Currently, pretreatment with lidocaine is commonly administered to prevent propofol injection pain. However, it appears that effective reduction of this pain requires that a tourniquet must be applied prior to the lidocaine dose. Magnesium has been investigated as a premedication prior to injection of propofol, but the results have been mixed. No studies to date have looked at the combination of lidocaine and magnesium in a syringe for the pre-treatment of propofol injection pain. We speculated that the combination of lidocaine and magnesium would have an additive effect with regard to reducing the pain associated with the injection of propofol.

METHODS: 158 patients were studied in a prospective, double-blinded fashion. Patients were randomly assigned to one of four groups (lidocaine 50 mg group, magnesium sulfate 0.25 mg group, lidocaine 50 mg + magnesium sulfate 0.25 group, and 0.9% normal saline. Study drugs were diluted to 10 mL using 0.9% normal saline. Study drugs were administered through a 20 gauge IV in the dorsum of the hand. Following injection of 50 mg of propofol, subjects were asked a standard question about pain on injection and observed for any behavioral signs of pain.

RESULTS: The probability to have pain in the combination IV lidocaine/magnesium group was 0.41 and the IV lidocaine group was 0.29. The two groups did not have a significant difference in pain reduction and yielded a p-value of 0.4537. The IV magnesium alone group had the highest probability to have pain after propofol injection 0.57, more so than the IV saline solution group that had a probability of 0.46. IV magnesium was also found to result in more severe pain than lidocaine alone and the combination of magnesium and lidocaine.

CONCLUSIONS: We were unable to find that magnesium, either alone or combined with IV lidocaine, was able to offer any significant advantages when compared to IV lidocaine alone. Possible explanations for this effect are the relative acidity of the magnesium solution compared to the other study solutions or the intrinsic ability of the magnesium to produce pain may be particularly pronounced in the small veins in the dorsum of the hand. In conclusion, IV magnesium pre-treatment either alone or combined with lidocaine appears to offer no benefits compared to IV lidocaine alone for the relief of propofol injection pain.
Evaluating the Effects of Statewide Smoking Regulations on Smoking Behaviors Among Participants in the Survey of the Health of Wisconsin (SHOW)

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Mentor: F. Javier Nieto, MD, MPH, PhD

Support: SHOW: National Institutes of Health (#1RC2HL101468-01); The Wisconsin Partnership Program (06012009); UW Institute for Clinical and Translational Research (KL2 RR025012); Shapiro Summer Research Program

BACKGROUND AND AIMS: On July 5, 2010 Wisconsin Act 12 went into effect, banning smoking in public places and places of employment across Wisconsin. Studies have shown that such laws reduce exposure to secondhand smoke, but there is limited evidence about the impact of such laws on exposure to smoke outside of the home and on household smoking policies. The goal of this study was to evaluate the effects of smoke-free legislation among participants in the Survey of the Health of Wisconsin (SHOW).

METHODS: A smoking history and demographic information was gathered from 1,341 SHOW participants from 2008-2010. This information allowed evaluation of the effects of Wisconsin Act 12 on smoking behaviors by comparing the behaviors of those surveyed before and after July 5, 2010.

RESULTS: The proportion of survey participants that reported exposure to smoke outside the home decreased from 55% to 32% after the statewide ban (p-value <0.0001). A similar reduction was observed for exposure to smoke at home (13% to 7%; p-value = 0.002). Smoke-free legislation in Wisconsin also increased the percentage of participants with strict no-smoking policies in their households from 74% to 80% (p-value = .04). These results varied by age, income, and education with those who were older, wealthier, and more educated generally having larger improvements.

CONCLUSIONS: Smoke-free legislation appears to reduce secondhand smoke exposure and to increase no-smoking policies in households. Further research should be conducted to see if these effects are maintained.
Natural History of Nonalcoholic Hepatic Steatosis: Risk for Progression to NASH and Cirrhosis

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Mentor: Perry J. Pickhardt, MD

Support: Shapiro Summer Research Program; Department of Radiology

BACKGROUND: Hepatic steatosis, also known as fatty liver disease (FLD), is a common finding at abdominal imaging - the reported prevalence of FLD ranges from 3% to 39% in the literature. FLD can be subcategorized into alcoholic fatty liver disease (AFLD) or nonalcoholic fatty liver disease (NAFLD) depending on its underlying cause. Several studies suggested that NAFLD may progress into nonalcoholic steatohepatitis (NASH) and/or cirrhosis. However, the risk for progression to NASH and cirrhosis is currently unknown. Our aim was to assess the risk of NAFLD progressing into NASH or cirrhosis by performing long-term clinical follow-up in patients with incidental findings of asymptomatic moderate-to-severe NAFLD.

METHODS: Noncontrast CT images through the liver performed over a 12-month interval from 2001-2002 in a consecutive adult cohort were reviewed. The primary inclusion criterion was a noncontrast liver attenuation =45 HU, which is effectively 100% specific for moderate-to-severe steatosis (=30% fat at histology). Main exclusion criteria were: pre-existing liver disease (beyond steatosis), alcoholism, or <1 year of clinical follow-up. For patients satisfying the above inclusion/exclusion criteria, extensive medical record review was performed to assess for development of clinically symptomatic NAFLD after the index CT.

RESULTS: From an initial cohort of 4,414 adults, 503 (11.4%) had a non-contrast CT liver attenuation =45 HU. After excluding 221 total patients for inadequate follow-up (n=131), pre-existing liver disease (n=61), and alcoholism (n=29), the final study cohort consisted of 282 adults (mean age, 51.4 years at index CT). Length of clinical follow-up averaged 7.3±4.0 years (range, 1.0-10.4 years). None (0%) of the 282 patients developed symptomatic steatosis, NASH, or cirrhosis over the observation period.

CONCLUSIONS: The risk of disease progression in patients with moderate or even severe steatosis incidentally detected at CT appears to be very low, questioning the need for further work-up. Our longitudinal study was unable to find a link between incidental asymptomatic steatosis and symptomatic NAFLD, including NASH and cirrhosis.
Evaluating the Effect of Brain Aneurysm Repair Modalities on Cognitive and Emotional Function

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Mentor: Michael Koenigs, PhD

Support: Shapiro Summer Research Program; Department of Psychiatry

BACKGROUND: Patients experiencing ruptured brain aneurysms are currently treated with either open surgical clipping or endovascular coiling. The aim of this ongoing study is to compare neuropsychological and psychosocial outcomes between clipped and coiled patient groups. Most studies comparing the two repair methods have focused on neuropsychological outcomes and the reports are conflicting specifically on executive function, memory, and attention. Additionally, observation and comparison of psychosocial outcomes between groups has been limited to the use of self report questionnaires and reports are also conflicting. Lastly, most study sizes have been n<40 (n=20 clipped, n=20 coiled).

METHODS: A robust test battery was assembled to measure neuropsychological and psychosocial outcomes. Neuropsychological measures include memory, executive function, intelligence, and visual spatial ability. Tests include the Wechsler Adult Intelligence Scale IV, the California Verbal Learning Test, Trails Test, and the Boston Naming Task. Psychosocial measures will be assessed using performance based tasks in addition to self report questionnaires, and include moral judgment and decision making, recognition of facial expressions of emotion, depression, and anxiety. Tests for these measures include the State Trait Anxiety survey, Beck Depression Inventory, Iowa Gambling Task, a utilitarian judgment task, a moral decision making task, and a recognition of facial expressions of emotion task. Testing will be performed on a group of clipped (n=50) and coiled (n=50) patients matched on age, sex, education level, aneurysm location, and aneurysm severity.

RESULTS: Currently, there is an insufficient amount of data to report and collection is ongoing. A number of control subjects have been tested to work through potential problems with the administration of the test battery. Values in the normal range have been obtained for quantifiable tests in control subjects, and several patients have been tested thus far.

CONCLUSIONS: There is no data to draw any conclusions from at this point in time. However, when data becomes available it will hopefully contribute to a conflicting body of evidence regarding neuropsychological outcomes between the clipping vs. coiling procedures. Additionally, the comparison of psychosocial outcomes between the two methods will be a novel contribution of this study.
**Wire-Guided Intubation through a Face Mask using the Seldinger Technique in an Urgent Difficult Airway**

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**Mentor:** Kristopher Schroeder, MD

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

**BACKGROUND:** We report two cases of urgent intubation through an anesthesia facemask while maintaining ventilation in patients with difficult airways and grossly distorted airway anatomy using a Seldinger wire with a pediatric bronchoscope. In both cases, conventional airway management techniques would have been very difficult or impossible and a surgical airway was a likely option. In situations where an LMA or other supra-glottic airway can't be placed, especially in emergent situations, there are few intubation techniques that can be done. This is a problem for anesthesiologists and this technique can be used to help fill this area of patient management.

**METHODS:** Following airway topicalization, each patient was sedated. A pediatric FOB was placed through a 19mm OD 15mm ID bronchoscopy port through a conventional disposable anesthesia facemask through the nares and into the trachea. A 140 cm Coated Amplatz guide-wire was then threaded through the bronchoscope and visualized at the carina. The guide-wire was left in place following FOB removal. A 14 FrenchOD 70 cm radiopaque endotracheal exchange catheter was placed over the guide-wire into the airway. The anesthesia facemask was then removed and an endotracheal tube was placed over the exchange catheter. After the endotracheal tube was in place, the exchange catheter and guide-wire were removed and the endotracheal tube cuff was inflated. Endotracheal placement was confirmed by equal bilateral breath sounds and positive end-tidal CO2.

**RESULTS:** Both patients were successfully intubated using the Seldinger wire despite their distorted airways. Neither case had complications in the procedure or with the endotracheal tube once it was placed. The difficulty of intubation and seriousness of their conditions necessitated that the patients remained intubated after their procedures. Both were extubated without complication when it was clinically acceptable.

**CONCLUSIONS:** We report a technique that both facilitates intubation and provides an alternative method of securing an urgent difficult airway using a conventional anesthesia disposable facemask in patients with grossly distorted airway anatomy where a surgical airway is likely necessary. The procedure allows the patient to be ventilated and have oxygen delivered using a facemask throughout the procedure. The use of a Seldinger guide-wire can create a less time sensitive intubation for difficult airways while allowing the patient to breathe spontaneously.
BACKGROUND: The IRB process can be tricky especially for first time medical researchers. This poster will provide recommendations and useful resources for aspiring researchers as well as some do’s and don’ts. The five key elements to successfully navigating the IRB process for the first time will be discussed in detail. These keys are 1) developing a research question and determining the scope of the research project; 2) selecting collaborators including a strong mentor; 3) correctly identifying the risk to research subjects 4) mentor, departmental, local and off-site approval of the project; 5) reporting and continued review of the research. In support of the five key elements of the IRB process, a list of helpful IRB resources will be provided. Finally, issues to consider when conducting research internationally and at multiple sites will be presented. This will include advice about record keeping and contacts, obstacles encountered when formatting and submitting the research proposal to other institutions, and finally what to do if you run into trouble or are not sure how to proceed.

CONCLUSIONS: Obtaining IRB approval or exemption is the cornerstone of any research project. The finer nuances of the IRB process can be difficult for novice researchers. However, resources exist to help streamline the process and assure the integrity of the research.
Ratio of Neutrophil to Lymphocyte Counts - Rapid and Simple Test to Predict Upstaging prior to Radical Cystectomy for Urothelial Carcinoma

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Mentor: Tracy M Downs, MD

Support: Shapiro Summer Research Program; Department of Urology

BACKGROUND: Approximately 50% of patients undergoing Radical Cystectomy (RC) will be upstaged. Although hydronephrosis, tumor multifocality, lymphovascular invasion and carcinoma in situ help predict upstaging, many patients are upstaged in the absence of these risk factors. Neutrophil-lymphocyte ratio (NLR) is an indicator of systemic inflammation and has been shown to be prognostic for outcomes in other cancers but evidence is lacking in bladder cancer. The purpose of our study was to evaluate the ability of preoperative NLR to predict pathologic upstaging to Non Organ Confined (NOC) disease.

METHODS: After IRB approval, the records of consecutive patients undergoing RC for urothelial carcinoma from 2002 to 2011 at the University of Wisconsin Hospital were reviewed. Patients with an NLR within 100 days of surgery were eligible for analysis. Organ Confined disease (OC) was defined as ≤T2 and non-organ confined (NOC) disease was defined as ≥T3. Pathological upstaging was defined as any increase in AJCC T stage recognized from cystectomy pathology. Differences in preoperative NLR between groups were evaluated with an unequal variance t-test.

RESULTS: Of 345 consecutive patients undergoing RC, 76 patients met our study criteria. Overall, 42 (55.4%) patients were upstaged, 17 (22.4%) were unchanged, and 17 (22.4%) were downstaged. 39 (51.3 %) of patients were upstaged to NOC. Patients who were upstaged to NOC demonstrated statistically significant greater NLRs (4.17± 0.88) as compared to patients who remained OC (2.60 ± 0.38 p =0.02). Receiver operator curves were constructed and the area under the curve (AUC) for NLR was greater compared to a validated bladder cancer upstaging nomogram (NLR 0.718 vs nomogram 0.663). In our study, 22 patients (upstaged to NOC) could have been counseled about the benefits of neoadjuvant therapy based on their preoperative NLR.

CONCLUSIONS: Preoperative NLR is a simple measurement that can be used to identify high-risk patients that may be upstaged at the time of radical cystectomy and who may benefit from neoadjuvant chemotherapy prior to radical cystectomy.
Walkable Neighborhoods, Physical Activity, and Coronary Heart Disease Risk: Results from SHOW

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Support: Shapiro Summer Research Program; Discretionary funds from the Department of Population Health Sciences; National Institutes of Health (#1RC2HL101468-01); Wisconsin Partnership Program (06012009); UW Institute for Clinical and Translational Research (KL2 RR025012).

BACKGROUND: Physical activity levels appear to be influenced by the built environment where people live. Walk Score is a free and easily available web-based tool for measuring neighborhood walkability that has recently been shown to correlate with other objective and subjective measures of the built environment. However, it is unclear how Walk Score relates to physical activity levels and health. The goal of this study was to examine the relationship between Walk Score, physical activity, and chronic disease risk factors including coronary heart disease risk.

METHODS: The Survey of the Health of Wisconsin (SHOW) collected health related data on 1,572 Wisconsin residents (age 21-74) between 2008 and 2010. Data collection included questions on neighborhood characteristics and physical activity levels as well as anthropometry and physical exam. Walk Scores and Framingham coronary heart disease risk scores were calculated for each participant.

RESULTS: Compared to low Walk Scores, high Walk Scores were positively associated with walking or biking for transportation (OR 4.9, p < .0001) and low coronary heart disease risk (OR 1.8, p = .0006), though the latter relationship was attenuated (OR 0.8, p = .5) when physical activity was included in the model. Among the non-Hispanic white group, high Walk Score was also associated with being physically active (OR 1.6, p = .02). The inverse relationship was seen in the non-white or Hispanic group (OR 0.2, p = .04).

CONCLUSIONS: Increased neighborhood walkability may lower the risk of coronary heart disease and physical activity levels may mediate this relationship. The reason for the discrepancies in the relationship between walkability and physical activity among different racial or ethnic groups needs further exploration.
Irx4 is a Marker for Cardiac Ventricular Progenitor in Mouse Embryonic Stem Cells

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Mentor: Gary E. Lyons, PhD

Support: Shapiro Summer Research Program; UW Cardiovascular Research Center

BACKGROUND: Cardiovascular disease is the leading cause of morbidity and mortality worldwide. Cell therapy has emerged as a potential alternative to current treatments for cardiac ischemia. Cardiac progenitors have become a popular cell therapeutic option due to cardiovascular potency, and avoidance of tumorigenesis. Since the effects of ischemia are primarily observed in the ventricular myocardium, a ventricular progenitor population would be the optimal cell type for regeneration. Irx4, a transcription factor and the earliest known ventricular-specific marker in development. Irx4 transcripts are detected in progenitors of the cardiac crescent, prior to formation of a beating heart. We hypothesized that Irx4 will be a suitable marker for purifying a ventricle-specific precursor population from differentiating mouse embryonic stem cells (mESCs).

METHODS: To purify Irx4+ progenitors and ventricular myocytes, Mr. Nelson designed a construct that directs the insertion of 3 reporter genes into the 3’ untranslated region of the Irx4 gene, in mESCs. mESCs were cultured in cell media with Leukemia Inhibitory Factor (LIF) and differentiated by suspension in 30 ul drops of growth media without LIF. To form embryoid bodies (EBs), cells were incubated for 8hrs-14 days, depending on the desired differentiation time point. EBs were harvested and dissociated into single cell cultures. For immunofluorescence (IF) experiments, cells were plated onto fibronectin-coated coverslips. Cells were fixed with 4% PFA, and stained for various markers.

RESULTS: IF staining of embryonic sections confirmed ventricular specificity of Irx4. Mic2v and smMHC co-stain, along with CD31 stain, assesses the multipotency of the hygro-purified Irx4+ progenitors. Purified myocytes are ventricular (vCM), and express gap junction marker, Cx43, suggesting that the myocytes are capable of coupling to adjacent cells.

CONCLUSIONS: The results show that hygro-purified Irx4+ progenitors were multipotent and able to differentiate into vCMs, smooth muscle cells, and endothelial cells. Expression of Cx43 on the surface of purified vCMs signifies the presence of gap junctions, a characteristic of mature myocytes. Further characterization of the hygro-purified progenitors is needed to confirm their differentiation abilities, specifically the percentage of each cardiovascular lineage. The putative ventricular progenitors will ultimately be assessed for their cardioregenerative capability in mouse MI models.
Treatment of Pulmonary Emboli: Defining Clinical Parameters for Safe Outpatient Therapy

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Mentors: James Svenson, MD, MS; Allan Mottram, MD

Support: Shapiro Summer Research Program; Department of Medicine

BACKGROUND: Patients frequently present to the emergency department with pulmonary embolism (PE), a potentially fatal condition. Traditionally, these patients have been admitted to the hospital. Significant costs are incurred in hospital admission as well as putting patients at risk for hospital complications. Only a fraction of these patients have complications or conditions due to their PE that would warrant hospital admission. Many are discharged after 1-2 days without any more treatment than they could have received as an outpatient. Previous attempts to define a population safe for outpatient therapy have looked at complication rates; however, outcomes in these studies look at complications in the first 1-3 months, not within the critical first several days.

The purpose of this study develop and validate a set of clinical parameters that would define a subgroup of patients that present to the ED with pulmonary embolism that have low risk for short term complications. We hypothesize that a subset of patients at low risk for complications in the first few days after diagnosis can be identified.

METHODS: This is a retrospective chart review. All patients presenting to the UW ED with a diagnosis of PE between 2006 and 2010 were eligible for inclusion. A detailed chart review was performed and data which included demographic, clinical, laboratory and outcome information in the first week after diagnosis were abstracted. Bad outcomes were defined as death, significant oxygen or ventilatory needs, rehospitalization, surgical intervention, hemorrhage, thrombolysis, new symptoms requiring further workup, uncontrolled pain, fever, new clot formation, or symptomatic cardiac disturbances (ischemia, arrhythmia). Statistical analysis will be performed to approximate a set of criteria obtainable in the ED that can be used to predict warranted hospitalization.

RESULTS: There were 296 patients with a diagnosis of PE. 32% of patients warranted hospitalization per our chosen outcomes and 6% warranted hospitalization for pre-existing comorbidities. The remaining 62% (n=163) of patients totaled 309 unwarranted hospital days. Statistics to develop predictive criteria are pending.

CONCLUSIONS: Our data suggest that a majority of patients presenting to the ED with PE could be safely treated as outpatients. This could result in significant cost savings and reduce hospital complications.
Latino Lay Health Advisors: Background, Motivations, Challenges, and Strengths

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Mentors: Lina Vera-Cala, MD, MSc; Ana Martínez-Donate, PhD

Support: Shapiro Summer Research Program; Wisconsin Idea Undergraduate Fellowship; SMPH Rural and Urban Scholars in Community Health (RUSCH) Program

BACKGROUND: Lay health advisors (LHA) have been advocated as agents to promote health and prevent disease in the Latino population in the United States. Despite the widespread support and use of LHA to address diverse health issues, little research has focused on these health promotion agents and there is a lack of investigations to characterize their socio-demographic profile, background, education, motivation, challenges and traits of success.

The goal of our study was to gather such data from two LHA-model programs being utilized by Planned Parenthood of Wisconsin (PPWI) to educate Latinas in the Madison and Milwaukee areas about health topics such as breast and cervical cancer, the availability of preventive screening programs, and how to navigate the health care system.

METHODS: Four focus groups and self-administered surveys were conducted to gather qualitative and quantitative data from 22 LHAs. Each focus group was composed of 4-6 LHAs and lasted approximately 2 hours. Questions explored challenges, barriers, and strengths of the programs and their impact on the LHA’s personal lives. Focus groups were voice recorded, transcribed, and coded for content analysis. Focus group participants also completed a paper self-administered survey on socio-demographics, as well as prior knowledge and experience.

RESULTS: -LHA are motivated by a desire to improve the health of their communities and acquire and/or expand their work experience. -LHA face many barriers, including scheduling issues, recruiting participants, and monetary issues -Successful LHA are more effective with a detailed training background and strong support system from the program management.

CONCLUSIONS: LHA are effective health communicators and educators in underserved populations; agencies using LHA as health promotion agents can improve the design and implementation of similar educational programs by understanding the LHA’s motivation to serve their community, barriers while working within the community, and selecting to train LHA with successful traits.
Evaluating the Masako Maneuver Using High-resolution Manometry and Electromyography

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Mentor: Timothy M. McCulloch, MD

Support: Shapiro Summer Research Program; Department of Surgery

BACKGROUND: The Masako maneuver is used in swallowing rehabilitation to improve swallowing muscle strength. However, the physiological changes during the maneuver are not fully understood. The purpose of this study was to utilize high-resolution manometry (HRM), intramuscular fine-wire electromyography (EMG), and surface electromyography (sEMG) to determine the effects of different degrees of tongue protrusion on pharyngeal and upper esophageal sphincter (UES) pressures and durations.

METHODS: Pharyngeal HRM, EMG of the superior pharyngeal constrictor (SPC), and sEMG of the submental muscle complex (SM) measures were collected from seven participants (ages 20-27) without dysphagia. The participants performed three different tasks: 1. Saliva swallowing with the tongue in a natural position; 2. Saliva swallowing with the tongue held just past the teeth and not beyond the lips (modified Masako), and 3. Saliva swallowing with maximal tongue protrusion (traditional Masako).

RESULTS: HRM data suggest that the modified Masako maneuvers did not have a significant effect on maximum pressure and the duration of pressure generation in velopharynx (VP) and tongue base (TB) regions (p>.05). UES pre-swallow maximum pressure during the modified maneuver increased significantly (p=0.0437) and total swallow duration was significantly longer (p<.01). During the traditional Masako maneuver, the duration of pressure generation in the VP region increased significantly (p= 0.0474) and UES post-swallow maximum pressure increased significantly (p<.01) compared to a saliva swallow. EMG data reveal that the modified Masako maneuver had a significant impact on the amplitude and duration of SM muscle activity (p<.01; p<.01). During the traditional Masako maneuver, SPC and SM activity increased significantly ( p<.01; p<.01) and the durations of both muscle activity were increased (p<.01; p<.01).

CONCLUSIONS: These results suggest that different muscles are involved in order to swallow in the presence of tongue protrusion. These findings reflect that young, healthy adults are able to maintain a relatively constant pattern of swallowing in the presence of less than maximal tongue protrusion. However, further studies are required to determine if tongue protrusion may elicit different pressure and muscle activity patterns in patients with dysphagia. A characterization of the changes from the Masako maneuver in patients with dysphagia may lead to individualized, swallowing therapies.
Physical Activity Levels and Health-Related Quality of Life in Young Female Athletes with Knee Injuries

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Mentor: Kathleen Carr, MD

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

BACKGROUND: Young female athletes have a higher incidence of knee injuries than males. Common injuries include anterior cruciate ligament (ACL) tears and anterior knee pain (AKP). Little is known about the long-term effects of these injuries; outcomes of interest are physical activity level and health-related quality of life (HRQOL). In a healthy adult population, higher levels of physical activity are associated with increased HRQOL. This goal of this analysis was to determine if a similar association exists following knee injury in young female athletes, and to determine if there is a difference in these variables over time between ACL tears and AKP.

METHODS: Data collection for this ongoing prospective observational study began in Aug 2006. Subjects include adolescent and young adult females who sustained a knee injury while participating in a sport or fitness activity. HRQOL, knee function, and physical activity level were assessed with the SF12v2, IKDC, and IPAQ self-report surveys at 6 intervals: pre-injury (retrospective); baseline; 3, 6, 12, and 24 months post-injury. This sub-analysis compares HRQOL and physical activity levels in ACL and AKP subjects at baseline, 12, and 24 months. Paired differences were assessed with the Wilcoxon Signed-Rank Test; correlations between SF12 and IPAQ variables were assessed with the Spearman Rank Correlation.

RESULTS: All subjects had an increase in SF12 scores at 12 and 24 months, and no difference between injury types was observed over time. The ACL group had a greater increase in total activity from baseline to 12 and 24 months, but there were no differences in total activity between the ACL and AKP groups at 12 and 24 months. There were no differences in SF-12 or IPAQ scores between the ACL and AKP subjects at 12 and 24 months. There was no correlation between activity levels (IPAQ) and perceived quality of life (SF-12) at any time point for either injury group.

CONCLUSIONS: Our results suggest that there is no correlation between HRQOL and physical activity levels in female athletes who have sustained a knee injury in the first two years post injury. Female athletes with either an ACL tear or AKP had improvement in HRQOL over the two years following injury, and this trend was not different between injuries. This knowledge could potentially have psychological benefits for athletes who sustain more severe knee injuries, and understanding these outcomes will enable sports medicine providers to better affect the physical, psychological and social health outcomes of their patients.
Multimodality Image Fusion to Guide Transendocardial Stem

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Support: Shapiro Summer Research Program; University of Wisconsin Cardiovascular Research Center

BACKGROUND: Stem cells have the potential to prevent the adverse remodeling following myocardial infarction (MI). Closed chest injection of stem cells into the peri-infarct myocardium using minimally invasive (transendocardial) catheters is an appealing, minimal risk method of cell delivery that may offer enhanced acute retention over other delivery approaches. However, accurately targeting cells to the peri-infarct zone requires robust real-time imaging. Delayed enhancement MRI, real-time 3D ultrasound, X-ray imaging and electromagnetic tracking may be combined to offer robust imaging of the infarct, real-time motion compensation and catheter tracking. As a first step, we developed a robust moving heart phantom to enable further experimentation.

Hypothesis: the fusion of delayed enhanced MRI to real-time 3D ultrasound to electromagnetic catheter tracking is feasible in an appropriate moving heart phantom and swine.

METHODS: We used the multi-modal navigation system to guide a catheter into a moving heart phantom and swine with an induced MI. In order to successfully complete these measurements we had to rebuild the parts of the heart phantom and recalibrate the real-time 3D ultrasound probe. Afterwards, we manipulated the injection catheter and injected colored dyes into removable targets in the heart model. We photographed the targets and measured the distance from actual injection to center of the target. In the experiment with a swine, we induced a myocardial infarction and tested the feasibility of our system. We also explored the possibility of fusing a delayed enhanced MRI, a real-time 3D ultrasound and electromagnetic tracking in human.

RESULTS: We successfully developed a robust moving heart phantom and demonstrated the feasibility of target registration error in 35 experiments. We also implemented the model in a swine with an induced MI. Furthermore, the fusion of delayed enhanced MRI, a real-time 3D ultrasound and electromagnetic tracking in human appears very promising.

CONCLUSIONS: Multi-modality image fusion combining several independent imaging modes to perform targeted transendocardial injections is feasible.
A Phase III Skin Cancer Chemoprevention Study of DFMO in Subjects with a History of Non-Melanoma Skin Cancer (NMSC): Follow-up of NMSC Events Greater than 5 Years Post-Study Participation

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Support: Shapiro Summer Research Program; Department of Medicine; University of Wisconsin Carbone Cancer Center

BACKGROUND: The most common malignancy in the United States is non-melanoma skin cancer (NMSC) with > 2 million new cases in 2010. The economic burden & increasing incidence in younger populations, especially women, reinforces the value of skin cancer prevention. A strong link between epithelial carcinogenesis & elevated polyamines led to a NCI-sponsored phase III double-blind, placebo-controlled skin cancer chemoprevention trial of the polyamine synthesis inhibitor α-difluoromethylornithine (DFMO) (500 mg/m2/day for up to 5 years) in 291 subjects with a history of NMSC. Subjects receiving DFMO developed significantly fewer Basal Cell Carcinomas (0.28 vs. 0.40 BCC/person/year, P = 0.03) as compared to placebo subjects & DFMO appeared well tolerated with the only significant observed event of clinically imperceptible ototoxicity.

METHODS: The continued interest in DFMO as a chemopreventive agent & assessment of latent toxicity or continued skin cancer protection provided cause to update the clinical data and health status of subjects from the above study. Medical records of 243 subjects from UW Health were reviewed for skin cancer events by histology, other neoplasia, significant other diagnoses & survival. As primary analyses, the rate of skin cancer recurrence was compared between the original DFMO & placebo randomization arms. Using a two-sample t-test, these data were assessed for skin cancer recurrence rates from the previous study period alone, recurrence rates from the current study alone & recurrence rates from the studies combined.

RESULTS AND CONCLUSIONS: No signs of latent or cumulative toxicity were seen in 2000 person years of study data. Subjects taking DFMO had a significantly lower rate of BCCs, but after discontinuation of the original study, the BCC event rate equalized between DFMO and placebo subjects. There was an insignificant trend toward greater DFMO protection against Squamous Cell Carcinomas, evidenced by a lower post study event rate (DFMO 0.057 SCC/person/year, placebo 0.107, p=0.367; Total SCCs: DFMO 114, placebo 171) implying a potential delayed effect. These data support the continued evaluation of DFMO as a chemopreventive agent.
Excessive Weight Gain After Total Thyroidectomy: Myth Or Reality?

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Support: Department of Surgery NIH Training Grant: T35 DK 062709-6

BACKGROUND: Total thyroidectomy is used as a treatment option for patients with a variety of benign and malignant thyroid disorders. Many patients who undergo thyroidectomy express concerns of potential weight gain after surgery. Average weight gain in the general population is 3.35 lb over 4 years. For this study, we sought to determine if patients undergoing thyroidectomy experienced greater than expected weight gain compared to the general population.

METHODS: Between January 2005 and December 2010, 374 patients underwent total or completion thyroidectomy at our institution. A retrospective analysis of weight change from time of surgery to the latest follow-up was compared with pathology diagnosis, symptoms of hyperthyroidism, and euthyroid status. Exclusion criteria included age <18 years, patients who received post-operative gastric-bypass surgery or became pregnant within 1 year post-surgery. Statistical analysis was performed using SPSS.

RESULTS: Our patient population gained a mean of 3.55 ±14.67 lb over an average of 29 months following total thyroidectomy, which is similar to the expected weight gain in the general population. Patients with Graves’ disease had a greater weight change than all other pathology diagnoses (8.75±13.42 lb vs. 2.54±13.67 lb for benign, 2.55±14.48 lb for Hashimoto’s thyroiditis, 3.65±15.96 lb for PTC, p=0.036). Patients with hyperthyroidism (low pre-operative TSH values) showed significantly more weight gain compared to pre-operative euthyroid patients who actually lost weight after total thyroidectomy (8.27±12.95 lb vs. - 0.98±10.54 lb, p<0.01). Interestingly, there were no significant differences found in weight gain/loss between patients who achieved a euthyroid status immediately after surgery as compared with those with initially low or high TSH values.

CONCLUSIONS: Based on our analysis, with the exception of patients with hyperthyroidism, it is a myth that patients experience excessive weight gain after total thyroidectomy. In fact, patients with normal thyroid function preoperatively actually lose an average of 1 lb after surgery in comparison to the population norm of a 3 lb weight gain.
Evaluating Portal Venous Hemodynamics with 4D Flow: How Essential is the Temporal Dimension?

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Support: We gratefully acknowledge funding by NIH grant 2R01HL072260, GE Healthcare, Department of Radiology, and Shapiro Summer Research Program for their assistance and support.

BACKGROUND: Portal hypertension (PHTN) is a life-threatening consequence of cirrhosis. Current techniques to evaluate PHTN include ultrasound and 2D PC-MRI, but they have important limitations. A comprehensive diagnostic method to assess both the hemodynamics and morphology of the entire abdomen from a single examination is highly desirable and was recently introduced in the form of a 4D flow MRI sequence, PC-VIPR. While scan time for a PC-VIPR acquisition is relatively short (~12 min), further reductions may be possible by exploiting the non-pulsatile nature of portal venous blood flow. The purpose of this study was to compare the accuracy of time-averaged versus time-resolved 4D flow MRI and to determine the degree of scan time reduction that can be achieved while maintaining high quality angiograms and accurate quantification of blood flow.

METHODS: Forty-four subjects (29 cirrhosis patients, 15 volunteers) were included in this HIPAA-compliant and IRB-approved study after obtaining informed consent. All imaging was performed on a 3.0T clinical scanner using a 4D flow MR sequence, PC-VIPR. Images were reconstructed as a time-resolved series and different time-averaged reconstructions using 100% and 33% of the acquired projections to mimic a shorter scan time. Angiograms for all datasets were generated, segmented (Mimics), and visualized (Ensight). A pulsatility index of the portal vein was calculated (PI = V’max-V’min / V’mean). Flow quantification consistency was assessed by comparing the sum of superior mesenteric and splenic vein flow to portal venous flow. Angiographic quality was graded by two experienced radiologists (scale 1-4, 4=best).

RESULTS: The pulsatility index was calculated to be 0.45±0.25. Flow measurements were more consistent in the fully-sampled time-averaged (5.2% error) than the time-resolved (3.9% error) data. Error in the reconstruction with 25% of the data was 4.5%. Angiography scores for the 100% and 33% reconstructions were 3.98 and 3.11, respectively.

DISCUSSION: As expected, results show improved hemodynamics and angiography at longer scan times. However, a scan time of 4 min appears sufficient to visualize and quantify flow in the portal venous system with only slightly degraded image quality compared to the 12 min scan. Therefore, we conclude it may be possible to reduce scan time using time-averaged reconstruction for visualization and quantification in the portal venous circulation.
Retrospective Review of Outcomes in Ulcerative Colitis Patients Intolerant of Mesalamine

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Support: Shapiro Summer Research Program; Department of Medicine

BACKGROUND: Mesalamine, also known 5-aminosalicylic acid, is used to treat inflammatory bowel disease specifically ulcerative colitis (UC) and Crohn’s disease (CD). Clinical trials have reported that 3% of the UC patients are intolerant of mesalamine based medications including sulfasalazine. It was hypothesized that UC patients who could not tolerate mesalamine would have worse clinical course and outcome, namely, higher rates of biologic therapy use (infliximab, adalimumab, and certolizumab) and colectomy, than their counterparts.

METHODS: The electronic health records (Healthlink) of the UW Hospital and Clinics were accessed to obtain information regarding biologics use among the UC patients who received colectomy. Two groups were compared; Group 1, UC patients intolerant of mesalamine who received colectomy, and Group 2, ulcerative colitis patients tolerant of mesalamine who received colectomy.

RESULTS: 8.4% of the UC patients who received colectomy were intolerant of mesalamine products. This is significantly higher than the 3% reported in the literature. Of the 299 patients who received colectomy as a consequence of their UC, 25 were intolerant of mesalamine and 274 were tolerant of mesalamine. 24% (67 of 274) of those who were tolerant of mesalamine and had colectomy have used biologics whereas 52% (13 of 25) of those who were intolerant of mesalamine and had colectomy have used biologics.

CONCLUSIONS: Among the UC patients who received colectomy, those who could not tolerate mesalamine were more likely to be on biologic therapy and had colectomy at a higher rate than those who could tolerate mesalamine. This may reflect an institutional bias in that the University of Wisconsin Hospital and Clinics is a tertiary care system that receives more complicated cases. A study should be done to establish the baseline rate of colectomy performed among the UW patients because this may not be 3%. In future study, all the UC patients in UW system should be evaluated to see whether they are mesalamine intolerant. Then, each group should be stratified by respective severity of UC (length and inflammation), and duration of medication used, types of complications, and colectomy rates.
Evaluating Effectiveness of Disaster Medicine Training for Medical Students

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Support: Shapiro Summer Research Program; Department of Medicine

BACKGROUND: Disasters, natural and manmade, can occur anywhere at any time. Thus, it is vitally important that all health care professionals understand the basics of response to a disaster, especially in the rural setting of our state. At UW-SMPH, one mandatory training day is incorporated into the fourth year curriculum to introduce topics of preparedness and media communication. We hypothesize that this training is insufficient to instill adequate knowledge and confidence in future doctors.

METHODS: A voluntary cross sectional survey was formulated and distributed to current first (M1s) and fourth (M4s) year medical students. We addressed three topics: prior experience and future plans, knowledge of disaster medicine and preparedness, and confidence. We used Qualtrics Survey Hosting Service (http://survey.wisc.edu) to distribute and collect survey responses.

RESULTS: In total, we collected 116 responses from 30 M4s (20% response rate) and 86 M1s (50%). Given the differences in clinical training between M4s about to start their residency and M1s it was expected that the M4s would have a significantly better knowledge base. Contrary to expectation, there were minimal differences in the rate of correct responses in seven of eight questions asked. On average the M4s were correct 79% of the time while the M1s were 68% correct (P value=0.348). The M4s did have a significantly higher level of confidence than M1s. Moreover, the M4s who had their training day in May had a nearly significant difference in confidence in responding to “natural” and “nuclear/biologic/chemical” disasters than the M4s who had their training in November (P values=0.054, 0.089 respectively). Additionally, 69% of students agreed or strongly agreed that training should be required and 82% felt they would need training at some point in their career. However, only 28% expressed strong or very strong interest in taking an elective course in disaster medicine.

CONCLUSIONS: The insignificant difference in knowledge despite three additional years of training and overall low rate of correct responses indicates that students are in need of additional training. The difference between perceived need for and interest in training shows that while students recognize the importance of, they are not willing to pursue elective training. Together, these data point to a need for additional training to be incorporated into the required curriculum.
Effect of Human Serum on Complement Activation by Ch14.18 mAb

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Support: Shapiro Summer Research Program; Department of Human Oncology

BACKGROUND: Current clinical trials of pediatric neuroblastoma utilize a regimen consisting of the Ch14.18 monoclonal antibody. Clinical observations suggest that the pain associated with Ch14.18 administration correlates with administration of fresh antibody rather than serum antibody levels in the patient. Previous research has shown that the perception of pain is due to complement activation by Ch14.18. Therefore, we hypothesized that there is an effect of human serum on Ch14.18 such that complement activity is reduced after the antibody has had prolonged exposure to human serum.

METHODS: Ch14.18 was incubated in human serum samples for 12-14 hours at 37°C and added to chromium-labeled M21 human melanoma tumors cell in a standard chromium release assay to measure complement mediated cytotoxicity.

RESULTS: Initial results showed decreased complement mediated killing after Ch14.18 was incubated at 37°C in the presence of human serum. However, the addition of freshly thawed serum to incubated Ch14.18 demonstrated the return of complement activity. Comparison of rabbit and human serum showed a rapid decrease in complement ability of human serum following initial thawing. Use of rabbit serum in place of human serum showed no effect of incubation on complement-mediated killing by Ch14.18.

CONCLUSIONS: Our data suggest that incubation in human serum does not decrease the ability of Ch14.18 to activate complement.
Comparative Analysis of Existing Surgical Risk Assessment Tools to Predict Post-Operative Mortality Rates After Radical Cystectomy

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Support: Shapiro Summer Research Program; Department of Urology

BACKGROUND: Radical cystectomy with urinary diversion is the gold standard treatment for muscle invasive transitional cell carcinoma. However, radical cystectomy has the highest morbidity and mortality rates of commonly performed urologic surgery, with large series reporting complication rates between 22%-57% and 90-day mortality rates of 3-4%. Unfortunately, there are no widely accepted methods to identify which patients will suffer early mortality and not benefit from surgery.

The objective of our study was to compare validated surgical risk tools to predict mortality rates in patients undergoing radical cystectomy and urinary diversion.

METHODS: We retrospectively reviewed the physiologic parameters, operative parameters and 90-day mortality in 99 consecutive patients who underwent radical cystectomy and urinary diversion at our institution from 2008-2010. We did not exclude patients who had non-transitional cell cancer on final pathology (Patient No 1 and No. 2) and leukemoid reaction from bladder cancer (Patient No. 6) Predicted mortality were calculated using the POSSUM, P-POSSUM, SAPS II and APACHE II. Observed and predicted surgical outcomes were compared. Student’s T-test, Fisher’s exact test and univariate logistic regression analysis was used to evaluate 90-day mortality.

RESULTS: Our observed mortality rate was 6%. The mean predicted mortality rates for the different surgical risk tools were the following: POSSUM (20.3%), P-POSSUM (7.0%), APACHE II (5.4%) and SAPS II (3.6%) for the entire cohort of patients. The mean predicted mortality rates for the 6 patients who died were POSSUM (28.2%), P-POSSUM (12.4%), APACHE II (4.3%) and SAPS II (5.1%). Individual physiological and operative parameters that were significant and associated with 90-day mortality (Serum K+; P=0.006, Abnormal ECG; P=0.04) and the Physiological summary score (P=0.001) from the POSSUM, P-POSSUM). Serum K+ was not significant on SAPS II and APACHE II.

CONCLUSIONS: Current risk stratification methods were inaccurate in predicting 90-day observed mortality rate in our cohort of patients undergoing radical cystectomy (RC). Individual Physiologic factors (Serum K+ and ECG) were associated with increased 90-day mortality rate. Operative severity was not predictive of early mortality. Perioperative complications (minor vs major) contributed to increased 90-day mortality rates. Cystectomy specific risk assessment tools are needed to aid in appropriate patient selection.
Early Evaluation of a Program to Integrate Antiretroviral Therapy into Zambian TB Clinics

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BACKGROUND: The World Health Organization recommends all HIV positive tuberculosis (TB) patients start antiretroviral therapy (ART), regardless of CD4 count. In Lusaka, approximately 70% of TB patients are HIV positive.

METHODS: An integrated model was implemented in one government-run Lusaka health center. Using existing staff, TB patients underwent HIV testing and those positive were offered immediate enrollment into HIV care at weekly ‘HIV clinics’ within the TB clinic. Unless contraindicated, ART was initiated within 2-4 weeks of enrollment. Data from a pre-implementation cohort was collected for comparison to post-implementation patients as part of program evaluation.

RESULTS: Preliminary results from patients initiating TB treatment in the first month post-implementation show that the number of HIV positive TB patients enrolling into HIV care within one month of TB treatment start date increased from 35.7% (40/112) to 41.3% (19/46), p=0.51. The number of HIV positive patients initiating ART within one month of TB treatment start date increased from 14.3% (16/112) to 23.9% (11/46), p=0.14.

CONCLUSIONS: While preliminary results are not significant, the proportion of patients enrolling into HIV care has increased moderately and the proportion of patients initiating ART within one month has almost doubled, suggesting that an integrated model can increase the number of TB/HIV co-infected patients who initiate ART early. Longer-term evaluation is underway to determine if these trends will continue with more patients and longer follow-up.
Effect of Multiple Risk Factors on Newborn Iron Status

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BACKGROUND: Iron deficiency (ID) is the most common nutrient deficiency worldwide. Inadequate fetal iron allotment increases the risk for infantile ID anemia (IDA), because half the iron needed for infant growth is obtained before birth. In the US, risk factors for ID are maternal IDA, diabetes, obesity, low birth weight, fetal undergrowth or overgrowth (SGA or LGA), and mothers from ethnic or lower socioeconomic groups. Impaired fetal iron may disrupt neurological and behavioral development. Because the effects of ID and IDA may have long-term effects, the American Academy of Pediatrics (AAP) recently recommended utilizing risk factors to more aggressively screen for ID and IDA. Within a prospective study of IDA in infancy, we hypothesized that newborns with multiple risk factors exhibit poorer iron status at delivery than those with quantitatively fewer risks. Because of our previous work, we hypothesized that the combination of LGA newborns born to women with obesity and diabetes during pregnancy would have poorer iron profiles than those with other combinations of multiple risk factors.

METHODS: Newborns ≥35 weeks gestational with ≥1 risk factors for ID were recruited. Risk factors included: maternal IDA or diabetes, newborns SGA or LGA, mothers from ethnic minority groups, and/or lower socioeconomic status. We included maternal obesity at delivery (BMI ≥30 kg/m2) as a risk factor. Cord blood storage iron (serum ferritin), transport iron (serum transferrin), steady state RBC iron (ZnPP/H), and recent RBC iron (reticulocyte-enriched or RE ZnPP/H) were measured and compared against controls. ZnPP/H increases with inadequate iron available for incorporation into hemoglobin, with RE ZnPP/H increasing ZnPP/H sensitivity. Number of risk factors was determined and risk groups were demarcated as high-risk (≥3 risk factors) and low-risk (1-2).

RESULTS: We identified 111 high-risk and 181 low-risk newborns. All parameters in the high and low-risk groups differed from controls, p<0.0005. High-risk newborns exhibited higher ZnPP/H and higher RE ZnPP/H than the low risk group, p<0.04, but had similar serum ferritin and serum transferrin levels. Three specific risk factors: LGA newborns born to obese, diabetic mothers were compared to newborns with 3 or more alternate risk factors. The LGA/obese/diabetes group had higher ZnPP/H, RE ZnPP/H, lower serum ferritin, p<0.03 and similar serum transferrin.

CONCLUSIONS: Our results support the AAP recommendations to screen at birth for historical factors that place infants at-risk to develop infantile ID, but add that multiple risk factors may confer greater risk. The combination of gestational obesity and diabetes with an LGA newborn conferred greater risk than other combinations of ≥3 risk factors. Identification of specific risk factors could be particularly important for assessing iron status at birth.
Day of Surgery Associated with Length of Stay in Patients Undergoing Thoracic Surgery

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BACKGROUND: Elucidation of factors contributing to prolonged length of hospital stay (LOS) can inform innovations and legislation aimed at improving patient care and reducing healthcare costs. We hypothesized that the day of the week (i.e. Monday-Friday) that a patient undergoes surgery does not impact median LOS.

METHODS: A total of 242 patients undergoing lobectomy or segmentectomy (n=161), wedge resection (n=57), or pneumonectomy (n=24) for a primary lung cancer, as well as 78 patients undergoing esophagectomy for a primary esophageal cancer, at an academic medical center between January 2009 and December 2010 were included in the study. Patient data was obtained from the Thoracic Surgery Outcomes Database, a prospectively collected and contemporaneously updated research database of all thoracic surgery patients at our institution. Multiple linear regression with ranks was used to determine whether a difference in median LOS exists across different days of surgery for patients undergoing lobectomy/segmentectomy, wedge resection, and esophagectomy. Single linear regression with ranks was used for the pneumonectomy group.

RESULTS: Multivariate analysis demonstrated a longer median LOS for patients undergoing lobectomy/segmentectomy on Friday (2.7 days, p<0.05) than for their Monday counterparts (2.3 days). Tuesday, Wednesday and Thursday lobectomy/segmentectomy patients did not have a longer median LOS. Multivariate analysis showed that median LOS was greater for patients undergoing wedge resection on Friday (3.7 days, p=0.05) than for their Monday counterparts (2.6 days). Wednesday and Thursday wedge resection patients did not have a longer median LOS. There was no evidence of an association between day of surgery and median LOS among patients undergoing pneumonectomy or esophagectomy.

CONCLUSIONS: Our study suggests that patients undergoing lobectomy/segmentectomy or wedge resection on Friday are more likely to have a prolonged LOS than their counterparts undergoing surgery on Monday through Thursday. This association was not observed in patients undergoing surgeries associated with longer median LOS, such as pneumonectomy or esophagectomy. Further study is necessary to determine which factors contribute to prolonged LOS on Friday, and whether this association is present at a national level.
Platelet-Rich Plasma for the Treatment of Chronic Plantar Fasciopathy in Adults: A Case Series

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

BACKGROUND: Platelet-rich plasma (PRP) is an emerging treatment for various tendinopathies, including plantar fasciopathy (PF). Therapy consists of injecting concentrated autologous platelets into the plantar fascia. It is hypothesized that PRP promotes healing through increased concentrations of growth factors that are released by activated platelets at the injection site. The efficacy of PRP injections for PF is unclear. The purpose of this study was to report the outcomes of a single PRP injection for improving self-reported pain and disability in adults with chronic PF.

METHODS: Prospective case series study. Nineteen subjects (mean age=43.2) with a minimum 6-month history of PF, confirmed through physical examination and imaging, received a single 3mL PRP injection of the proximal plantar fascia. All subjects failed at least 3 months of conservative therapy (NSAIDs, physical therapy, night splinting, orthotics, and/or corticosteroid injection) prior to PRP injection. Four subjects were unavailable for analysis at 32 weeks (underwent surgery, n=1; lost to follow-up, n=3). Self-reported pain and disability were assessed using the Foot and Ankle Ability Measure (FAAM) and Single Assessment Numeric Evaluation (SANE) instruments. The individual values for FAAM and SANE scores were compared at baseline and 32 weeks post-injection using the Wilcoxon signed-rank test.

RESULTS: Sixteen plantar fascia (n=15 participants) were available for analysis. The FAAM Activities of Daily Living subscores were significantly improved (p=0.002) from baseline (mean=59.5±17.1) to 32 weeks post-injection (mean=80.0±18.6). The FAAM Sports subscores also significantly increased (p=0.008) from baseline (mean=36.7±21.8) to 32 weeks (mean=63.3±28.7). Similarly, participants reported significant improvement (p=0.004) in SANE scores from baseline (mean=49.6±20.9) to 32 weeks post-injection (mean=65.3±25.9).

CONCLUSIONS: A single injection of autologous PRP significantly improved patient-reported pain and disability in participants with chronic recalcitrant PF at 32 weeks post-injection. This prospective case series suggests that treatment with PRP may be a safe and effective alternative to surgery in this patient population. Prospective randomized controlled clinical trials with longer follow-up are warranted to further investigate the efficacy of autologous PRP for chronic PF.
Utilization of Steroids for Dermatological Disorders in the Emergency Department

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Support: Shapiro Summer Research Program; Department of Dermatology

BACKGROUND: Currently little is known about emergency department utilization for dermatological disorders. The purpose of this project is to determine the types and frequency of skin disorders that are encountered in the emergency department and to determine how topical corticosteroids are used in the treatment of these conditions. The projected final outcome of the study is use of the data to create a pertinent supplemental educational program for physicians who practice emergency medicine regarding treatment of dermatological disorders with topical and oral corticosteroids.

METHODS: An IRB approved retrospective chart review of 917 medical records of patients seen in the Emergency Department (ED) was performed to determine the types and frequency of skin disorders that were evaluated in that location from 2008-2010. Patients seen for cutaneous problems were selected using 55 dermatological ICD-9 codes. Data from each encounter includes gender, race, ethnicity, insurance status, affiliation with primary care physician, month of visit, presentation to the ED, ED diagnosis, ED treatment, if and where patients followed up for further care, if the diagnosis agreed with the ED diagnosis and the follow up treatment. A survey will be distributed to ED physicians to determine their confidence level with the diagnosis and treatment of specific dermatoses. The survey will specifically ask the physicians to rank their comfort level from “not at all” to “extremely” with using over-the-counter (OTC) 1% hydrocortisone cream, low-potency topical steroids, mid-potency topical steroids, high-potency topical steroids and systemic steroids to treat patients with inflammatory skin disease. The results from the chart review and survey will be combined to create an educational program for physicians in the ED regarding treatment the use of steroids in the treatment of these dermatoses.

RESULTS: More than half of all steroids used in the emergency room were systemic. The chart review showed that 51% of all the topical steroids that were used to treat dermatoses in the ED were OTC 1% hydrocortisone cream. Forty-one percent of the topical steroids used were in the mid-potency (ex, triamcinolone 0.1%) category, 4% used were high-potency topical steroids (ex, clobetasol 0.05%) and 3% were topical steroids in the low-potency category (ex, desonide 0.05%). The ED physicians have not yet taken the survey and therefore that data has not been collected.

CONCLUSIONS: Chart review reveals that patients presenting to the ED with inflammatory dermatoses are most likely to be treated with either systemic steroids or OTC 1% hydrocortisone cream. Systemic steroids and OTC 1% hydrocortisone cream are at two opposite ends of the steroid potency spectrum and use of each has a varying benefits and side effects. The infrequent use of low, mid and high-potency topical steroids shows that physicians may benefit from supplemental education regarding the effective use of topical treatments. Increased training on the use of class I (high) through class VI (low) topical steroids would expand the ED physician’s armamentarium to aid in the treatment of patients with acute onset inflammatory skin problems while minimizing their exposure to side effects. Survey results, once collected, will provide information regarding ED physician perceptions about the use of topical and systemic to treat dermatoses in the ED.
Susceptibility of Enzyme-Treated *Candida albicans* Biofilms to Killing by Macrophages

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**Mentors:** David R. Andes, MD; Jeniel E. Nett, MD, PhD

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

**BACKGROUND:** *Candida albicans* is a leading cause of hospital-acquired infections, and frequently colonizes implanted devices by growing as a biofilm. Problematically, these biofilms are immune-resistant. To better understand the interaction of *C. albicans* biofilms with the host immune system, we examined the effects of enzymatic pre-treatment of biofilms on the ability of murine macrophages to kill *C. albicans* biofilm cells. Enzymes were chosen to target known *C. albicans* matrix components, including beta-1,3-glucan, alpha-mannose, beta-mannose, chitin, DNA, and protein.

**METHODS:** *C. albicans* strain SC5314 was grown for 24 h at 37°C in a microtiter plate to generate biofilms. Susceptibility curves for biofilms incubated with each enzyme alone were generated by addition of XTT reagent plus optical density reading to assess the number of viable cells present after 18h. Enzymes tested included DNAse 1, proteinase K, lyticase (targeting beta-1,3-glucan), alpha-mannosidase, beta-mannosidase, and chitinase. A range including sub-inhibitory and inhibitory enzyme concentrations was used in the subsequent killing assays. To assess whether enzymatic treatment affects the ability of macrophages to kill *C. albicans* biofilm cells, we treated biofilms with enzyme and J774 murine macrophages for 18h. Macrophages were then hypotonically lysed, and XTT plus optical density readings were used to assess biofilm viability.

**RESULTS:** DNAse did not reduce biofilm viability at any concentration tested, and Proteinase K caused biofilms to disintegrate before having any effect on biofilm viability. Susceptibility curves were generated for the remaining enzymes. Killing assays demonstrated no change in biofilm viability after treatment with alpha-mannosidase plus macrophages as compared to either treatment alone. However, lyticase, beta-mannosidase, and chitinase plus macrophages each resulted in reduced biofilm viability compared to treatment with macrophages or enzyme alone.

**CONCLUSIONS:** Our preliminary studies demonstrate that macrophages plus lyticase, beta-mannosidase, and chitinase may have synergistic effects on killing of *C. albicans* biofilm cells. If corroborated by additional replicates, these studies would suggest that beta-1,3-glucan, beta-mannose, and chitin may have roles in biofilm resistance to killing by macrophages. Further studies are needed to determine the mechanism by which synergistic biofilm killing occurs with enzyme plus macrophages.
Interpersonal Trust, Race/Ethnicity, and Access to Healthcare

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Support: Shapiro Summer Research Program; Department of Medicine

BACKGROUND: Interpersonal trust between a patient and their physician is important to delivering effective medical care. Compared to non-Latino white populations, interpersonal trust has been shown to be lower in racial/ethnic minority groups and may contribute to health disparities. Our objective was to examine the relationship between race/ethnicity and interpersonal trust, and if healthcare access modified this relationship.

METHODS: We conducted a cross-sectional survey of a convenience sample of African-American (n=142), white (n=155), and Mexican American (n=143) adults shopping in a diverse group of Chicago supermarkets. We used the validated 11-item Hall-Trust-Scale to measure interpersonal trust. The scores were normally distributed and we used tertiles indicating “low”, “middle”, and “high” interpersonal trust in a multivariate logistic regression analysis. We first examined the relationship between race/ethnicity and interpersonal trust. Then we added 4 measures of healthcare access: experiencing difficulty seeking care, 2 cost barrier factors, and appointment wait time. Analyses were adjusted for relevant sociodemographic characteristics.

RESULTS: The majority of respondents were female, married, had a family income>$16,000, unemployed, and had a high school degree or less. The Hall measure had high reliability (α=0.91). Before adjustment, there was no significant difference in interpersonal trust between the 3 racial/ethnic groups (P=.678) and this relationship did not change after adjustment. Before adjustment, all 4 access barriers were statistically significant predictors (P<.05) of lower trust. After adjustment, only difficulty seeking care, longer wait time to last doctor’s appointment, and not following physician advice/treatment plan because of cost were significantly (P<.05) associated with lower trust. We found no significant difference in interpersonal trust by race/ethnicity. However, barriers accessing healthcare was significantly related to lower physician trust.

CONCLUSIONS: We found no significant difference in interpersonal trust by race/ethnicity. However, barriers accessing healthcare was significantly related to lower physician trust. Our findings underscore the importance of focusing on reform efforts such as improving access to timely healthcare by reducing costs, wait times, and other access barriers as a means to reduce health disparities.
Analysis of LIKE COLLEGE Study Recruitment

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Support: Shapiro Summer Research Program; Department of Pediatrics

BACKGROUND: Substance abuse in college students causes many deaths each year. Screening is available but does not reach many students. The LIKE COLLEGE study is using drug and alcohol references and photos seen on Facebook as a possible screening tool. These will be compared to interviews which is the current screening tool for finding at risk students. This study proposed to recruit 400 students from two universities (University of Wisconsin and University of Washington). In order to recruit this number of students many tactics were attempted. Each of these recruitment tactics were analyzed to determine which were beneficial. The recruits were also analyzed to determine if they are in fact a representative subset of the student population.

METHODS: Freshman lists were acquisitioned from the Registrar’s Office. 400 names were chosen randomly from each university list. Postcards were first sent to student’s home addresses. An email with an information sheet was then sent. One week later students were called. The following week students were emailed again and then called again. Two weeks later students who had not responded were mailed a gift. The following week students received a Facebook message. The last attempt was the next week with a final phone call.

RESULTS: Chi squared tests were employed to determine if the sample was different from the student population. It was found that the total gender distribution from the schools was representative of the student populations. Recruitment of a representative ethnic distribution was more successful at the University of Washington than at the University of Wisconsin.

CONCLUSIONS: The ethnic distribution was not representative of the University of Wisconsin. There were many more Caucasian students recruited than expected. This is probably due to the fact that the recruitment was designed by Caucasian researchers and students and therefore is probably more appealing to Caucasian students than minorities.
**Hesperetin Activates Notch1 Signaling, Induces Cell Differentiation, and Causes Apoptosis in Anaplastic Thyroid Cancer**

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**Support:** Department of Surgery NIH T35 Training Grant DK062709

**BACKGROUND:** Anaplastic thyroid cancer (ATC) is characterized by aggressive growth and extremely poor prognosis. In addition, the undifferentiated nature of ATC in which sodium iodide symporter (NIS) expression is reduced makes treatment such as radioactive iodine ineffective. Therefore, there is an urgent need for strategies that sensitize ATC cells to iodine treatment. It has been reported that the Notch1 signaling pathway, which affects cell proliferation and differentiation, is inactivated in ATC. Therefore, we evaluated whether Hesperetin, a naturally occurring flavanone and potential Notch activator, affects cell proliferation and up-regulates thyroid-specific differentiation markers such as NIS in ATC.

**METHODS:** To determine whether Hesperetin activates Notch1 in ATC, expression of Notch1 mRNA and protein was evaluated upon treatment of a human derived ATC cell line (HTH7). mRNA levels of Notch1 response genes (*Hes1* and *Hey1*) were measured, and the Notch1 activity was assessed using CBF-1-luc binding assay. Cell proliferation was measured by viable cell counts every 24 hours post-treatment (0-200mM) for 72 hours and the underlying mechanism was investigated by western blot. Expression of thyroid-specific differentiation markers including Thyroid Transcription Factor 1 (TTF-1), Thyroid Transcription Factor 2 (TTF-2), Paired Box Gene 8 (PAX-8), Thyroid Stimulating Hormone Receptor (TSHR), and NIS were also measured.

**RESULTS:** Hesperetin caused activation of Notch1. Treated cells displayed elevated Notch1 protein and increased mRNA levels of *Hes-1* and *Hey-1*. Treatment induced a dose-dependent increase in Notch1 activity as evidenced by increased luciferase activity. Hesperetin treatment also resulted in a time and dose-dependent decrease in cell proliferation: at 72 hours, 50mM and 100mM Hesperetin resulted in a 27% and 47% reduction respectively compared to control. Protein expression of apoptotic markers cleaved PARP, cleaved Caspase-3, and BAD increased with treatment. Importantly, Hesperetin up-regulated NIS mRNA levels and other thyrocyte markers (TTF-1, TTF-2, PAX-8 and TSHR), evidence that Hesperetin induces differentiation in ATC.

**CONCLUSIONS:** Hesperetin activates the Notch1 signaling cascade and has a significant antiproliferative effect on ATC that can be largely attributed to apoptosis. Hesperetin also induces differentiation in ATC, and by up-regulating markers such as NIS, could be useful in combination with radioactive iodine for treating ATC.
Performance Data to Predict Athletic Injury

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

BACKGROUND: The vertical jump (VJ) test is quick and non-invasive. For these reasons it has various uses in sports; ranging from assessing lower limb strength, designing injury rehabilitation programs, and predicting athletic performance. The force plate is the gold standard to measure VJ because it measures unilateral velocity, power, and force throughout the jumping process. Bilateral discrepancies may be a warning sign for injury. The goal of this project is to use VJ data to identify people at risk for knee ligament injuries.

METHODS: To perform the VJ test athletes stood on the force plate with their hands on their hips and performed a counter-movement jump and landed back on the plate, their hands remained on their hips throughout the process. Each athlete jumped 3 times per session. VJ data and injury reports were collected from 167 athletes on various UW-Madison varsity sports teams. VJ data and injury information was compared to each other. Athletes who suffered a knee ligament injury that had performed a pre-injury VJ were identified. This group is called the "predictive group" and contains 6 athletes. VJ data of these athletes was analyzed to find trends that may indicate an athlete is at increased risk for suffering a knee ligament injury. A group of non-athletes performed the VJ test and re-tested 2 days later to check testing reliability.

The greatest bilateral percentage force difference (GPFD) was calculated for every athlete tested. To determine if a certain GPFD put an athlete at risk for knee ligament injury the predictive group was compared to groups of athletes who never suffered a lower extremity injury (LEI) and those who had no LEI six months before the VJ test.

RESULTS: Preliminary data showed each athlete in the predictive group had a bilateral force difference during the jump process. The leg that eventually became injured had lower force and power than the uninjured leg. Average GPFD for the groups were: predictive = 19.7%, no history of LEI = 16.5%, and no LEI 6 months prior to jumps = 16.7%. Reliability testing results: intraclass correlation coefficient ICC(2,1)=0.99; SEM=0.03 BodyWeight; Difference in Means=0.03 BodyWeight.

CONCLUSIONS: VJ and injury data will continually be collected until there are 30-40 subjects in the predictive group. If athletes with a high GPFD are at increased risk for sustaining a knee ligament injury it could lead to focused injury prevention training programs.
The Impact of Prior Breast Augmentation on Short and Long Term Surgical Outcomes for Women Diagnosed with Breast Cancer

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Mentor: Lee G. Wilke, MD

Support: Shapiro Summer Research Program; Department of Surgery

BACKGROUND: As augmentation mammoplasty rates increase, the number of women with breast cancer and implants will also increase. For patients undergoing mastectomy, the data related to the maintenance or exchange of an implant and subsequent outcomes are sparse. We performed a retrospective cohort study to examine outcomes after mastectomy versus BCT in breast cancer patients with previous cosmetic implants. Our primary aim was to determine the difference in the number and timing of planned or unplanned major and minor interventions.

METHODS: We identified patients with cosmetic implants diagnosed with a breast malignancy who were treated at one of two universities from 1998 to 2010. Charts were retrospectively reviewed to assess the numbers of subsequent major and minor interventions in addition to the time to each intervention. Major interventions were defined as either expected or unexpected hospitalizations or operations after the original cancer surgery. Minor interventions included outpatient visits for symptom management. Statistical comparisons were performed.

RESULTS: Seventy-two patients were identified; 30 mastectomy and 42 BCT. Mean age was 49.7 years. Average length of follow-up was 5.1 years. Forty percent of women undergoing mastectomy maintained their original implant in contrast to 83% of women with BCT. Within the mastectomy cohort, the women had an average of 1.60 additional major interventions and 0.57 minor interventions. The BCT patients had a lower average of 0.48 additional major interventions and 0.17 minor interventions. After BCT, 27% had a major intervention within 1 year, whereas 57% of mastectomy patients had a major intervention in the first year and 89% experienced a major intervention within 5 years. In multivariate analysis, patients had a 2.75 times (p =0.0059) increased risk of major intervention if mastectomy was performed in comparison to BCT.

CONCLUSIONS: In this retrospective study, women with cosmetic augmentations who have BCT have a 2 times greater likelihood of maintaining their original implant and a significantly reduced risk of requiring planned or unplanned interventions. Our findings are limited by our inability to control for the impact of stage on surgical decision-making and lack of assessment of cosmetic outcomes. However, for women who are candidates for either surgery, our data suggests that BCT may be preferred. This data can be used pre-operatively to advise women of their treatment options.
Characterizing Frequent Fliers and Hotspotters in the Emergency Department

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Support: Shapiro Summer Research Program; Department of Medicine Division of Emergency Medicine

BACKGROUND: With continually rising numbers of emergency department (ED) visits and increasing wait times, attention has focused on patients who make frequent ED visits. Efforts have been made to characterize this population in the hopes of implementing systems or protocols to reduce their need for ED usage. These efforts have yielded conflicting results largely because of great variance within the population.

OBJECTIVE: The objective of this study is to examine the medical and demographic characteristics of frequent ED users and to describe the pattern of ED use over time. We want to characterize distinct subgroups in order to target effective strategies to reduce ED use.

METHODS: This is a retrospective review done in an academic center ED with an annual volume of 45,000. All patients with ≥ 7 visits in any calendar year between 2008-2010 were identified. Demographic and ED encounter-specific data for each visit was then obtained. We define “frequent fliers” as those with ≥ 7 visits but < 10% admissions and “hot spotters” as those with ≥ 7 visits with a greater than 50% admission rate.

RESULTS: There were 591 patients who had ≥ 7 visits in any one of the calendar years. Of these, 88 (15%) had ≥ 7 visits in two of the years, and 24 (4%) had ≥ 7 visits in all three calendar years. Of these 158 were frequent fliers and 193 hot spotters. ED use over time was similar in the two groups. The average age of frequent visitors was 43 years. The frequent fliers were younger (35) than hot spotters (50). 57% of frequent visitors were women (61% for frequent fliers, 47% for hot spotters). The average length of stay for all frequent visitors was 4.2 hours. Frequent fliers averaged 3.4 hours and hot spotters 4.7. Average ED acuity for all frequent visitors was 3. Hot spotters were more acute (2.9 vs. 3.2) than frequent fliers. The majority of chief complaints for frequent fliers were pain or psychiatric related whereas the hot spotters had, in general, more medical complaints. Frequent fliers account for 2.9% of total ED caseload but only 0.8% of hospital admits from the ED. In contrast, hot spotters account for 3% ED cases, but 7% of hospital ED admits.

CONCLUSIONS: Frequent users of the ED are a heterogeneous group. Hot spotters and frequent fliers are distinct subgroups of the group of frequent users. Efforts to target this group of patients to reduce ED use must formulate appropriate interventions recognizing these differences.
Improved Evaluation of African American Infant Mortality Statistics in Wisconsin: Determining Data Analysis Strategies for the Lifecourse Initiative for Healthy Families (LIHF)

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

BACKGROUND: The U.S. infant mortality rate (IMR) is higher than those in many other industrialized countries. In addition, the IMR has been consistently highest for infants of non-Hispanic black mothers. Therefore, because IMR is an indicator for the level of a country’s health, reducing IMR and IMR racial disparities are crucial public health goals. Wisconsin has one of the highest black to white IMR ratios in the country. However, infant mortality is a relatively rare event and it is difficult to interpret changes in rates in small geographic areas over short periods of time. Therefore, what are the best methods of analyzing and monitoring Wisconsin community targeted data on non-Hispanic black IMRs?

METHODS: I completed a literature review of strategies that have been utilized to analyze NHBIM data and ways to design metrics that yield statistically useful information about rare events. I consulted with multiple key informants with expertise in epidemiology, biostatistics, and maternal and child health in the Milwaukee and Madison metro areas. Finally, a power analysis was created for the existing data.

RESULTS: Multiple-year aggregates and/or moving averages should provide enough events for analyses. Statistical power estimates can be done for simple 2-way comparisons as long as the compared communities have relatively low mobility and have similar characteristics. The power analysis controls for confounding factors that vary between communities and is based on the total expected number of events across two time periods and the IMR ratio comparing the post-intervention period to the pre-intervention period. This will allow one to determine approximately how many events are needed pre-intervention to obtain a given power.

CONCLUSIONS: A power analysis and aggregated infant mortality rates will be used to monitor IMR change in targeted communities across groups and across years while considering proximal factors related to infant mortality as additional areas of study.
Presurgical fMRI and Morbidity Outcomes in Patients with Vascular Lesions

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BACKGROUND: fMRI is being increasingly used as an adjunct imaging technique for preoperative planning for patients with various brain lesions. The proximity of the lesion to eloquent cortex is a major factor in guiding surgical planning. Our group has previously reported significant association between the distance between brain tumor periphery and area of fMRI activation (Lesion-Activation Distance; LAD) and morbidity and mortality outcomes. This study investigated the relationship between vascular lesion LAD and morbidity.

METHODS: This study was a retrospective analysis of data from patients with vascular lesions [Arteriovenous Malformations (AVMs) (n=49), and cavernomas (n=57)], who had received fMRI as part of their preoperative planning. The preoperative fMRI included motor (n=87) and/or language mapping (n=102). The fMRI paradigms were chosen based on observed preoperative weakness (aphasia, paresis) and anticipated functional areas of the brain that may be affected by treatment.

RESULTS: Multiple logistic regression analyses showed that a model that combines Age and Language LAD was a significant predictor of postoperative deficits (p= 0.04). Broca's LAD (1-2 cm) X Age was a significant predictor of postoperative deficits (change in odds ratio (OR) =0.82, CI: 0.68-0.98). The relationship between Broca's LAD and postoperative aphasia and Broca's LAD and pre and postoperative aphasia trended towards significance (p = .08 and p = .07 respectively). Wernicke's LAD, independently or combined with Age, was not a significant predictor of postoperative deficits. Binary logistic regression analysis for SMC LAD and postop deficits did not reach significance (p = .10). There were no significant differences in postoperative language or motor deficits as a function of gender or handedness.

CONCLUSIONS: These results suggest that both age and the proximity of a vascular lesion to language LAD are factors that can help predict postoperative outcomes, especially for Broca's LAD. The lack of similar results when investigating the relationship between Wernicke's LAD and postoperative deficits suggests potential brain reorganization and/or robustness of this brain region. These results have implications for the potential use of fMRI as a presurgical tool for language mapping in patients with vascular lesions.
Angiosarcoma Outcomes and Prognostic Factors: The UW Experience

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Support: Shapiro Summer Research Program; Department of Human Oncology, NIH Grant 1UL1RR025011

BACKGROUND: Angiosarcoma is an aggressive sarcoma with differentiation towards endothelium, and is notorious for locoregional recurrence and distal metastases. The prognosis remains poor despite aggressive therapeutic interventions.

METHODS: To identify factors that impact angiosarcoma outcomes we reviewed the patient, tumor and treatment characteristics of angiosarcoma patients evaluated at the UW Hospital between 1988 and 2011.

RESULTS: The cohort consisted of 47 female and 31 male patients, age 19-90 y.o (median age 68 y.o.) at diagnosis. Mean tumor size was 5.5 cm. 43 (55%) patients presented with localized disease while 35 (45%) presented with metastatic disease. The most common primary site was visceral (40%) followed by cutaneous (33%), breast (17%) and other (10%). The overall 5-year survival (OS) was 46% with a median OS of 33 months. By univariate analysis, tumor characteristics that negatively influenced the outcome included the presence of metastatic disease at presentation, location (visceral vs other) and the size (<= 5 or >5 cm). Prior radiation and epithelioid morphology did not impact survival. Surgery positively influenced OS (median OS >60 mo vs 11 mo) and survival in patients with metastatic disease (median OS 17 vs 7 mo). Neither radiation nor chemotherapy significantly impacted OS, but a trend towards benefit of radiation therapy was seen in patients with localized disease. A trend toward benefit in OS with chemotherapy was also seen in patients with metastatic disease. Paclitaxel-based regimens showed benefit in comparison to other chemotherapeutic regimens in patients with metastatic disease but it did not reach statistical significance. In multivariate analysis, the presence of metastatic disease at presentation was the single most important factor (median survival of 11 months vs >60 months in patients with localized disease).

CONCLUSIONS: Our data confirms the poor prognosis of angiosarcoma despite aggressive therapeutic interventions and support the need for novel treatments in this disease.
Importance of Pre-op Platelet Count in Predicting Outcome for Resection of Hepatocellular Carcinoma

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Support: Department of Surgery NIH Training Grant T35 DK062709

BACKGROUND: Preoperative liver function prior to resection of hepatocellular carcinoma (HCC) is assessed using the Child-Turcotte-Pugh and MELD score. Low preoperative platelet count can be indicative of portal hypertension and can be predictive of unfavorable outcomes, but has not been explored to a great extent. We predict that low platelet count is independently associated with increased morbidity and mortality following surgical resection of HCC, and incorporation of platelet count into current liver function scores will be predictive of poor postoperative outcomes.

METHODS: A retrospective analysis was performed with the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) liver cases from 2005-2009 database. Of the 7902 patients in the database, 726 were selected with postoperative diagnosis of “malignant neoplasm of liver primary”, indicating HCC. A normal platelet count was defined as >150/nL, and a low platelet count as ≤150/nL.

RESULTS: As predicted, patients with a low platelet count had a significantly higher complication rate (p=.01) and death rate (p=.0008) following surgical resection of HCC than did patients with a normal platelet count. Also, when platelet count was incorporated into current liver function tests, increasing score value trended positively with increased morbidity and mortality, indicating potential predictive significance of pre-op platelet count.

CONCLUSIONS: Low preoperative platelet count is independently associated with postoperative morbidity and mortality following resection of HCC, and can be used as a parameter to assess liver function preoperatively. Future steps involve analyzing the modified liver score with platelet count included to determine if it is more predictive of postoperative outcomes than current liver scores. To do this, we will test the scores in a multivariate regression model for the postoperative endpoints of major complications and mortality.
Neurocatheter Convection Enhanced Delivery Performance in a Gel Model of the Brain

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Support: Kinetics Foundation, Los Altos, CA

BACKGROUND: Convection enhanced delivery (CED) is an advanced technique used to distribute therapeutic agents into targeted regions of the brain. In order for fluid convection to occur, pressure gradients must be maintained during the infusion process. This is typically accomplished through the use of mechanically controlled infusion pumps and has been found to have a penetrative advantage compared to diffusion-driven administration. Studies have found this approach to be more efficient and clinically useful as compared to simple diffusion-driven administration as it produces a larger and more precise volume of delivered agent over a shorter period of time. CED also produces a more evenly distributed and larger volume of drug over diffusion-driven delivery. Because direct intracranial administration of drugs can be delivered using this method, larger molecules that could not otherwise penetrate the blood-brain barrier can be introduced to the tissues of the brain.

METHODS: We tested the hypothesis that the ERG Valve-tip (VT) catheter with an infusion protocol of a steady 1µL/min infusion rate is comparable to the newly FDA approved MRI Interventions SmartFlow (SF) catheter with the UCSF infusion protocol in an agarose gel model. Specific performance characteristics of the two CED infusion catheter systems, namely backflow, infusion cloud morphology, volume of distribution (mm3) delivered volume (Vd/Vi) ratios, rate of infusion (µL/min), and pressure (mmHg), were examined to ensure published performance standards.

RESULTS: No significant difference was found in performance parameters between the VT and SF catheter except for a higher incidence of backflow with the SF catheter. Backflow was found to be significantly greater when protocols with higher infusion rates were used.

CONCLUSIONS: This is the first time benchmark characteristics in CED between these two otherwise similar single end-port valve-tip with stylet and end-port non-stylet neurocatheter infusion systems have been compared. Results of the current study in agarose gel models suggest that performance of the VT catheter is comparable to the SF catheter and warrants further investigation as a tool in the armamentarium of CED techniques for eventual clinical use and application.
Hereditary Medullary Thyroid Cancer: Age-Appropriate Thyroidectomy Improves Disease-Free Survival

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Support: Department of Surgery NIH T32 Grant 5T32DC009401 (Bless, PI)

BACKGROUND: Hereditary Medullary Thyroid Cancer (MTC) accounts for 25% of MTC cases and is characterized by different genetic mutations. The ideal age for prophylactic thyroidectomy is based upon the specific RET mutation. The aim of this study is to determine if such age-appropriate prophylactic thyroidectomy results in improved disease-free survival.

METHODS: We identified 28 patients undergoing thyroidectomy for hereditary MTC from 1994 to 2010 at our institution. Age-appropriate thyroidectomy was defined according to the North American Neuroendocrine Tumor Society (NANETS) guidelines for the different mutations. Patients having age-appropriate prophylactic surgery (Group 1, n=9) were compared to those having thyroidectomy after the recommended age (Group 2, n=19).

RESULTS: The mean age was 13 ± 2 years and 61% were female. Patients in Group 1 were younger than Group 2 (4 ± 1 vs. 17 ± 2 years, p=<0.01). There were no significant differences in the gender, RET mutation types, or tumor characteristics between these two groups. Patients who had age-appropriate thyroidectomy were cured with no disease recurrence as compared to those having surgery after the recommend age (p=0.05). Subanalysis of the patients that did not follow the recommended guidelines identified that patients who underwent surgery within a median of 2 ± 2 years of the guidelines had a significantly longer disease-free survival than those having surgery after a median of 16 ± 2 years past the guidelines (p=0.03).

CONCLUSION: Patients with hereditary MTC should undergo age-appropriate thyroidectomy based on RET mutational status in order to avoid recurrence. Patients who do not follow the guidelines should have surgery as early as possible in order to improve disease-free survival.
Thiocoraline Regulates Neuroendocrine Phenotype and Inhibits Proliferation in Carcinoid Tumor Cells

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Support: Department of Surgery NIH T35 Training Grant DK062709

BACKGROUND: Carcinoid tumors are rare, slow growing neuroendocrine neoplasms that typically arise in the gastrointestinal tract or bronchi. Hormone overproduction associated with these tumors adversely impacts patient quality of life. Also, due to the difficulty in obtaining an early diagnosis and relatively ineffective chemotherapy, metastatic disease often results. This precludes potentially curative surgical treatment. Therefore, novel treatment strategies targeted at reducing hormone secretion and tumor markers offer both palliative and therapeutic treatment options. The present study was performed to assess the antiproliferative effects of thiocoraline, a compound derived from marine bacterium Verrucosispora sp., on human carcinoid cell lines in vitro.

METHODS: Human pancreatic carcinoid BON and pulmonary carcinoid H727 cells were treated with increasing thiocoraline concentrations (0 – 50 nM) for up to 6 days to determine the effect on cellular proliferation by 3-(4,5-Dimethylthiazole-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Total cellular proteins isolated from thiocoraline treated cell lines were analyzed by Western blot for the neuroendocrine tumor marker human achaete-scute complex-like1 (ASCL1) and chromograninA (CgA), a clinically relevant test to monitor carcinoid serotonin hypersecretion. Western analysis was performed to determine the mechanism of growth regulation by analyzing the levels of cell cycle and apoptotic regulatory proteins.

RESULTS: Following 48 hour thiocoraline treatment, CgA and ASCL1 expression levels in both cell lines were reduced in a dose dependent manner. These changes correlated with the MTT cell viability assays, which showed both a dose and time dependent reduction in cell proliferation. Thiocoraline increased poly(ADP)-ribose polymerase (PARP) cleavage, an apoptosis marker, and decreased X-linked inhibitor of apoptotic protein (XIAP) expression, an anti-apoptotic marker, suggesting that thiocoraline mediates growth inhibition via apoptosis.

CONCLUSIONS: Our findings indicated the in vitro antiproliferative effect of thiocoraline on carcinoid tumor cell lines is via apoptosis. Tumor cell growth reduction with a concomitant fall in hormone secretion, reflected by decreased neuroendocrine tumor marker CgA expression, occurred with nanomolar dosing. These effects warrant further preclinical studies to identify the potential use of thiocoraline as a palliative or antineoplastic carcinoid tumor therapy.
Early Graft Failure After Lower Extremity Arterial Bypass: Results From More Than 200 Hospitals

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Support: Shapiro Summer Research Program; Department of Surgery

BACKGROUND: Early graft failure (EGF) is a serious complication after lower extremity arterial bypass. EGF has not been examined using national data since the widespread adoption of percutaneous treatments for LE arterial occlusive disease. To address this gap, we utilized data from the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP), which includes more than 200 academic and community hospitals.

METHODS: Patients who underwent lower extremity arterial bypass from 2005 to 2009 were selected from the ACS NSQIP database. The frequency of 30-day EGF NSQIP variable “OTHGRAFL” was determined. Univariate and multivariate methods were utilized to identify risk factors for EGF.

RESULTS: Of 13,751 patients who underwent open lower extremity arterial bypass, 733 (5.6%) had EGF. Patients who suffered EGF had a longer mean length of hospital stay (11.4 vs. 6.4 d, p<0.001), and had higher rates of reoperation (83.3% vs. 14.8%, p<0.001) and 30-day mortality (5.6% vs. 2.2%, p<0.001). The rate of other complications in patients who suffered EGF was 37.2%, compared to 19.1% in those who did not have EGF (p<0.001). In patients who had both EGF and another complication, the majority (77.3%) experienced the other complication subsequent to EGF. In a multivariable model, factors associated with EGF included age younger than 50 (OR, 1.48; 95% CI, 1.13-1.96), female gender (OR, 1.24; 95% CI, 1.06-1.44), smoking (OR, 1.23; 95% CI, 1.04-1.46), prior operation (OR 1.34, 95% CI, 1.04-1.73), femoral to tibial bypass (OR 2.10; 95% CI, 1.78-2.49), prosthetic graft (OR, 1.25; 95% CI, 1.05-1.50), and emergent operation (OR, 1.68; 95% CI, 1.29-2.19).

CONCLUSIONS: In an era of increased utilization of percutaneous techniques, EGF after open lower extremity arterial bypass remains a common event, with serious consequences. EGF is strongly associated with developing other complications, reoperation, and mortality. We have identified a number of risk factors for EGF, which may be of use for pre-operative counseling and decision making.
Evaluation of Three Patients with Cricopharyngeal Dysfunction: Can High-Resolution Manometry Help Predict Surgical Success?

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Support: Shapiro Summer Research Program; Department of Surgery, Division of Otolaryngology- Head and Neck Surgery

BACKGROUND: Dysphagia is a medical condition which is becoming more prevalent as our population ages. Traditionally, individuals with dysphagia undergo videofluoroscopic evaluation to help diagnose the etiology of their swallowing dysfunction. This technique has its limitations allowing only a passive viewing of anatomical structures of swallowing. High-resolution manometry (HRM) allows us to record the pressures created by these structures with fidelity previously unachievable. Our study evaluated three patients with oropharyngeal dysphagia and compared their pre-surgical swallowing metrics to post-surgical outcomes.

METHODS: Our study evaluated three patients with oropharyngeal dysphagia (age = 72.3 ± 4.6; range = 66 – 74). They preformed clinical videofluoroscopic swallow studies followed by a HRM evaluation. Manometry data was extracted and analyzed using ManoView software and a customized MATLAB program to calculate oropharyngeal pressure generation. These swallowing metrics were then correlated with post-surgical patient outcomes.

RESULTS: Patient 1 generated maximum pressures of 137.35, 146.00, and 83.97 mmHg in their velopharynx, tongue base, and cricopharyngeus respectively. Patient 2 generated 140.25, 113.42, and 71.73 mmHg in their velopharynx, tongue base, and cricopharyngeus respectively. Patient 3 who suffered from post-polio syndrome produced velopharynx and tongue base pressures (93.58 and 46.08 mmHg respectively) which were a full standard deviation lower than the comparison group (154 ± 42 in the velopharynx and 307 ± 172 mmHg in the tongue base). The greatest predictor of surgical success appeared to be an elevated hypopharyngeal intrabolus pressure. Patient 1 who responded well to surgery had a pre-surgical hypopharyngeal intrabolus pressure of 14.60 mmHg compared to Patient 2 and 3 who actually had negative hypopharyngeal intrabolus pressures and did not respond well to surgery. Our non-dysphagic comparison group averaged .99 mmHg.

CONCLUSIONS: Videofluoroscopic swallowing studies are limited when it comes to dysfunction at the level of the cricopharyngeus. Patients can often present with similar complaints of dysphagia and videofluorographic findings of cricopharyngeal bar. With HRM, we are able to measure the pressures generated in the oropharynx and differentiate between patients with elevated hypopharyngeal intrabolus pressures who should respond well to surgical intervention and those who would do better with alternative therapies.
Interdisciplinary Cancer Care Team Composition and Communication

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Support: Shapiro Summer Research Program; The Center for Patient Partnerships

BACKGROUND: Many healthcare professionals work together as members of an interdisciplinary team during the course of treatment for cancer. The make-up and coordination of interdisciplinary healthcare teams is not uniform and many challenges remain including communication, time constraints, large distances, funding, and reimbursement questions. In addition, the role of the patient on the healthcare team is ill defined, particularly as patient autonomy and involvement is becoming increasingly important. This study investigated trends in team communication and areas of potential improvement.

METHODS: This study used a qualitative approach to evaluate communication among members of a single healthcare team. We selected and interviewed a patient and the individuals he identified as part of his healthcare team. All team members were asked questions concerning team composition, team interactions, communication and subsequently, trends were delineated.

RESULTS: All individuals interviewed mentioned interdisciplinary meetings as a major contributor to good communication and many interviewees desired a more established role for a patient navigator specifically with a medical background. Some areas for improvement included flagging of issues to ensure the most important details were apparent during transitions between providers. Additionally, a greater involvement of the patient in the team or at a minimum, ensuring the patient was cognizant of the communication happening between the team members could improve patient satisfaction. Time remains the limited factor in the implementation of many measures.

CONCLUSIONS: Future studies are needed to investigate: the optimal role of the patient on a cancer care team; the role, qualifications, and duties of patient navigators to enhance communication; regional and institutional variations; and simple methods to streamline communication and involve the patient.
**Potential Role of Mesenchymal Stromal Cells in Pancreatic Islet Transplantation**

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**Mentors:** Jaehyup Kim, MD; Peiman Hematti, MD

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

**BACKGROUND:** Type 1 diabetes mellitus (T1DM) is one of the most prevalent autoimmune disorders of childhood, with approximately 70,000 cases occurring annually worldwide. T1DM results from autoimmune destruction of the insulin-secreting beta cells in the pancreas. Loss of beta cells leads to insufficient insulin levels and poor glycemic control, which causes numerous microvascular and macrovascular complications associated with significant morbidity and mortality. Exogenous administration of insulin remains the mainstay of T1DM treatment, and it can maintain normal blood glucose levels and has been credited with improved survival and reduced complications due to diabetes. However, this therapy requires multiple daily injections of insulin or the use of insulin pumps as well as major lifestyle modifications.

**PROPOSAL:** On the other hand, transplantation therapies could ideally achieve stable glycemic control in patients without the need for exogenous insulin. Therefore, insulin replacement by pancreas or islet cell transplantation is being actively sought as a potential therapeutic option. Pancreas transplantation requires major surgery and leads to surgery-associate complications such as bleeding, excessive exocrine drainage of the implanted pancreas, and side effects of life-long immunosuppressive medications. Consequently, pancreas transplantation is reserved for patients with long-standing diabetes and numerous other clinically significant complications. Researchers believe islet cell transplantation could be a more widely applicable treatment for T1DM. Indeed this therapy has improved in recent years, but issues associated with the lack of reliable long-term insulin independence post-transplant still exist. The gradual loss of function of islet allografts stems from many problems including acute and chronic rejection leading to poor initial engraftment and destruction over time. Immunosuppressive drugs have improved allograft function, but these drugs also have significant adverse effects. We believe cell-based immunomodulatory modalities, specifically mesenchymal stromal cells (MSCs), should be investigated as alternatives to immunosuppressive drugs in pancreatic islet transplantation. In our lab, we showed that pancreatic islet derived MSCs have phenotypic and immunomodulatory characteristics similar, but not identical, to bone marrow derived MSCs. Pancreatic islet derived MSCs could play an important role in improving pancreatic islet transplantation in the future by promoting engraftment and creating a favorable immune environment for acceptance of the islet allograft.
Characterizing Uptake and Retention of 18F-FDG in Mesenchymal Stem Cells to Facilitate Tracking In Vivo

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Support: Shapiro Summer Research Program; UW Cardiovascular Research Center

BACKGROUND: Cardiovascular diseases are a major health concern in Western countries, with ischemia accounting for the greatest loss of cardiac mass and contractile force. Despite advances in cell culture and cell based therapies, regeneration of damaged tissue has yet to be achieved. Mesenchymal stem cells (MSCs) are ideally suited for 'off-the-shelf' therapy for myocardial infarction (MI). Systemic and local myocardial cell delivery methods are being evaluated, but the best method to enhance cell retention is unknown. 18F-fluorodeoxyglucose (FDG) labeled MSCs have been proposed to measure acute cell retention; however, little is known on labeling efficiency and effects of the labeling procedure on cell viability.

METHODS: 5-15 million cells were incubated with 10-15 mci of FDG at 37 degrees for 1 hour with intermittent mixing followed by 2 washes. Labeling efficiency was defined as radioactivity in the pellet after 2 washes divided by the total radioactivity of all the supernatant collected. Effects of insulin on FDG uptake and effects of FDG on cell viability (trypan blue) were evaluated. Intramyocardial injection of MSCs was done in a swine MI model using a transendocardial injection catheter. Injection was guided using a custom X-ray/MRI fusion interventional guidance system followed by PET-CT scan.

RESULTS: Labeling efficiency ranged from 4-8%. There was no change in cell viability post labeling. Insulin had no effect on FDG uptake by MSCs. Number of cells and initial FDG activity were the greatest factors affecting labeling efficiency. Acute cell retention following intramyocardial injection was 64% at 1 hour.

CONCLUSIONS: Labeling MSCs with FDG is feasible and does not influence cell viability. Intramyocardial injection and quantification of FDG labeled MSCs is feasible.
Does Appendiceal Length Correlate with the Likelihood of Developing Acute Appendicitis?

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BACKGROUND: To determine if the spectrum of appendiceal lengths differs among patients with proven acute appendicitis compared with normal adult controls without appendicitis.

METHODS: The main study group was comprised of 321 consecutive adults with surgically proven appendicitis who all underwent preoperative MDCT. Appendiceal length at gross pathology was compared with MDCT measurement using curved reformatted reconstructions along the long axis of the appendix. Appendiceal length was measured in a similar fashion at MDCT in a control group of 321 consecutive adults without appendicitis undergoing colonography screening.

RESULTS: Mean appendiceal length and standard deviation of length at MDCT were both significantly greater in controls compared with the acute appendicitis group (7.87±3.49 cm versus 6.76±1.94 cm; p<0.001). Appendicitis cases outnumbered normal controls at every 0.5-cm interval between 4.0 cm and 9.5 cm, whereas both long and short normal controls predominated at every 0.5-cm interval outside this range. The odds ratio (OR) for acute appendicitis within the 4.0-9.5 cm interval was 5.4 relative to appendiceal lengths outside this interval; the OR for the 2.25-13.75 cm interval was 37.9. 88.5% (284/321) of appendicitis cases fell within the 4.0-9.5 cm range, compared with 56.1% (180/321) of controls (p<0.001). Appendiceal length at MDCT correlated well with gross pathology for the appendicitis group (mean length, 6.76 versus 6.56 cm), validating the curved reformat measurement approach at MDCT.

CONCLUSIONS: Appendiceal length strongly correlates with the likelihood of developing acute appendicitis. Specifically, both “long” and “short” appendix measurements are frequently seen in adult controls but rarely present with appendicitis, for which most cases fall between 4.0 and 9.5 cm.
Clinicopathological Characterization of Glioblastoma

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BACKGROUND: Glioblastoma multiforme (GBM), or WHO grade IV astrocytoma, is the most prevalent and aggressive primary human brain cancer. Current therapies, including maximal surgical resection, radiation therapy, and chemotherapy, prolong median survival to approximately 14 months from diagnosis. GBM oncogenic mechanisms remain poorly defined. A better understanding of GBM oncogenesis will potentially lead to improved diagnostic and therapeutic strategies and thereby improve patient outcomes.

METHODS: One strategy for elucidating GBM tumorigenesis involves the characterization of molecular markers on GBM cells using immunohistochemistry (IHC). Specific GBM molecular markers may be expressed and associated with cancer proliferation, therapeutic resistance, stem cell-like behavior, or tumor recurrence. Oncogenic protein markers associated with these characteristics in GBM include EGFR, CNP, Nestin, and p53. Creation of a clinically annotated tissue microarray containing 208 GBMs collected at UW from 1999-2008 enabled rapid IHC analysis of molecular marker expression. IHC analysis was correlated to the therapies and outcomes for this large patient set to discover clinically relevant data.

RESULTS: Clinical data were compiled from 170 patient records with one or more GBM samples in the tissue microarray, covering the variables of demographics, treatment course, overall survival, and tumor progression. The microarray was interrogated using three different antibodies for IHC analysis (CNP, EGFR, and Nestin). CNP IHC analyses demonstrated that CNP-positive tumors are correlated with significantly higher median patient survival than CNP-negative tumors (14 months vs. 10 months; p=0.0154).

CONCLUSIONS: This study generated a clinically correlated GBM tissue microarray database, and demonstrated the utility of this experimental system to discover clinically relevant prognostic marker (CNP) in GBM via a readily applied IHC analysis.
Ground Reaction Forces and Osteogenic Index of the Sport of Cyclocross

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

BACKGROUND: Increasing weight-bearing activity has been suggested to improve bone health and minimize fracture risk. Cyclocross, in contrast to conventional cycling, demands bouts of weight-bearing activity as cyclists dismount and remount their bicycles to jump over barriers and run pitched terrain. This study aims to measure peak and mean vertical ground reaction forces (vGRF) during cyclocross-specific activities and calculate their osteogenic index (OI).

METHODS: Twenty-five healthy cyclocross athletes (18 M, 7 F) participated: 35.5(8.3) yrs old, 73.3(10.2) kg, 3.8(2.5) yrs of competition. vGRF was measured with pressure sensitive insoles (Novel Inc.) during seated cycling and four activities: barrier flat, barrier uphill, uphill run-up, downhill run-up. Peak vGRF and mean vGRF (%BW) across loading cycles were determined for each activity. OI of each activity was computed using: OI=peak vGRF (%BW) x ln(loading cycles + 1). vGRF and OI comparisons were made using repeated measure ANOVA. Relationship between cycling speed and vGRF was assessed with Pearson correlation coefficient.

RESULTS: Number of loading cycles per activity was 11.9(2.3) for barrier flat, 17.0(3.0) barrier uphill, 14.2(2.5) uphill run-up, 23.8(5.1) downhill run-up. All activities had significantly (p<0.05) higher peak vGRF, mean vGRF and OI than seated cycling. The barrier flat condition had the significantly (p<0.05) highest peak vGRF (2.9 (0.4) %BW) and mean vGRF (2.3 (0.3) %BW). Downhill run-up had the significantly (p<0.05) highest OI of 6.5(1.1). During barrier flat and barrier uphill conditions the peak vGRF occurred during a jumping or landing maneuver, while the peak vGRF during uphill run-up and downhill run-up occurred on the initial foot strike following cycle dismount. Mean vGRF was positively correlated with maximum cycling speed for all activities except uphill run-up.

CONCLUSIONS: Peak vGRF generated during the barrier flat activity measured in this study is similar in magnitude to previously reported GRFs during running and soccer. vGRFs during all four activities were significantly higher than seated cycling. OI of the barrier flat condition alone is higher than seated cycling for an equivalent number of loading cycles. Cyclocross-specific activities may be more beneficial to bone health than seated road cycling.
A Qualitative Investigation of a National Advanced Care Planning Health Policy

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Mentors: Sarah Davis, JD, MPA; Kathy O’Connell, PhD, ATC; Meg Gaines, JD, LLM

Support: Shapiro Summer Research Program; The Center for Patient Partnerships

BACKGROUND: The original Patient Protection and Affordable Care Act intended to have a provision for reimbursement of health care providers for End-of-Life Counseling, now termed, Advanced Care Planning (ACP). However, strong opposition and negative publicity eventually required the administration to remove any ACP provisions all together. Late 2010, an amendment passed for the Social Security Act for Medicare payment schedules that included reimbursement to providers for ACP and consultation that went into effect on January 1, 2011; however, it was repealed 4 days later. New legislation was introduced on April 15, 2011, H.R. 1589, titled the Personalize Your Care Act of 2011. This act would provide reimbursements for voluntary, personalized patient-physician consultations regarding ACP, provide federal grants for programs, create standards for electronic health records and improve portability of advance directives.

METHODS: This was a qualitative research study completed in two parts. First, was a comprehensive literature review of ACP services, including assessment and summary of the proposed legislation as described above, and review of literature and outcomes as related to the services to be reimbursed by said legislation. Second, semi-structured interviews were completed with key informants on the topic of ACP and health policy. Data was collected from interviews, observations, notes and review of literature for analysis. Key topics and themes from findings are to be featured.

RESULTS: Analysis of literature review, observations and key informant interviews are ongoing and will be presented.

CONCLUSIONS: Integration of ACP as health care policy is integral as a part of a patient-centered care approach to medicine. However, adoption of legislation from a national level remains contentious. Prioritization, acceptance and implementation of comprehensive ACP programs need to come from local and regional communities.
Serological Analyses in Children with Neuroblastoma: Clinical Associations

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Support: Shapiro Summer Research Program; Department of Human Oncology

BACKGROUND: A monoclonal antibody, ch14.18, against the tumor-associated disialoganglioside GD2, has been shown through both preclinical and clinical data to have activity against neuroblastoma. In a Children's Oncology Group (COG) phase III study, ch 14.18, in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and isotretinoin, was compared to standard isotretinoin therapy for treatment of pediatric neuroblastoma. The clinical results were published in the New England Journal of Medicine in September of 2010, and showed a 20% increase in event-free survival at 2 years post-treatment. This project's goal was to determine if any measured serologic parameters were associated with anti-tumor effect, toxicity, or any other relevant clinical outcomes from the COG phase III study.

METHODS: Serologic samples from patients enrolled in the COG ANBL-0032 phase III trial were gathered from days: -1 (pre-course 1), 6 (post-C1), 80 (pre-C4), 90 (post-C4), 111 (pre-C5) and 118 (post-C5). They were analyzed via enzyme linked immunosorbent assay (ELISA) to determine the concentration of ch14.18 (ch14.18 level), concentration of soluble IL-2 receptor (sIL2R level), and presence of human anti-chimeric antibody (HACA). Data was then formatted for computer analysis and submitted for correlative analysis by COG and University of Wisconsin Carbone Cancer Center (UWCCC) biostatisticians.

RESULTS: Preliminary serologic analysis of ANBL-0032 samples showed a mean post-course (i.e. days 6, 90, 118) ch14.18 level of 8169 ng/ml. The mean trough level (i.e. days 80, 111) of ch14.18 was 1122 ng/ml. The mean baseline sIL2R level was 2555 pg/ml, with a mean increase of 7458 pg/ml after each treatment course. HACA response (OD>0.5) was noted in 6 of 131 patients analyzed. The analysis of correlations between these serological results and clinical outcomes is still pending review by COG and UWCCC biostatisticians.

CONCLUSIONS: Preliminary results show increases in the serum level of both ch14.18 and sIL2R in the days after clinical treatment with ch14.18, IL-2, GM-CSF, and isotretinoin. HACA responses were relatively uncommon, with 6 occurring in the 131 patients analyzed.
Investigating the Relationship Between Fetal Iron Deficiency and Eosinophilia at 6 months-12 months

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Support: Shapiro Summer Research Program (RW); University of Wisconsin Cardiovascular Research Center (RW); Meriter Foundation (PJK); Wisconsin Partnership Collaborative Health Sciences Program Grant (PJK, CLC); Thrasher Research Fund (PJK); UW Graduate School Competition (PJK); NIH: 1UL1RR026011 CTSA Program NIH: T32HD048302 Health Disparities Research Scholar.

BACKGROUND: Asthma is very prevalent in the U.S. Newborns with iron deficiency (ID) had enhanced risk of recurrent wheeze in childhood and later asthma diagnosis. A prior study showed lower umbilical cord iron was associated with persistent wheezing in infancy, associating the two diseases.

METHODS: Two indices of eosinophilia were defined; % eosinophilia is ≥4% of total WBCs and absolute number (AN) eosinophilia is ≥470/mm3 eosinophils. Since eosinophilia at 6-12 months of age is a biomarker for recurrent wheeze in infancy, we hypothesize that eosinophilia will correlate with low iron stores at birth. Newborns ≥35 weeks gestational age with one or more risk factors for ID were recruited. Risk factors included: maternal ID, maternal diabetes, large or small for gestation newborns, mothers from minority groups, and/or with low socioeconomic status. Cord blood indices of storage iron (plasma ferritin), steady state red blood cell (RBC) iron (zinc protoporphyrin/heme or ZnPP/H), and recent RBC iron (reticulocyte-enriched or RE ZnPP/H) were measured. At 6-12 months, eosinophil % and AN eosinophils were determined. Linear regression and unpaired t tests were performed.

RESULTS: No linear relationship was found between 6-12 month eosinophil % or AN eosinophil count and any cord blood iron marker. Mean ferritin levels did not differ based on % eosinophil, but was lower in those with AN eosinophilia, p=0.02. Mean transferrin for those with and without AN eosinophilia were similar, p=0.32. Higher cord RE ZnPP/H trended higher in those with % eosinophilia, p=0.053, but was higher in those with AN eosinophilia, p=0.02. The ΔZnPP/H (difference between RE ZnPP and steady state ZnPP/H) was significantly higher in those with % and AN eosinophilia, p=0.02, p=0.007, respectively. Graphically, few ferritin values in children with either the % or AN eosinophilia were found above the 75 percentile of normal cord ferritins.

CONCLUSIONS: Associations existed between eosinophilia at 6-12 months and both RBC and ferritin indices in cord blood. Poor fetal iron status in late gestation affects immune cell differentiation. Studies show that a predominance of T helper type 2 (Th2) cells is seen in asthmatic children and that a postpartum amplification may exacerbate this shift. In vitro work shows that Th2 clones are relatively resistant to cellular iron depletion. Further investigation is necessary to define the association between iron depletion, eosinophilia and a Th2 shift.
Identification of Clinical and Pathologic Factors Associated with Recurrence of Renal Cell Carcinoma

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Support: Shapiro Summer Research Program; Department of Urology

OBJECTIVE: To identify clinical and pathological factors associated with disease recurrence in a cohort of renal cell carcinoma (RCC) patients with no known metastatic disease at the time of surgery. Clinical and pathologic risk factors were compared with tissue expression of 3 putative biomarkers for RCC recurrence.

METHODS: After IRB approval, we used an institutional database to identify patients who underwent a radical or partial nephrectomy for RCC with no lymph node or distant metastasis at surgery. Immunohistochemistry was used to determine CRP, NFkB and Ki-67 expression within tumor and benign samples from a RCC microarray. VECTRA image analysis was used to report expression of the biomarkers. Univariate and multivariate analysis was used to identify risk factors for disease recurrence.

RESULTS: The analysis included 222 patients with a median follow up of 60.5 months. There was recurrent disease in 40 (18.0%) patients. Significant risk factors identified from univariate analysis include: Fuhrman grade, histologic subtype, sarcomatoid de-differentiation, AJCC stage, venous thrombus, and perinephric fat invasion. On multivariate analysis, Fuhrman grade and perinephric fat invasion remained significant. Intratumoral NFkB activation was related to stage and grade but not risk of tumor recurrence. Intra-tumoral Ki-67 and CRP expression correlated to increased risk of tumor recurrence.

CONCLUSIONS: We identified 7 risk factors for disease recurrence in RCC. Further investigation and validation of these risk factors is necessary to create a prognostic model for disease recurrence.
Identification of Epigenetic Regulators of Fetal Hemoglobin Expression

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Support: Shapiro Summer Research Program; Department of Cell and Regenerative Biology

BACKGROUND: Individuals with Sickle Cell Disease or beta-Thalassemia who have hereditary persistence of fetal hemoglobin (HbF) have fewer complications and a better prognosis than individuals with normal expression of adult Hb. The gamma globin gene is repressed in the adult by a number of components including the transcriptional coactivator Bcl11a, and epigenetic modifications, such as histone and DNA methylation. Active epigenetic modifying enzymes represent targetable proteins for small molecule inhibition, and knowledge of the specific actions of the factors involved will be beneficial in the development of future therapy for these diseases.

METHODS: In this study, I demonstrated that knockdown of two cell cycle-associated epigenetic enzymes, the histone mono-methyltransferase SetD8 and the histone demethylase Phf8, induce Hbb-βh1 and Hbb-y in mouse G1E-ER-GATA1 cells.

RESULTS: Interestingly, although these enzymes have opposing biochemical actions, their knockdown caused similar and additive induction of Hbb-βh1. These observations were independent of any significant alteration in Bcl11a expression. These results provide initial support for an important role of these epigenetic regulators in mediating gamma globulin repression.

CONCLUSIONS: This is an important step in the elucidation of potential therapies for SCD and thalassemias, which are associated with considerable morbidity and mortality due to ineffective therapy and represents a major public health problem, especially in developing regions of the world.
Emergency Department On-Site: Integrating Doctors, PAs, and Nurses into Event Medical Care

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BACKGROUND: The US Open golf tournament is a massive event with over 300,000 people on grounds throughout 10 days and over 700 patient contacts. Traditionally, large-scale events are staffed with the local BLS and Paramedic services, and sometimes 1 or 2 MDs, PAs, or RNs. Studies indicate ~75% of EMS contacts are transported. Instead of this traditional, mainly EMS model, the Medical Plan for this event was a unique model integrating MDs, PAs, and RNs for high-level treatment on-site in order to avoid the potentially catastrophic effects of a massive patient burden on local EMS, Fire, and hospitals.

METHODS: Care was given from three Medical Aid Stations, staffed with a minimum of one emergency medicine MD or PA, one emergency medicine or critical care nurse, and one other emergency medicine MD/PA/RN provider. Information was gathered on each patient including age, gender, authorization (spectator, VIP, etc.), chief concern, site of care, and disposition. Contacts were categorized as Basic Clinical Interventions or Advanced Clinical Interventions. A literature search was performed on average transport rates for BLS and ALS services.

RESULTS: 729 patient contacts were made requiring basic clinical interventions or more. According to contemporary studies, an average of 75% of contacts with EMS are transported. If a similar rate were sustained at this event, almost 550 patients might have been transported, which would certainly have overwhelmed the hospital system. The medical plan integrating MDs, PAs, and RNs provided high-level treatment and release in the field, effectively triaging the number transported down from ~550 to 12. In comparison to the traditional model, integration of advanced medical operations into on-site triage and treatment reduced the transport rate by 4,580%. Patients treated had a 100% positive outcome rate. Ten of the 12 patients who were transported were admitted to the hospital.

CONCLUSIONS: This unique medical plan integrating MDs, PAs, and RNs to treat and release in the field at large-scale events successfully absorbed the large volume of patients from overwhelming the local hospital system. The accuracy of treat and triage is shown in the high rate of transports admitted and uniformly positive outcomes of treated-and-released patient contacts. Planning for future large-scale events with the potential to overwhelm local resources should incorporate similar integration of MDs, PAs, and RNs for on-site triage and treatment.
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