

Washington University in St. Louis School of Medicine
Eighth Annual Research Training Symposium & Poster Session
October 22nd & 23rd, 2013
Farrell Learning and Teaching Center

Tuesday, October 22nd

2:30 - 4:30 pm Farrell Learning and Teaching Center Atrium and Hearth
Poster Session

Wednesday, October 23rd

12:00 – 12:15 pm Connor Auditorium

Welcome and Opening Remarks

W. Edwin Dodson, MD

Associate Vice Chancellor and Associate Dean of Admissions

Professor of Pediatrics and Neurology

Washington University in St. Louis School of Medicine

12:15 – 1:15 pm Connor Auditorium

Keynote Address

David F. Ransohoff, MD

Professor of Medicine

Clinical Professor of Epidemiology

Director, Clinical Research Curriculum (K30)

The University of North Carolina at Chapel Hill

1:15 – 2:30 pm Connor Auditorium

Oral Presentations

1:15 – 1:30 pm

David Bundy, BS

1:30 – 1:45 pm

Kshamata Shah, BPT

1:45 – 2:00 pm

Heather Frey, MD

2:00 – 2:15 pm

Elna Nagasako, MD, PhD, MPH

2:15 – 2:30 pm

Andrea Wang-Gillam, MD, PhD

This symposium is made possible by the Clinical Research Training Center (CRTC), a component of the Washington University Institute of Clinical and Translational Sciences (ICTS). The ICTS is part of a national consortium of medical research institutions, funded through the Clinical and Translational Science Awards (CTSA) that includes sixty medical research institutions in thirty states and the District of Columbia, working together to improve the way biomedical research is conducted across the country. The CTSA consortium shares a common vision to reduce the time it takes for laboratory discoveries to become treatments for patients, and to engage communities in clinical research efforts. It is also fulfilling the critical need to train the next generation of clinical researchers. The CTSA initiative is led by the National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health. The CRTC is supported by NCATS Grant Numbers UL1 TR000448, KL2 TR000450, and TL1 TR000449, Washington University in St. Louis School of Medicine, and Barnes-Jewish Hospital Foundation.

This symposium & poster session is co-sponsored by the Office of Medical Student Research, Washington University in St. Louis School of Medicine.

We gratefully acknowledge the support of Dr. Larry J. Shapiro, Executive Vice Chancellor for Medical Affairs and Dean, Washington University in St. Louis School of Medicine.

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Programs Represented

Center for Health Policy

The Washington University Center for Health Policy conducts research in an effort to improve the future health of Americans by affecting health policy on the federal, regional, state and local levels.

Program Director: William Peck, MD

Website: <http://healthpolicy.wustl.edu/>

Clinical Research Training Center (CRTC) KL2 Career Development Awards

The KL2 Career Development Awards Program at Washington University in St. Louis provides high-quality, multidisciplinary training in clinical and translational research to promote the career development of future clinical investigators. The program is comprised of postdoctoral scholars and junior faculty committed to multidisciplinary clinical research. KL2 Career Development Awards provide financial support and benefits that allow scholars to focus on mentored, multidisciplinary research, supplemented by applicable coursework.

Program Director: Victoria Fraser, MD

Website: <http://crtc.wustl.edu>

Clinical Research Training Center (CRTC) K12 Paul Calabresi Career Development Awards for Clinical Oncology

The K12 Career Development Award for Clinical Oncology at Washington University in St. Louis provides high-quality, multidisciplinary training in clinical and translational research to promote career development for future clinical investigators. The goal of the K12 Paul Calabresi Career Development Award for Clinical Oncology is to train a new generation of highly skilled investigators with specialized expertise who will be well prepared to lead cancer research. The K12 Clinical Oncology program supports the development of postdoctoral scholars and junior faculty through patient oriented cancer research training, curricula, and mentored projects.

Program Director: Ramaswamy Govindan, MD

Website: <http://crtc.wustl.edu>

CRTC Master of Science in Clinical Investigation (MSCI) Degree Program

The MSCI Degree Program at Washington University is designed as a one to three year full- or part-time degree program for young investigators committed to pursuing academic careers in clinical research. The unique program combines didactic coursework with mentored research and career development opportunities and provides students with the knowledge and tools to excel in the areas of clinical investigation most relevant to their careers.

Program Director: David K. Warren, MD, MPH

Website: <http://crtc.wustl.edu>

CRTC Postdoctoral Mentored Training Program in Clinical Investigation (MTPCI)

The CRTC Postdoctoral Program MTPCI provides multidisciplinary clinical and translational research training to promote the career development of junior faculty and postdoctoral fellows by helping them become clinical and translational researchers. Through didactic coursework, structured mentorship, and interactions with a diverse peer group of trainees, the CRTC Postdoctoral Mentored Training Program in Clinical Investigation (MTPCI) enables Scholars to learn how to: develop effective research projects, utilize human subjects in clinical trials, collect, analyze and summarize data, apply epidemiologic principles and tools, consider relevant ethical and legal issues, write grants and manuscripts, and compete for research funding.

Program Director: Jane Garbutt, MBChB

Website: <http://crtc.wustl.edu>

CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program

The CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program provides career development for medical and allied healthcare students through didactic coursework, mentored training, work-in-progress research discussions, journal clubs, and conferences. This program supports a select group of trainees as they embark on patient-oriented research careers by teaching them how to: design and conduct clinical research, analyze data, consider relevant ethical and legal issues, write manuscripts and grants, develop and present scientific posters, and compete for research funding.

Program Director: Jay Piccirillo, MD, FACS

Website: <http://crtc.wustl.edu>

CRTC Doris Duke Clinical Research Fellowship

The Doris Duke Clinical Research Fellowship Program at Washington University is part of the Medical Research Program of the Doris Duke Charitable Foundation. One of the foundation's goals is to further the prevention and cure of disease by supporting and strengthening clinical research and by narrowing the gap between basic biomedical discoveries and their translation into the prevention, treatment and cure of human diseases. The program provides the opportunity for clinical research, individual guidance by a faculty mentor and advisory committee, stipend, health insurance and travel allowance. The 2013-2014 academic year marks the end of this research program.

Program Director: Jay Piccirillo, MD, FACS

Website: <http://crtc.wustl.edu>

Dames Fellowship

The Dames Fellowship supports a medical student to conduct summer research in cell biology and physiology.

Program Director: Koong-Nah Chung, PhD

Website: <http://medadmissions.wustl.edu/unlimitedopp/studentresearch/Pages/StudentResearch.aspx>

David F. Silbert Summer Fellowship

In his memory, the David F. Silbert Summer Fellowship was set up to support short-term research internships for medical, graduate, or other students interested in his area of research. David's research focused on genetic biochemical and/or biophysical approaches to the study of specific membrane lipids in signal transduction pathways and in the assembly and function of eukaryotic cell membranes. Since his death from cancer in 1997, a number of biophysical techniques have been developed that address these issues. These techniques include, but are not limited to state-of-the-art fluorescence methods, structural determination using NMR or x-ray methods and computational approaches. All these techniques are directed towards understanding the role of macromolecular interactions in cellular function. It is now clear that membrane lipids and membrane proteins are functionally involved in all aspects of the regulation of cellular processes and that these processes must be studied at the level of macromolecular function.

Program Director: Linda Pike, PhD

Website: <http://biochem.wustl.edu/resources/archives/awards-fellowships/silbert-fellowship/2012-david-f-silbert-summer-fellowship-research>

Dean's Fellowship

This program is designed to provide medical students with a hands-on research experience. This can be a first-time experience or a project related or unrelated to research done as an undergraduate. Excellent mentors from a broad range of basic and clinical sciences are available. A Washington University Summer Research Fellowship can provide a strong background for application to the MA/MD and MD/PhD (MSTP) degree programs, can lead to abstracts at meetings and to publications, and can be important for applications for competitive residencies.

Program Director: Koong-Nah Chung, PhD

Website: <http://medadmissions.wustl.edu/unlimitedopp/studentresearch/Pages/StudentResearch.aspx>

DeNardo Education and Research Foundation Grant

The purpose of the DeNardo Education and Research Foundation is to support education and research in the health sciences, broadly defined, with preference for activities that relate to the field of medicine. DeNardo Summer Research Scholars will be engaged in basic and clinical research during the summer following the first year of medical school. The program gives medical students hands-on laboratory research experience with outstanding investigators and helps prepare them for careers in academic medicine.

Program Director: Koong-Nah Chung, PhD

Website: <http://medadmissions.wustl.edu/unlimitedopp/studentresearch/Pages/StudentResearch.aspx>

Forum for International Health and Tropical Medicine

The Forum for International Health and Tropical Medicine (FIHTM) brings together students and physicians at Washington University who are interested in international health. FIHTM aims to promote understanding of global health by enabling medical students to experience firsthand its locales, modes of delivery, disparities, and cultural manifestations. FIHTM organizes the Global Health Symposium each spring, as well as regular discussion lunch meetings with students and faculty. In addition, the group coordinates Spring Break community service trips for the first and second year medical classes. FIHTM offers financial and logistical assistance to students who wish to gain healthcare experience abroad and helps interested students find mentors within the university.

Program Director: Kathy Diemer, MD

Website: <http://fihtm.wustl.edu>

Howard Hughes Medical Institute Summer Medical Fellows Program

The Summer Medical Fellows Program is primarily aimed at students who later intend to apply for the year-long Medical Fellows Program. Summer Medical Fellows spend eight to 10 weeks doing full-time research with an HHMI investigator, early career scientist, HHMI professor, or Janelia researcher. Fellows are exposed to high-quality science, have a chance to increase their scientific knowledge and research skills, and interact with world-class investigators in a rich training environment. Fellows can gain insight into a career as a medical scientist and determine if they would like to continue their research training in a year-long program. This program is for medical, dental, and veterinary students attending schools located in the United States. Up to 20 fellowships are awarded annually.

Program Director: Melanie Daubs

Website: <http://www.hhmi.org/programs/medical-research-fellows-program/summer-program>

Mallinckrodt Institute of Radiology

Now in its 15th year, the Mallinckrodt Institute of Radiology Summer Research Program offers undergraduate and medical students an opportunity to conduct research in the following aspects of radiological sciences research: Magnetics resonance imaging, Magnetic resonance spectroscopy, Positron emission tomography, X-ray computed tomography, Contrast agent development, Diagnostic radiology, Molecular imaging, Nuclear medicine, Radiopharmaceutical development, Neuroscience imaging, Cardiovascular imaging, Optical imaging, Ultrasound.

Program Director: Suzanne Lapi, MD

Website: <http://www.mir.wustl.edu/education/internal.asp?NavID=95>

MA/MD

Created in 1982, the Master's Degree Program allows medical students to participate in cutting-edge biomedical or clinical research and earn a Master of Arts degree in preparation for a career in academic medicine. The program is highly flexible and is intended not only for those who have previous research experience, but also for students who are novices in research. The objective is to provide an individualized research experience in an excellent environment, and students are encouraged to explore a wide range of research possibilities.

Program Director: Deborah Rubin, MD

Website: <http://www.dbbs.wustl.edu/divprograms/mamd/Pages/mamd.aspx>

MD5

The One-Year Research Without Degree Program (MD5) is available to all Washington University medical students at any point in the curriculum. Students who wish to take advantage of this program should select a research mentor and obtain permission to work with him/her for one year. The arrangement should then be approved by the mentor and by the associate dean for medical student research through the application process.

Program Director: Koong-Nah Chung, PhD

Website: <http://medadmissions.wustl.edu/unlimitedopp/studentresearch/Pages/StudentResearch.aspx>

Movement Science Program (MSP)

The Program is an integral member of one of the world's largest academic biomedical research institutions; collaboration occurs with nearly every department in the School of Medicine, as well as with colleagues in biomedical engineering, psychology, and biology. Researchers lead studies in a comprehensive array of topics from the basic physiological mechanisms of tissue injury to studying health interventions at the community level. Investigations involve subjects across the life span. The Movement Science Program is supported by NIH training grant T32HD007434.

Program Director: Michael J. Mueller, PhD, PT, FAPTA

Website: <https://physicaltherapy.wustl.edu/Education/DoctoralEducation/PhDinMovementScience>

Master of Population Health Sciences (MPHS)

The Master of Population Health Sciences (MPHS) degree program equips clinicians and clinical doctorates with the advanced research methods skills needed to design clinical outcomes research, interpret results and apply findings to improve clinical effectiveness. MPHS students establish a wide network of mentors and collaborators by interacting with Washington University medical and public health faculty who are renowned for their teaching, patient care and ongoing cutting-edge research around the world. With no research thesis requirement, the degree can be obtained in as few as ten months, which allows students to easily integrate the training into a clinical career, including during the medical school, residency and fellowship years. The Washington University in St. Louis School of Medicine MPHS program is one of a few in the country and one of the only in the Midwest that offers population health-based research methods training for clinicians.

Program Director: Graham Colditz, MD, DrPH

Website: <http://www.mphs.wustl.edu/>

NIDA T32 Training Program in Epidemiology, Services and Prevention Research

The NIDA T32 pre- and post-doctoral Research Training Program in Drug Abuse Epidemiology, Services and Prevention (DEASP) provides outstanding training for fellows in a range of sub-specialties including epidemiology, biostatistics, psychiatric and behavioral health comorbidity, community implementation science, concerning public health aspects of addiction and addictive behaviors. The Department of Psychiatry also offers biomedical science mentoring in areas of genetics, basic and cognitive neuroscience, psychophysiology and imaging for those public health researchers who wish to integrate biomedical research tools with their research specialty.

Program Director: Rumi Kato Price, MPE

Website: <http://www.psychiatry.wustl.edu>

Office of the Provost, Diversity & Inclusion Grant

The Washington University, Office of the Provost, Diversity & Inclusion Grant helps train 5 Meharry Medical College students in the Washington University in St. Louis School of Medicine's (WUSM) Summer Research Program each summer. The benefits of the partnership include: 1) Exposing the Meharry medical students to cutting-edge science at WUSM, 2) Benefiting our WUSM faculty's research, 3) Enhancing the diversity culture of WUSM, and 4) Increasing our pipeline of under-represented medical students into our residency programs.

Program Director: Koong-Nah Chung, PhD

Website: <http://provost.wustl.edu/diversity/diversity-inclusion-grants>

Otolaryngology NIH T32 Physician Scientist Program (PSP)

This training program provides a pathway directing medically trained individuals toward a successful research career in academic otolaryngology. This research experience is offered at two levels. At the first level, medical students are selected to participate in this program for approximately three months during the summer. Mentored research projects for medical students are conducted by selected trainees to stimulate a general interest in research and specific interest in otolaryngological research. At the second level, residents selected into the 7-year "Advanced Physician Scholars Program" by a special residency match mechanism perform mentored research in depth, in a contiguous two-year period, free of clinical responsibilities. Funding for this program is provided by a National Institutes of Health (NIH)-National Institute on Deafness and Other Communication Disorders (NIDCD), Ruth L. Kirschstein National Research Service Award (NRSA) Institutional Research Training Grant (T32) entitled "Development of Clinician/Researchers in Academic ENT", 5T32DC000022-22.

Program Director: Jay Piccirillo, MD, FACS

Website: <http://medadmissions.wustl.edu/unlimitedopp/studentresearch/Pages/StudentResearch.aspx>

Rehabilitation and Participation Science (RAPS) Doctoral Program

The mission of the Rehabilitation and Participation Science PhD program is to develop scientists in the areas of rehabilitation and participation science to improve the human condition. We employ an interdisciplinary approach including the fields of neuroscience, engineering, occupational science, psychology, and environmental science. Our graduates will generate new knowledge to minimize limitations of persons with disability and chronic health conditions and increase their ability to participate in family, work and community life. They will address questions about the relationships among occupation, activity, participation, and health; or examine how bio-behavioral or environmental mechanisms such as sensory, motor, or cognitive function, social support, or technology enable daily life performance.

Program Director: Carolyn Baum, PhD, OTR/L, FAOTA

Siteman Cancer Center Leah Menshouse Springer Summer Student Program

The Leah Menshouse Springer Summer Student Program at the Siteman Cancer Center provides opportunities for undergraduate, premed and medical students enrolled at Washington University or other accredited universities to work on cancer research projects during the summer. Opportunities range from basic laboratory research to clinical research to prevention/control and population research.

Program Coordinator: Theresa Waldhoff

Website: <http://www.siteman.wustl.edu/contentpage.aspx?id=254>

Society of Nuclear Medicine Molecular Imaging Grants and Awards

The grants, supported by SNMMI's Education and Research Foundation, represent the society's commitment to advancing molecular imaging and therapy by supporting the next generation of researchers.

Program Director: Kristi Padley

Website: <http://interactive.snm.org/index.cfm?PageID=1083>

Summer Medical Education Research Fellowship (SMERF)

The Summer Medical Education Research Fellowship supports medical students to conduct summer research in medical education.

Program Director: Koong-Nah Chung, PhD

Website: <http://medadmissions.wustl.edu/unlimitedopp/studentresearch/Pages/StudentResearch.aspx>

T32 NIH Cardiopulmonary Surgery Training Grant

This program has been continuously funded since 1994. It is anticipated that in the next ten years there will be a shortage of cardiothoracic surgeons. To meet the future needs it is essential that an increased number of academic surgeons are trained. An essential element is training these individuals to be independent investigators. Therefore, the overall aims of the program are to provide a stimulating environment and research training for academic cardiothoracic surgeons. The specific goals are to: 1) attract the most innovative, inquisitive, diverse, and motivated candidates; 2) provide them with the highest possible level of training in the basic science of cardiovascular and pulmonary physiology and pathology; and 3) foster critical thought to prepare the trainees for an independent academic career and leadership role. A strength of the program is its interdisciplinary approach to scientific problem solving in which clinically recognized problems are studied in animal models of human disease at the integrative, cellular, and molecular levels, which can then be translated to clinical solutions. A key component of this training program is the faculty, which includes 26 faculty members with over \$22 million of NIH support and extensive experience in research mentoring. They represent four separate departments with a history of collaborative research. Over the last 25 years, the laboratory has trained 72 postdoctoral fellows. Of these 46 are in academic medicine, six are division chiefs or department chairpersons, and one is a principal investigator at the NIH.

Program Director: Ralph J. Damiano, Jr., MD

T32 NIH NIDDK Diabetes Training Grant

The goal of the program is to expose medical students to career opportunities in basic or clinical research related to diabetes and related metabolic diseases.

Program Director: Clay Semenovich, MD

Website: <http://medicalstudentdiabetesresearch.org/>

T35 NIH NHLBI Training Grant

This program is designed to provide medical students with a hands-on research experience. This can be a first-time experience or a project related or unrelated to research done as an undergraduate. Excellent mentors from a broad range of basic and clinical sciences are available in research areas related to heart, lung and blood diseases and disorders. A Washington University Summer Research Fellowship can provide a strong background for application to the MA/MD and MD/PhD (MSTP) degree programs, can lead to abstracts at meetings and to publications, and can be important for applications for competitive residencies.

Program Director: Koong-Nah Chung, PhD

Website: <http://medadmissions.wustl.edu/unlimitedopp/studentresearch/Pages/StudentResearch.aspx>

T35 NIH NIDDK Short-Term Training Program

The goal of the trans-NIDDK Short-Term Training Program for Medical Students is to expose medical students to career opportunities in basic or clinical research related to diabetes, obesity, endocrine disorders, metabolic diseases, nutritional disorders, digestive diseases, liver diseases, kidney diseases, urologic diseases and hematological disorders.

Program Director: Thomas J. Baranski, MD, PhD

Website: <http://medadmissions.wustl.edu/unlimitedopp/studentresearch/Pages/StudentResearch.aspx>

Abstracts for Oral Presentations

In the Order Presented

Bundy, David

CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program, CRTC MSCI Degree Program

Doctorate in Biomedical Engineering Program

Department of Biomedical Engineering, Washington University in St. Louis

Mentor: Eric Leuthardt, MD

Human electrocorticographic correlates of contralateral and ipsilateral reaching movements

Bundy DT; Sharma M; Szrama N; Pahwa M; Hacker C; Mitchell T; Leuthardt EC

Introduction: Brain-Computer Interface (BCI) systems utilizing electrocorticography (ECoG) have the potential to restore function after motor impairment. While BCIs traditionally use cortex contralateral to an impaired limb, these areas would be altered after a stroke.

Previous studies have shown that there is a unique neural physiology related to ipsilateral limb movements; however, the encoding of kinematics within these signals is uncertain. This study was designed to examine the characteristics of ECoG signals during 3D reaching movements of the ipsilateral and contralateral limbs that could be used in a potential BCI system.

Methods: Data were collected from five intractable epilepsy patients implanted with subdural ECoG grids. A behavioral task was designed in which ECoG signals and 3D hand positions were simultaneously recorded while participants performed 3D center-out reaching movements with either the arm contralateral or ipsilateral to the electrodes. In 4 of the 5 patients, datasets from both limbs were collected. ECoG signals were analyzed to identify the cortical activity and signal characteristics that are related to kinematic information in each hand. Machine learning techniques were used to decode kinematic information about reaching movements.

Results: We found that activity in electrodes located in sensorimotor, premotor, and frontal cortices demonstrated significant spectral power changes during planning and execution of movements of both the contralateral and ipsilateral limb. Furthermore, we demonstrate the utilization of ECoG signals for decoding of 3D movement kinematics of both the ipsilateral and contralateral arms.

Conclusions: These results demonstrate the presence of neural representations and the use of these neural representations for decoding of 3D movement kinematics in human ECoG signals. Furthermore, the data demonstrates that cortical activity displays similarities and differences in the representation of movement information of the two limbs based upon the electrode location and frequency bin. These findings can be extended into the unaffected hemisphere in stroke survivors for development of an ECoG BCI system for stroke.

Shah, Kshamata

Movement Science Program

Program in Physical Therapy, Washington University in St. Louis School of Medicine

Mentor: Michael J Mueller, PT, PhD

Relationship between advanced glycation end-products and upper extremity movement impairments in people with diabetes mellitus

Shah KM; Clark BR; McGill JB; Lang CE; Mueller MJ

Introduction: In people with diabetes mellitus (DM), the relationship between accumulation of advanced glycation end-products (AGEs) and shoulder structural changes, movement and function is not understood. We hypothesize that the Skin Intrinsic Fluorescence (SIF), an indicator of the AGEs in the skin, will correlate with the biceps (BT) and supraspinatus (SST) tendon thickness measures, peak humerothoracic elevation, and function measures at the shoulder.

Methods: In this preliminary examination, 16 subjects with Type 2 DM were recruited (8F/8M; Age 63.6 (6.3) yrs; BMI 30.6 (4.1) kg/m²). The main outcome measures were: SIF, measured using SCOUT DS device (VeraLight Inc., Albuquerque, NM); BT and SST thickness, measured using ultrasound; three-dimensional peak humerothoracic elevation, measured using an electromagnetic tracking device, and Shoulder Pain and Disability Index (SPADI) questionnaire, used as a measure of upper extremity function.

Results: Mean measurements for the outcome variables were as follows: SIF = 2.47 (0.37) Arbitrary Units; BT thickness = 3.7 (1.2) mm; SST thickness = 5.9 (1.0) mm; peak humerothoracic elevation angles = 143.1 (10.5) degrees; SPADI = 24.9 (30.0) %. The SIF measures correlated negatively with the peak humerothoracic elevation motion ($r = -0.52$; $P=0.03$), and correlated with the tendon thickness measures (BT, $r = 0.45$; $P=0.08$; SST, $r = 0.25$; $P=0.36$), and SPADI ($r = 0.58$; $P=0.02$). 50% ($P<0.05$) of the variance in the SPADI scores was explained by SIF, BT thickness and peak humerothoracic elevation.

Conclusions: These preliminary results indicate that SIF, an indicator of the accumulation AGEs, is inversely related to peak humerothoracic elevation, and directly related to tendon thickness and upper extremity pain and disability. Clinicians should be aware that accumulation of AGEs in individuals with DM may have deleterious effects on structural changes, joint mobility and function of the upper extremity. Early detection of these impairments may help in developing appropriate treatment strategies (i.e. exercise and pharmaceutical) to prevent additional detrimental changes.

Frey, Heather, MD

CRTC Postdoctoral Mentored Training Program in Clinical Investigation (MTPCI), CRTC MSCI Degree Program
Division of Maternal-Fetal Medicine

Department of Obstetrics and Gynecology, Washington University in St. Louis School of Medicine

Mentors: Alison G Cahill, MD, MSCI; George A Macones, MD, MSCE; David K Warren, MD, MPH

Neonatal outcomes in the setting of category II fetal heart rate tracings: Does meconium matter?

Frey HA; Tuuli MG; Shanks AL; Macones GA; Cahill AG

Introduction: Category II (Cat II) fetal heart rate tracings (FHR) are of indeterminate significance, thus improved risk stratification of Cat II FHR is needed. We tested the hypothesis that meconium (mec) in the setting of Cat II FHR increases the risk of adverse neonatal outcome.

Methods: This study was conducted within a prospective cohort of 5000 women with singleton pregnancies admitted in labor at term. Pregnancies with Cat II FHR in the 60 minutes prior to delivery were included. FHR data were extracted by trained nurses blinded to clinical outcome. The exposure was presence of mec. The primary outcome was a composite neonatal morbidity defined as ≥ 1 of the following: neonatal death, neurologic morbidity (hypoxic encephalopathy, seizures, hypothermic therapy), respiratory morbidity (RDS, TTN, ventilatory support), hypotension requiring treatment, and suspected or confirmed sepsis. Secondary outcomes were nursery admission, cord pH, 5-minute Apgar score, and components of the composite. Logistic regression was used to adjust for parity and gestational age. Among women with mec, we assessed the association between specific FHR characteristics and morbidity.

Results: Of the 3,257 women with Cat II FHR, 693 (21.3%) had mec and 2,564 (78.7%) did not. Mec was associated with higher risk of the composite morbidity (aOR 2.55, 95% CI 1.89-3.42) and increased risks of the secondary outcomes. The associations remained significant when infants with mec aspiration syndrome were excluded. There was a dose-response relationship between degree of mec and risk of neonatal morbidity (*thick* mec: aOR 3.36, 95% CI 2.39-4.73; *thin* mec: aOR 1.69, 95% CI 1.05-2.73). Tachycardia was more prevalent and accelerations were fewer during labor among neonates with mec and the composite morbidity, while decelerations were not significantly different.

Conclusions: The presence of mec is associated with an increased risk of neonatal morbidity in women with Cat II FHR. This clinical factor may assist clinicians in managing Cat II FHR in labor.

Nagasako, Elna, MD, PhD, MPH

CRTC KL2 Career Development Awards Program

Division of General Medical Sciences

Department of Internal Medicine, Washington University in St. Louis School of Medicine

Mentors: W. Claiborne Dunagan, MD; Sarah Gehlert, PhD

Patient perspectives on transitions of care between hospital and community settings

Nagasako E; Noel L; Schenk E; Gehlert S

Introduction: Despite changes in financial incentives and the development of evidence-based readmission reduction interventions, hospital readmissions remain a significant issue, with an estimated cost in the Medicare population of over \$17 billion per year. Obtaining community stakeholder input via formal research methods provides a potential mechanism for understanding the ways in which the implementation of readmission prevention interventions should be adapted for the local context. This study uses in-home interviews to identify patients' goals, barriers, and supports in the period after hospital discharge in order to gain an improved understanding of factors leading to readmission and to identify patient-centered ways to adapt existing interventions to the local context.

Methods: Qualitative study using in-home interviews of 30 patients, age 40 years or older, discharged from a large academic tertiary-care hospital with the diagnoses of heart failure, pneumonia, acute myocardial infarction, or chronic obstructive pulmonary disease between April 1, 2013 and August 31, 2013.

Anticipated Results: Preliminary results from analysis of the patient interviews have included themes related to the interaction between the patient's health state and health behaviors and the patient's relationships, the adjustment to the new physical and emotional states introduced by illness, and the role of self-efficacy and advocacy by others in health system interactions.

Conclusions: Preliminary study results suggest that factors in the patient's social environment affect the way in which patients experience the post-discharge period and their interactions with the health care system. Current models of readmissions risk prediction vary in the degree to which these factors are included and often focus on clinical factors such as comorbid conditions. Factors identified from this study can be further evaluated in the larger discharged patient population for prevalence and for utility in identifying patients for interventions to improve the transition from the hospital to community setting.

Wang-Gillam, Andrea, MD, PhD

CRTC KL2 Career Development Awards Program, CRTC MSCI Degree Program

Division of Oncology

Department of Internal Medicine, Washington University in St. Louis School of Medicine

Mentors: Lee Ratner, MD, PhD; Jason Weber, PhD

Identifying targetable pathways in pancreatic cancer from endoscopic ultrasound-guided fine-needle aspirates (EUS/FNA): providing a personalized approach to targeted therapy

Wang-Gillam A; Wani S; Langley E; Gao F; Murad F; Mullady D; Early D; Edmundowicz S; Linehan D; Kuller A; Jain A; Kim P; Singh S; Azar R

Introduction: Targeted therapy trials in pancreatic cancer patients have either failed or, at most, provided only marginal benefit. Identification of activated key signaling pathways would allow the optimal selection of patients for kinase inhibitor trials. Hence, we launched a study to profile targetable pathways from EUS/FNA samples using an ultrasensitive multiplexed protein microarray platform (CEER™, Prometheus).

Methods: Patients who underwent routine diagnostic FNA for a suspicious lesion in the pancreas underwent two dedicated passes for CEER™ profiling of the following phosphorylated (activated) key molecules: HER1, HER2, HER3, c-met, IGF-IR, PI3K, AKT, MEK, ERK, and other signaling proteins.

Results: Of 100 participants, final cytology results were: 73 carcinomas, 8 indeterminate, 13 negative, and 5 neuroendocrine. Pathway activation was heterogeneous in patients with carcinoma. Among 61 pancreatic cancer patients with adequate HER evaluation, a high prevalence of HER3 activation (62%) was observed, and concomitant activation of two or more HER pathways was seen in 52% of patients. In particular, activation of HER2 and HER3 was noted in 23% of carcinoma patients. High concordance of HER, PI3K and AKT activation was seen.

Conclusions: Our study confirmed the feasibility of profiling targetable pathways from FNA samples. Furthermore, it illustrates highly variable and concomitant pathway activation among pancreatic cancer patients, suggesting the feasibility of a personalized approach to targeted therapy. Future trials will need to be designed to explore the clinical benefit of combinations of HER-targeted agents in defined subsets of pancreatic cancer patients, and further evaluation of the HER3 pathway is especially warranted. An analysis of pathway interactions and prognostic effects is in progress.

Abstracts for Poster Session
Alphabetically by Training Program and Author

CRTC KL2 Career Development Awards Program

No **Beigelman, Avraham, MD, MSCI**

Poster CRTC KL2 Career Development Awards Program
Division of Allergy, Immunology and Pulmonary Medicine
Department of Pediatrics, Washington University in St. Louis School of Medicine
Mentors: Leonard Bacharier, MD; Mario Castro, MD, MPH

The association between vitamin D status and the rate of exacerbations requiring oral corticosteroids in preschool children with recurrent wheezing

Beigelman A; Zeiger RS; Mauger D; Strunk RC; Jackson DJ; Martinez FD; Morgan WJ; Covar R; Szeffler SJ; Taussig LM; Bacharier LB
Introduction: Vitamin D status is inversely associated with asthma morbidity among school age children and adolescents, but this association has not been studied among preschool children.

Methods: A post hoc analysis examined the relationship between baseline serum 25-hydroxyvitamin D (25-OH-VitD) levels and the rate of exacerbations requiring oral corticosteroids (OCS) during the 12-month Maintenance Versus Intermittent Inhaled Steroids in Wheezing Toddler (MIST) Trial. Study participants were 264 children aged 12-53 months with frequent episodic wheeze, positive modified Asthma Predictive Indices, and a significant exacerbation in the prior year.

Results: Median (Q1, Q3) baseline serum 25-OH-VitD level was 33.5ng/mL (26.4, 43.7). 25-OH-VitD level, as a continuous variable, was not associated with the rate of exacerbations requiring OCS ($p=0.65$). However, using vitamin D as a categorical variable showed that participants with vitamin D deficiency (25-OH-VitD<20 ng/ml; $n=18$) were more often non-Caucasian (72% vs 36%, $p=0.002$) and more often reported tobacco smoke exposure (72% vs 41%, $p=0.01$) than participants with 25-OH-VitD ≥ 20 ng/ml. Vitamin D deficient participants had a significantly higher rate of exacerbations requiring OCS than participants with 25-OH-VitD ≥ 20 ng/ml (1.46 vs. 0.93 exacerbations/child-year, $p=0.035$; rate ratio 1.56, 95% CI 1.03-2.37), and this finding remained significant after adjustment for race and smoke exposure.

Conclusions: These findings suggest that vitamin D deficiency in preschool children with severe intermittent wheezing is associated with an increased frequency of exacerbations requiring OCS.

No **Ju, Yo-El, MD**

Poster CRTC KL2 Career Development Awards Program, CRTC MSCI Degree Program
Division of Sleep Medicine
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Mentor: David Holtzman, MD

Functional brain networks in REM sleep behavior disorder

Ju YS; Nolan TS; Duntley SP; Larson-Prior LJ

Introduction: REM sleep behavior disorder (RBD) has a strong association with synucleinopathies. Prior psychometric studies have demonstrated subtle abnormalities of task-switching and visuospatial tasks in RBD, similar to deficits in synucleinopathies. In this study, we used resting state functional connectivity MRI (fcMRI) to assess the strength of brain networks and regions involved in attention, executive control, visual, auditory, and motor function.

Methods: Ten individuals with RBD were compared to ten age- and sex-matched controls. All underwent brain MRI including two blood-oxygen level dependent (BOLD) sequences acquired resting awake with eyes closed. Following standard pre-processing and regression of noise signals, BOLD time series were extracted from pre-defined regions of interest (ROI). The correlation coefficient between BOLD time series of each pair of ROIs was assessed. Correlation coefficients for ROI-pairs were averaged to assess the connectivity strength of each network. Paired t-tests were used to compare RBD cases and controls.

Results: There were no significant differences between RBD cases and controls in the strength of the executive control, attention, or default mode networks. However, there was a significant decrease in connectivity between visual cortex and attention network (RBD 0.06 vs Control 0.14, $p=0.02$). Additionally, the RBD group had almost no correlation between the visual and primary motor regions, significantly lower than the robust correlation in controls (RBD 0.08 vs Control 0.33, $p=0.008$).

Conclusions: In this group of otherwise cognitively normal RBD cases, there was significantly reduced connection strength between visual regions and the attention network, and between visual and motor regions. The strength of cognitive networks and other sensorimotor regions was not different between RBD cases and controls. These findings suggest that the decline in visuo-spatial performance in RBD reflects a specific functional network disturbance of the visual regions, rather than a generalized brain dysfunction. This implies that disconnection of visual regions from their usual functional networks occurs at the earliest preclinical stages of synucleinopathies.

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Kummer, Terrance, MD, PhD

CRTC KL2 Career Development Awards Program, CRTC MSCI Degree Program
Division of Neurocritical Care

Department of Neurology, Washington University in St. Louis School of Medicine

Mentor: David Brody, MD, PhD

Diffusion tensor imaging detects multifocal axonal injury in a mouse model of subarachnoid hemorrhage

Kummer T; MacDonald C; Milner E; Friess S; Zipfel G; Brody D

Introduction: Subarachnoid hemorrhage (SAH) from the rupture of an intracranial aneurysm shares key mechanical features with traumatic brain injury (TBI), including exposure to a sudden, global pressure wave generated by the arterial jet. It might, therefore, be anticipated that the diffuse mechanical injury of axons central to TBI pathophysiology is also an important component of cerebral injury after SAH. Elucidating these connections may lead to novel treatment approaches to both conditions.

Methods: We undertook a diffusion tensor imaging (DTI) study to understand the extent of axonal injury following SAH in a mouse model. We quantitatively compared changes in white matter anisotropy indicative of axonal integrity to histological evidence of axonal injury from the same tissue. We also examined the early time course of intracranial pressure (ICP) changes associated with SAH in this model system.

Results: Our results show that ICP increases rapidly after SAH, peaking in approximately 2 seconds, and similar to that seen after various models of experimental TBI. DTI reveals a significant decrement in relative anisotropy in white matter regions close to the site of arterial rupture, with smaller reductions observed in more distant white matter structures. Histological analysis of amyloid precursor protein, known to accumulate in traumatically-injured axons, reveals multifocal axonal injury in a large halo surrounding the focus of subarachnoid bleeding. Silver staining also reveals protein accumulation in ipsilateral white matter structures as is seen following TBI.

Conclusions: These investigations reveal that axonal injury is a feature of early brain injury following SAH in this model system. The functional implications of this injury subtype, and its relevance to humans is the subject of future investigations. Further analysis of this phenomenon may help illuminate the processes underlying cerebral injury from SAH, provide new prognostic indicators, and suggest novel treatment modalities for this devastating condition.

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Lane, Michael, MD, MSc

CRTC KL2 Career Development Awards Program

Division of Infectious Disease

Department of Internal Medicine, Washington University in St. Louis School of Medicine

Mentor: Dave Warren, MD

Management and outcomes of prosthetic joint infections: a retrospective analysis

Lane MA; Ganeshraj NS; Gu A; Bodavula P; Marschall J; Parsaei S; Warren DK

Introduction: There is significant variation in the management and outcomes of prosthetic joint infections (PJI).

Methods: We performed a retrospective review of all patients with PJI seen at Barnes-Jewish Hospital between July 2005 and June 2010. Patients were identified by discharge ICD-9-CM code for PJI (996.66) or from Infectious Diseases clinical databases. PJI diagnosis was confirmed based on intra-operative findings or attending physician diagnosis. We collected demographic data, comorbidities, treatment variation, and clinical outcomes.

Results: This study included 402 patients with PJI involving the knee (196, 49%), hip (160, 40%), shoulder (28, 7%) and elbow (16, 4%). Causative organism was cultured in 308 (76.6%) cases, while 91 (23.3%) were culture negative. Antibiotic exposure \leq 30 days prior to surgery was not associated with negative cultures ($p = .7$). Coagulase-negative *Staphylococcus* (CNS) (112, 36.4%), methicillin-sensitive *S. aureus* (69, 22.4%), and methicillin-resistant *S. aureus* (56, 18.2%) were the most frequently identified organisms. Polymicrobial infections were present in 57 (14.2%) of PJI. Knee PJI was most frequently treated with complete hardware explantation (122/196, 62%) and partial exchange (52/196, 27%). Hip PJI was most frequently treated with complete hardware explantation (93/160, 58%) and partial exchange (49/160, 31%). All-cause 1 year readmission occurred in 175 (44%) patients. Debridement & partial hardware exchange was not a risk factor for readmission for knee (OR 1.07, 95% CI 0.49-2.36) or hip (OR 1.06, 95% CI 0.46-2.46) PJI. Age, gender and race were not associated with readmission after hip or knee PJI. Patients with hip PJI due to CNS were less likely to be readmitted within 1 year (OR 0.36, 95% CI 0.15-0.87). Changes to antibiotic therapy were required in 27.9% (112) of patients. Drug reactions (26, 23.2%) and nephrotoxicity (17, 15.2%) were the most common reasons for change in therapy.

Conclusions: Debridement & partial hardware exchange is a common approach among patients with knee or hip PJI but was not associated with unanticipated readmission. Changes in antibiotic therapy were frequently necessary.

No **Liao, Steve, MD, MSCI**
Poster CRTC KL2 Career Development Awards Program
Division of Newborn Medicine

Department of Pediatrics, Washington University in St. Louis School of Medicine

Mentors: Terrie Inder, MD; Joseph Culver, MD; Jane Garbutt, MD

Bilateral cerebral tissue oxygen saturation monitoring may predict brain injury in very preterm infants

Liao SM; Mathur A

Introduction: Preterm infants are at high risk for developing intraventricular hemorrhages (IVH) due to various risk factors including impaired cerebral autoregulation. Near infrared spectroscopy (NIRS) measures cerebral tissue oxygen saturation (SctO₂) and has shown utility in bedside brain monitoring for both research and clinical management. We aim to explore the relationship between left and right side differences in SctO₂ during the first day of life and severity of IVH in a cohort of very preterm infants.

Methods: Infants less than 28 weeks estimated gestational age (EGA) were recruited for a prospective monitoring study. A NIRS probe (ForeSight, CAS Med, Branford, CT) was placed on each frontal-parietal area of the infant. Physiologic data (e.g. heart rate, pulse oximetry, respiratory rate, and mean arterial blood pressure when available) were simultaneously collected and synchronized with NIRS data. The earliest 4 hours of continuous bilateral SctO₂ recordings during the first day of life were averaged. The absolute values of the differences between the left and right SctO₂ means (Δ_{L-R} SctO₂) were calculated. Both clinical and research-related cranial ultrasound findings within the first month of life were used to define presence of IVH and severity. The NIRS data used for analysis were all obtained prior to the first cranial ultrasound.

Results: A sample of 19 infants with bilateral SctO₂ recordings during the first days of life has been analyzed so far [EGA of 25.7±1.3 weeks, mean birth weight of 862g ±165]. Infants with more severe IVH had a trend towards having larger bilateral SctO₂ differences during the first days of life [Δ_{L-R} SctO₂ = 4.5 ± 2.9 in infants with no apparent IVH (n=8), Δ_{L-R} SctO₂ = 6.0 ± 2.6 in infants with grades I and II IVH (n=3), Δ_{L-R} SctO₂ = 7.3 ± 5.0 in infants with Grades III and IV IVH (n=8)].

Conclusions: Persistently large differences in SctO₂ between two sides of the head early in postnatal life may be associated with more severe IVH in very preterm infants. This may indicate regional difference in cerebral autoregulation and bilateral SctO₂ monitoring may be a useful clinical tool.

030 **Maccotta, Luigi, MD, PhD**
CRTC KL2 Career Development Awards Program
Adult Epilepsy Division

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Mentors: Maurizio Corbetta, MD; R Edward Hogan, MD

Cross-hippocampal functional connectivity is abnormal in MRI-negative temporal lobe epilepsy

Maccotta L; Moseley E; Corbetta M; Hogan RE

Introduction: Several studies in recent years have shown that resting state functional networks show abnormalities in temporal lobe epilepsy (TLE). The abnormalities involve the medial temporal region, as well as neocortical temporal and extratemporal sites. However studies so far have not differentiated between patients in whom structural brain MRIs show evidence of mesial temporal sclerosis (MRI-positive) and patients in whom structural MRIs appear normal (MRI-negative). The latter group would particularly benefit from novel localization techniques that would improve the likelihood of seizure freedom after epilepsy surgery.

Methods: Here we explored functional network changes in patients segregated into MRI-positive and MRI-negative groups. Thirty-two patients with TLE underwent resting-state BOLD fMRI. Of these, 9 had MRI evidence of mesial temporal sclerosis (MRI-positive) and 23 had normal MRIs (MRI-negative). Each patient had video-EEG localization of seizures with unilateral seizure onset. A group of age-, gender-, and handedness matched healthy subjects (n = 32) served as controls. Anatomical segmentation was used to define regions of interest (ROIs) that were used as seeds in a functional connectivity analysis using typical methods.

Results: A main finding was that MRI-negative patients showed decreased functional connectivity between hippocampal heads compared to controls (p<.05). MRI-positive patients also showed significantly decreased connectivity compared to controls in the same location (p<.001), with an effect larger than the one seen in the MRI-negative group.

Conclusions: These findings suggest that cross-hippocampal functional connectivity disruption may be a marker of disease in TLE patients with normal structural brain MRIs, and may guide lateralization and possibly localization prior to epilepsy surgery, with the potential to improve surgical outcome.

No
Poster

Palanca, Ben, MD, PhD

CRTC KL2 Career Development Awards Program, CRTC MSCI Degree Program
Department of Anesthesiology, Washington University in St. Louis School of Medicine
Mentor: Marcus Raichle, MD

Functional neuroimaging of sevoflurane-induced unresponsiveness reveals reorganized resting-state networks and reduced global connectivity

Palanca BJ; Shannon BJ; Larson-Prior L; He B; Leuthardt EC; Snyder AZ; Evers AS; Avidan MS; Raichle ME

Introduction: The weakening of synchronized neural activity distributed across cortical and subcortical structures is a putative mechanism for the disruption of cognitive functions by anesthetics. Propofol sedation disrupts intrinsic attention networks linking neurons of frontal, parietal, and temporal regions. Sevoflurane sedation weakens inter-hemispheric connectivity among motor regions but its effects on attention networks remain equivocal. The purpose of our study was to determine how sevoflurane disrupts cortical and subcortical network connectivity given its distinct molecular pharmacology relative to propofol.

Methods: Simultaneous electroencephalography and functional magnetic resonance imaging (fMRI) data were acquired from fifteen healthy human participants. The spontaneously breathing volunteers were imaged at baseline and during administration of 0.6% for sedation and 1.2% for rendering unresponsiveness. The correlation strengths among brain regions (functional connectivity) were calculated from volumes sampling the thalamus, caudate, putamen, cerebellum, and the default mode, dorsal attention, salience, and frontoparietal control networks. Significance of functional connectivity changes were assessed by permutation tests at a region level and paired t-tests at a network level.

Results: Sedation at 0.6% sevoflurane strengthened the connectivity among attention networks without significant effects within individual networks. The unresponsiveness of 1.2% sevoflurane was associated with widespread weakening of connectivity within and among cortical attention networks and among subcortical structures. Residual functional connectivity remained but did not respect the topology of intrinsic attention networks.

Conclusion: The transition from wakefulness to unresponsiveness of sevoflurane sedation is associated with a biphasic perturbation in functional connectivity and a reorganization of network dynamics in a manner more complex than a global weakening of correlated brain activity with increasing sevoflurane dose.

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Pepino, M Yanina, PhD

CRTC KL2 Career Development Awards Program
Division of Geriatrics and Nutritional Science
Department of Internal Medicine, Washington University in St. Louis School of Medicine
Mentors: Nada Abumrad, PhD; Todd Braver, PhD

Sucralose affects glycemic and hormonal responses to an oral glucose load

Pepino MY; Tiemann CD; Patterson BW; Wice B; Klein S

Introduction: Nonnutritive sweeteners (NNS), such as sucralose, have been reported to have metabolic effects in animal models. However, the relevance of these findings to human subjects is not clear. We evaluated the acute effects of sucralose ingestion on the metabolic response to an oral glucose load in obese subjects.

Methods: Seventeen obese subjects (BMI: $42.3 \pm 1.6 \text{ kg/m}^2$) who did not use NNS and were "insulin-sensitive" (based on a Homeostasis Model Assessment of Insulin Resistance score ≤ 2.6), underwent a 5-hr modified oral glucose tolerance test on 2 separate occasions, preceded by consuming either sucralose (Experimental condition) or water (Control condition) 10 min before the glucose load in a randomized cross-over design. Indices of β -cell function, insulin sensitivity (S_i) and insulin clearance rates were estimated by using minimal models of glucose, insulin and C-peptide kinetics.

Results: Compared with the Control condition, sucralose ingestion caused: 1) a greater incremental increase in peak plasma glucose concentrations (4.2 ± 0.2 vs. $4.8 \pm 0.3 \text{ mmol/L}$; $P=0.03$), 2) a $20 \pm 8\%$ greater incremental increase in insulin area under the curve (AUC) ($P<0.03$), 3) a $22 \pm 7\%$ greater peak insulin secretion rate ($P<0.02$), 4) a $7 \pm 4\%$ decrease in insulin clearance ($P=0.04$), and 5) a $23 \pm 20\%$ decrease in S_i ($P=0.01$). There were no significant differences between conditions in active GLP-1, GIP, or glucagon incremental AUC or indices of the sensitivity of the β -cell response to glucose.

Conclusions: These data demonstrate that sucralose affects the glycemic and insulin responses to an oral glucose load in obese people who do not normally consume NNS.

No **Pusic, Iskra, MD**

Poster CRTC KL2 Career Development Awards Program, CRTC MSCI Degree Program
Division of Oncology

Department of Internal Medicine, Washington University in St. Louis School of Medicine

Mentors: John DiPersio, MD, PhD; Mario Castro MD, MPH

Development of antibodies to self antigens K-Alpha-1 Tubulin and Collagen V in patients with chronic graft-versus-host disease (cGVHD)

Pusic I; Saini D; Mohanakumar T; DiPersio J

Introduction: cGVHD is a multisystem alloimmune and autoimmune disorder characterized by production of antibodies (Ab), immune dysregulation and impaired organ function resembling autoimmune diseases. NIH Consensus Criteria for cGVHD defines bronchiolitis obliterans (BO) diagnosed clinically as a distinctive feature and BO diagnosed by lung biopsy as a diagnostic feature of cGVHD. Chronic rejection following human lung transplantation is associated with development of alloimmune response to donor mismatched HLA antigens. Recent studies in our laboratory and others have shown a strong correlation between development of autoimmunity to self-antigens K-alpha-1 tubulin and collagen V with tissue damage and immunopathogenesis of chronic lung rejection characterized by BO. In this study, we analyzed the presence of Ab to self-antigens K-alpha-1 tubulin and collagen V in patients with cGVHD.

Methods: Serum samples from patients with cGVHD were analyzed for Ab which binds to human recombinant purified K-alpha-1 tubulin and collagen V using ELISA assays. Analysis of variance was used to compare the means of different groups with $p < 0.05$ as an indicator of strong association.

Results: Study included 21 patients with cGVHD developing after allogeneic stem cell transplantation and 10 normal controls. 11/21 patients with cGVHD had lung involvement. Levels of K-alpha-1 tubulin Ab were higher in patients with lung cGVHD when compared to patients without lung involvement or normal controls ($p < 0.027$). Levels of Collagen V Ab were higher in patients with lung cGVHD when compared to normal controls ($p < 0.025$) but not when compared to patients without lung cGVHD. 64% of patients with lung cGVHD developed Ab to both antigens and 82% developed Ab to at least one antigen.

Conclusions: In this preliminary analysis development of Ab to K-alpha-1 tubulin and to collagen V appears to be highly associated with cGVHD and the highest titer these autoantibodies are seen in those patients with lung involvement. Studies are underway to define the kinetics of these Ab after stem cell transplantation as a potential predictor and biomarker of lung cGVHD.

No **Riek, Amy, MD, MS**

Poster CRTC KL2 Career Development Awards Program
Division of Endocrinology, Metabolism, and Lipid Research

Department of Internal Medicine, Washington University in St. Louis School of Medicine

Mentors: Carlos Bernal-Mizrachi, MD; Victor Davila-Roman, MD

Effects of vitamin D supplementation on blood pressure in patients with type 2 diabetes mellitus

Riek AE; Oh A; Bruchas RR; Bernal-Mizrachi C

Introduction: An interventional study showed that supplementing vitamin D and calcium in elderly non-diabetic women with hypertension and vitamin D deficiency reduced blood pressure (BP) compared to the calcium-treated group. However, there have been no studies to assess the effects of vitamin D on hypertension in those with type 2 diabetes mellitus (T2DM) who have higher cardiovascular disease risk.

Methods: We are conducting a randomized, double-blinded clinical trial of the effects of vitamin D (4000 IU/day) versus placebo over four months on BP in 96 patients with T2DM, moderate hypertension, and low 25-hydroxyvitamin D levels [$25(\text{OH})\text{D} < 25 \text{ ng/mL}$].

Results: 81 patients have completed the study, with 2 currently enrolled. Of enrolled patients, there are approximately equal distributions of gender (48% male) and race (50% black, 45% white, 5% other minorities). Most patients (70%) have a T2DM duration of < 10 years with good disease control (mean A1c 6.9%), and metformin is the most commonly-used medication. 62% have a concurrent diagnosis of hypertension and 25% a diagnosis of dyslipidemia. The mean 25(OH)D level increased from $16 \pm 5 \text{ ng/mL}$ at baseline to $26 \pm 12 \text{ ng/mL}$ after 4 months. In contrast, mean one-time BP (128/78 mmHg at baseline) showed no change over the four months, while 24-hour BP data have not yet been compiled.

Conclusions: These preliminary data suggest that we have successfully recruited a study population that reflects the demographics and health characteristics of the T2DM population in St. Louis, Missouri. The vitamin D treatment dose appropriately increases 25(OH)D levels as mean levels increased by 10 ng/mL with only half of patients on vitamin D. There was no change in overall BP throughout the course of the study, but until groups are unblinded, we will not know BP trends in treatment versus placebo groups. Trial recruitment should be complete in the next 6 months, and 24-hour BP data combined with detailed comorbidity data will allow analysis of the effects of vitamin D supplementation on BP in T2DM patients independently of other covariates.

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Santos, Carlos, MD

CRTC KL2 Career Development Awards Program

Division of Infectious Diseases

Department of Internal Medicine, Washington University in St. Louis School of Medicine

Mentors: Margaret Olsen, PhD, MPH; Daniel Brennan, MD

Delayed-onset cytomegalovirus (CMV) among kidney transplant recipients is associated with death

Santos CAQ; Brennan DC; Fraser VJ; Olsen MA

Introduction: Use of prophylactic anti-CMV therapy for 3 to 6 months after kidney transplant can result in delayed-onset CMV. It is not well studied since many patients are lost to follow-up as they transition care away from transplant centers. We hypothesized that delayed-onset CMV (occurring ≥ 100 days post-transplant) is associated with death and is now more common than early-onset CMV.

Methods: We assembled a retrospective cohort of 15,848 adult patients who underwent kidney transplant from 2004 to 2010 using administrative data from the California and Florida Healthcare Cost and Utilization Project – State Inpatient Databases. We identified demographic data, comorbidities, CMV coded during readmission and inpatient death. We used multivariate Cox proportional hazards modeling to determine risk factors for delayed-onset CMV and inpatient death.

Results: Delayed-onset CMV occurred in 4.0% of this study cohort, while early-onset CMV occurred in 1.2%. Risk factors for delayed-onset CMV included transplantation in high-volume (≥ 100 per year) centers (HR 1.4); previous transplant failure or rejection (HR 1.4); and residence in the lowest-income ZIP codes (HR 1.2). Risk factors for inpatient death included CMV occurring 101 to 365 days post-transplant (HR 1.5), CMV occurring > 365 days post-transplant (HR 2.1), increasing age (by decade: HR 1.5), non-white race (HR 1.2), residence in the lowest-income ZIP codes (HR 1.2), transplant failure or rejection (HR 3.2), prior solid organ transplant (HR 1.7), and several comorbidities.

Conclusions: Delayed-onset CMV coded during hospitalization was associated with inpatient death in this large cohort of adult kidney transplant recipients. Transplantation in high-volume centers, transplant failure or rejection and residence in the lowest-income ZIP codes were risk factors for delayed-onset CMV. Further research should be done to determine the reasons for the increased risk of delayed-onset CMV among patients transplanted in high-volume centers.

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Seifert, Michael, MD

CRTC KL2 Career Development Awards Program, CRTC MSCI Degree Program

Division of Pediatric Nephrology

Department of Pediatrics, Southern Illinois University/Washington University in St. Louis School of Medicine

Mentors: Daniel Brennan, MD; Keith Hruska, MD; Vikas Dharnidharka, MD, MPH

Elevated fibroblast growth factor 23 levels are associated with chronic rejection and declining kidney transplant function

Seifert ME; Chishti AS; Chiang ML; Selewski DT; Gipson DS; Hruska KA

Introduction: Chronic rejection (CR) is characterized by cumulative vascular injury that leads to kidney transplant failure. Chronic kidney disease-mineral bone disorder (CKD-MBD) contributes to vascular injury in native CKD, but its importance in CR is unknown. Fibroblast growth factor 23 (FGF23) is a CKD-MBD hormone that has been associated with remote transplant loss and mortality, but its association with biopsy-proven CR is unknown. We hypothesized that FGF23 and other biomarkers of CKD-MBD would serve as non-invasive biomarkers of CR.

Methods: Preliminary analysis of 26 pediatric kidney transplant recipients enrolled in an ongoing multicenter, case-control study of biomarkers of vascular injury in CR. Subjects with biopsy-proven chronic rejection were assigned to the CR group. Subjects were assigned to the No CR group if a recent biopsy (< 6 months prior) revealed no abnormality or estimated glomerular filtration rate (eGFR) was > 90 mL/min/1.73m² (Schwartz calculation). We measured plasma FGF23, Dickkopf-related protein 1 (Dkk1), and sclerostin (SOST) levels at enrollment using ELISA and correlated levels with eGFR and CR.

Results: 10/26 (38%) of subjects had biopsy-proven CR. We detected variable FGF23 levels in the CR group but the mean plasma FGF23 was significantly higher vs. No CR (104 ± 93 pg/ml vs. 47 ± 19 pg/ml, $p=0.03$). FGF23 levels were inversely correlated with transplant function ($r^2 -0.365$, $p=0.02$). Using logistic regression we found that for every 5 pg/mL increase in FGF23 the risk for CR increased nearly two-fold, even after correcting for age and gender [OR 1.994 (95% CI 1.725, 5.175)]. FGF23 was a superior biomarker of CR when compared to eGFR [OR 0.737 (95% CI 0.516, 1.053)]. Dkk1 and SOST levels were similar between groups.

Conclusions: Plasma FGF23 is inversely correlated with eGFR and is a better non-invasive biomarker for CR. These findings will be further validated as we complete enrollment and analysis for this study. We speculate that FGF23 is a potential diagnostic and therapeutic target for CR.

Smith, Gordon, PhD

CRTC KL2 Career Development Awards Program, CRTC MSCI Degree Program

Division of Geriatrics and Nutritional Sciences

Department of Internal Medicine, Washington University in St. Louis School of Medicine

Mentors: Bettina Mittendorfer, PhD; Brian Finck, PhD

Testosterone and progesterone, but not estradiol, stimulate muscle protein synthesis in postmenopausal women

Smith GI; Yoshino J; Reeds DN; Burrows RE; Bradley D; Kampelman JA; Moseley A; Mittendorfer B

Introduction: The effect of the female sex steroids, estradiol and progesterone, on muscle protein turnover is unclear.

Therefore, it is unknown whether changes in the sex hormonal milieu throughout the lifespan in women contribute to the changes in muscle protein turnover and muscle mass (e.g., age-associated muscle loss). The purpose of this study was to provide a comprehensive evaluation of the effect of sex hormones on muscle protein synthesis and gene expression of growth regulatory factors (i.e., myogenic differentiation 1 [*MYOD1*], myostatin [*MSTN*], follistatin [*FST*], and forkhead box O3 [*FOXO3*]).

Methods: We measured the basal rate of muscle protein synthesis and the gene expression of muscle growth regulatory factors in 12 premenopausal women and four groups of postmenopausal women (n = 24 total) who were studied before and after treatment with either testosterone, estradiol or progesterone, or no intervention (control group). All women were healthy and pre- and postmenopausal women were carefully matched on body mass, body composition and insulin sensitivity.

Results: The muscle protein fractional synthesis rate (FSR) was ~20% faster and *MYOD1*, *FST* and *FOXO3* mRNA expressions were ~40 to 90 % greater (all P < 0.05) in postmenopausal than premenopausal women. In postmenopausal women, both testosterone and progesterone treatment increased the muscle protein FSR by ~50% (both P < 0.01) whereas it was not affected by estradiol treatment and was unchanged in the control group. Progesterone treatment increased *MYOD1* mRNA expression (P < 0.05) but had no effect on *MSTN*, *FST*, and *FOXO3* mRNA expression. Testosterone and estradiol treatment had no effect on skeletal muscle *MYOD1*, *MSTN*, *FST* and *FOXO3* mRNA expression.

Conclusions: Muscle protein turnover is faster in older, postmenopausal compared with younger, premenopausal women but these age-related differences are not explained by the age- and menopause-related changes in the plasma sex hormone milieu.

CRTC K12 Paul Calabresi Career Development Awards for Clinical Oncology

No
Poster

Maggi, Leonard, PhD

CRTC K12 Paul Calabresi Career Development Awards Program for Clinical Oncology, CRTC MSCI Degree Program
Division of Molecular Oncology

Department of Internal Medicine, Washington University in St. Louis School of Medicine

Mentors: Jason Weber, PhD; Ramaswamy Govindan, MD

Targeting CDKN2A-controlled networks in lung cancer

Maggi LB; Forys JT; Govindan R; Weber JD

Introduction: PIK3CA inhibitors have been used in the clinic in an attempt to inhibit lung cancer growth with limited success. One possible explanation is that PIK3CA mutations cooperate with other genomic alterations to drive disease progression. Our preliminary studies indicate that IFN-beta is produced upon loss of ARF and mutation of p53. Data obtained from the TCGA dataset for squamous cell lung cancer demonstrates that both PIK3CA amplification and IFN-beta-induced JAK activation occur concurrently in a significant number of lung cancer samples. The long-term goal of this project is to develop a dual therapy for NSCLC that targets PIK3CA and IFN-beta-induced JAK activation. We hypothesize that dual treatment with PIK3CA and JAK inhibitors will target lung cancer cells harboring PIK3CA amplification, and JAK activation.

Methods: A number of biochemical, molecular biological and immunological techniques will be utilized to investigate the activation of the Type I IFN response resulting from ARF loss in lung cancer cell lines. Additionally, the effects of dual inhibition of PI3KCA and JAK on lung tumor cell growth and proliferation in vitro will be assessed.

Results: In human lung cancer samples in which ARF is lost, the Type I IFN response is activated as demonstrated by increased ISG15 staining. Lung cancer cell line data demonstrates that ARF loss in conjunction with p53 inactivation and PI3KCA activation leads to up regulation of IFN-beta and ISG15 – hallmarks of the Type I IFN response. Importantly, only lung cancer cell lines that have lost ARF in the context of p53 loss and PI3KCA activation are sensitive to the dual inhibition of JAK and PI3KCA. In cell lines in which ARF is present, inhibition of JAK has little to no effect.

Conclusions: Our preliminary in vitro results using lung cancer cell lines demonstrate a promising potential for inhibition of both PI3KCA and JAK in treating a subtype of lung cancer. Further preclinical studies in mouse xenograph models will assess the in vivo potential for this combined therapy and will pave the way for clinical trials to begin.

No
Poster

Wildes, Tanya, MD, MSCI

CRTC K12 Paul Calabresi Career Development Awards Program for Clinical Oncology, CRTC MSCI Degree Program
Division of Medical Oncology

Department of Internal Medicine, Washington University in St. Louis School of Medicine

Mentors: Graham Colditz, MD, DrPH; Nancy Morrow-Howell, PhD

The senescence-associated secretory phenotype (SASP) in multiple myeloma (MM)

Wildes TM; Paasch J; Fiala M; Chen L; Vij R; Stockerl-Goldstein K; Stewart S; Colditz G; Tomasson M

Introduction: The incidence of MM increases with age, yet some cytogenetic changes are actually more common in younger patients with MM. This suggests a mechanism other than chromosomal changes underlies the increased incidence with age. Senescent cells secrete proinflammatory cytokines, chemokines, growth factors and proteases resulting in the SASP, which can promote tumor growth. MM bone marrow stromal cells express the SASP. We hypothesized that SASP factors correlate with age in patients with MM.

Methods: Peripheral blood serum and matched bone marrow aspirate plasma from patients with MM were evaluated for factors associated with the SASP using quantitative multiplex immunoassay (*RBM*, Austin TX USA). SASP factors with a role in MM [interleukin-6 (IL-6), -8 (IL-8), -15 (IL-15), GM-CSF, ICAM1, osteoprotegerin (OPG), HGF, insulin-like growth factor-binding protein (IGFBP-1), IL1b, monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein-1 alpha (MIP-1a), angiogenin, leptin, vascular endothelial growth factor receptor 1 (VEGFR1) and stem cell factor (SCF)] were selected. The relationship between age and SASP factors were analyzed using Kendall tau rank correlation coefficient.

Results: Samples from 25 patients (each with peripheral blood serum and matched bone marrow aspirate plasma) were analyzed. The median age was 62 (range 47 - 74). Disease states were as follows: 36% newly diagnosed/untreated, 24% pretransplant and 40% relapsed. ISS stage included 40% stage I, 28% stage II and 32% stage III. Three of the selected SASP factors in the peripheral blood correlated with age: IL-8 (Kendall Tau 0.334, p=0.027), OPG (Kendall Tau 0.289, p=0.046) and MCP-1 (Kendall Tau 0.332, p=0.022). No SASP factors tested in the bone marrow plasma were significantly correlated with age.

Conclusions: We demonstrated age-associated differences in the SASP factors IL-8, OPG and MCP-1 in the peripheral blood of MM patients. Future research will examine differences between patients with MM and age-matched controls without cancer.

CRTC Postdoctoral Mentored Training Program in Clinical Investigation (MTPCI)

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Chamberlain, Aaron M, MD

CRTC Postdoctoral Mentored Training Program in Clinical Investigation (MTPCI), CRTC MSCI Degree Program
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Mentors: Ken Yamaguchi, MD, MBA; Leesa Galatz, MD; Jay Keener, MD; Jane Garbutt, MBChB

Total vs. Reverse Shoulder Replacement: a prospective randomized trial

Chamberlain AM; Keener JD; Galatz LG; Yamaguchi K

Introduction: The Reverse Shoulder Arthroplasty has revolutionized the management of complex shoulder pain and dysfunction due to rotator cuff tear arthropathy since its FDA approval in 2003. However, the role of the Reverse Shoulder Arthroplasty to manage pain secondary to osteoarthritis of the shoulder in the setting of an intact rotator cuff with underlying age-related rotator cuff degeneration is not clear and remains a challenging clinical question. This question continues to gain significance as the number of patients with shoulder arthritis is rapidly growing as is the number of arthroplasty procedures performed annually. The specific aim was to compare early postoperative pain relief in patients over the age of 70 who undergo either Total Shoulder Arthroplasty or Reverse Shoulder Arthroplasty in treatment of glenohumeral osteoarthritis.

Methods: Patients are invited to participate in the study if they present with pain secondary to glenohumeral osteoarthritis and are indicated for shoulder arthroplasty surgery. Patients are eligible for inclusion if they are age 70 or older, have radiographic signs of osteoarthritis, intact rotator cuff but with atrophy or fatty degeneration and limited forward elevation (less than 90 degrees). Patients agreeing to participate in the study are randomized to undergo Total Shoulder arthroplasty or Reverse shoulder arthroplasty. Pre-operative self-assessments including the Simple Shoulder Test (SST), the American Shoulder and Elbow Surgeons (ASES) score and visual analog scales (VAS) for pain will be compared with the same scores obtained postoperatively. Shoulder range of motion and radiographs will also be analyzed. Follow-up will be a minimum of one year.

Anticipated Results and Conclusions: Currently 10 patients have been enrolled in the study and none have completed one year of postoperative follow-up at this time. Continuous demographic, clinical and functional parameters will be analyzed with Student t-tests. An a priori power analysis shows that to demonstrate an effect size difference of 2 VAS points between the two treatment groups that 17 patients in each group will need to be enrolled. Statistical significance will be defined as $p < 0.05$. Our hypothesis is that early postoperative pain relief will be greater in those undergoing Reverse Shoulder Arthroplasty.

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Do we need to redefine post-partum hemorrhage for our modern population?

Conner SN; Tuuli MG; Colvin R; Odibo AO; Macones GA; Cahill AG

Introduction: The definition of post-partum hemorrhage (PPH) as estimated blood loss (EBL) $>500\text{mL}$ for a vaginal delivery and $\text{EBL} > 1000$ for cesarean was developed in the 1950's based on minimal outcome data. Since this definition, the obstetric population has changed dramatically. We sought to determine what threshold of EBL most accurately predicts the need for a transfusion, and ultimately, determine if we need to redefine PPH for our modern population.

Methods: We performed a prospective cohort study of 5000 consecutive women with a singleton term pregnancy admitted for labor at a tertiary care center from 2010-2012. Two groups were compared, those who needed a transfusion after delivery and those who did not. For each group, mean EBL and % blood volume loss (blood loss adjusted for maternal height and weight) were stratified for vaginal and cesarean deliveries. ROC curves were created and area under the curve (AUC) was calculated for EBL and % blood volume loss for predicting transfusion. Thresholds of 100mL increments were compared for accuracy in predicting need for transfusion using the Youden index(YI).

Results: Our study included 4864 patients with complete data for EBL. Transfusion was required for 0.65% of vaginal and 8.7% of cesarean deliveries. Mean EBL and % Blood volume loss were significantly higher in women requiring transfusion for vaginal and cesarean deliveries. The AUC for % Blood volume loss was slightly larger than that for EBL, but the differences were not statistically significant. The standard thresholds of 500mL for vaginal delivery and 1000mL blood loss for cesarean had the highest YI, and thus the best predictive ability of need for transfusion (sens=56% spec=89%, $\text{YI}=0.44$ for vaginal, sens=67% spec=72%, $\text{YI}=0.39$ for cesarean).

Conclusions: EBL and % Blood volume loss are both effective predictors of need for transfusion. The thresholds most predictive of a clinically significant EBL are 500mL for a vaginal delivery and 1000mL in a cesarean. We have validated the traditional definitions of PPH in our modern population.

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Mentors: Gregory Storch, MD; Richard Hotchkiss, MD; Joseph Carcillo, MD

Viral reactivation as a marker of immune suppression in septic children

Davila S; Storch G; Carcillo J

Introduction: Sepsis is a significant source of morbidity and mortality in children. A subset of children and adults develop abnormalities in immune function conferring higher mortality and rates of nosocomial infection. In adults, reactivation of latent viruses has been demonstrated in sepsis and in patients with known immune dysfunction. The primary hypothesis of this study is that septic children develop suppression of the immune system manifest by the reactivation of latent viruses. The objectives of this study are to 1) determine if viremia occurs in septic children 2) to determine the association between viremia and immune status 3) and to describe the relationship of viremia to outcome.

Methods: A retrospective study of 74 septic children admitted to the pediatric intensive care unit at the University of Pittsburgh was conducted. The patients were enrolled consecutively. Demographic data, clinical characteristics, and laboratory data were collected from subjects serially during their intensive care unit stay. Ex vivo LPS-induced TNF alpha expression was used as a marker of immune function. Patients with ex vivo LPS-induced TNF alpha expression TNF alpha levels less than 200pg/ μ l were defined as immune suppressed. Banked plasma was examined using laboratory developed real-time polymerase chain reaction for the presence of CMV, EBV, HSV, HHV-6 DNA, and adenovirus. Comparisons between non-immune suppressed and immune suppressed subjects will be done using chi-square for qualitative assays and t-test for quantitative assays. Logistic regression will be used to predict immune suppression using presence of viremia as a predictor variable and survival to ICU discharge using viremia as a predictor variable.

Results: The frequency of viremia in this cohort of septic children was: CMV 6.8%, EBV 13.7%, and HHV-6 8.2%, and adenovirus 27.4%. Of these patients, 28.8% of patients had at least one virus and 4.1% had two or more viruses during their intensive care stay. Further testing for HSV is planned. Analysis of this data with regard to immune suppression and mortality is ongoing.

Conclusions: The frequency of viremia in this cohort of septic patients is striking, and further analysis of these data may reveal a relationship of viremia to markers of immune function or survival. Viremia in this group of septic children may be explained by primary infection or reactivation of latent viruses. Future studies will be needed to describe the mechanisms by which viremia occurs in this population and the implication for treatment.

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Dickinson, John, MD, PhD

CRTC Postdoctoral Mentored Training Program in Clinical Investigation (MTPCI)

Pulmonary & Critical Care Division

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Autophagy deficiency induces goblet cell hypertrophy and blocks IL-13 MUC5AC secretion in airway epithelial cells

Dickinson J; Holtzman M; Stappenbeck T; Brody S

Introduction: Airway diseases including Cystic Fibrosis, Asthma and chronic obstructive pulmonary disease (COPD) are characterized by obstruction of small airways from excessive secretion of gel-forming mucins such as, MUC5AC. IL-13 plays a critical role in the transformation of epithelial cells to mucus secreting cells. However, the mechanism by which the secretory pathways of the mucus cell adapt to the IL-13 mediated acceleration in secretion activity is not known. Autophagy has recently been found to essential for a secretion intestinal Paneth cells. We hypothesized that autophagy proteins have parallel function in airway epithelial cells and represents a novel regulatory pathway that directs mucin secretion.

Methods: First, we examined the expression of key autophagy proteins in cultured human airway epithelial cells with and without IL13 treatment. Second, to assess the role of autophagy in mucin secretion, we utilized shRNA sequences to silence the critical autophagy gene, ATG5. Third, the relationship between autophagy and ROS generation from NADPH oxidases was evaluated by CM-H₂DCFDA labeling.

Results: IL13 increased LC3-II levels by protein blot and immuno-fluorescent staining. Silencing of ATG5 in airway epithelial cells resulted in a block in secreted MUC5AC with IL13 treatment with a corresponding accumulation of intracellular MUC5AC. Electron microscopy images confirm accumulation of normal appearing mucus granules at the apical cell surface in cells targeted with ATG5 shRNA. This phenotype was confirmed with drug treatment using desmethylclomipramine (DCMI), a known autophagy inhibitor. IL13 significantly increases ROS production in cultured hTECs. IL13 ROS production was attenuated in the ATG5 knockout cells.

Conclusions: Our findings suggest that autophagy is essential for airway mucous secretion particularly when accelerated by IL13. The autophagy pathway involves ROS as mediators of mucus exocytosis. We propose that autophagy may represent a novel pathway to target therapies to reduce mucus secretion in airway diseases.

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Drewry, Anne, MD

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Mentor: Richard Hotchkiss, MD

Persistent lymphopenia is associated with increased mortality in septic patients

Drewry AM; Skrupky LP; Hotchkiss RS

Introduction: Sepsis initiates both proinflammatory and anti-inflammatory mechanisms, with many patients progressing to an immunosuppressive state prior to death. The aim of this study was to compare the absolute lymphocyte counts of survivors and non-survivors during the first four days following the diagnosis of sepsis to determine if persistent lymphopenia through Day 4 predicted death.

Methods: Single-center retrospective cohort study of 335 adult patients with sepsis and positive blood cultures admitted to a large academic center from January 2010 through July 2012. Exclusion criteria included hematological disease, treatment with immunosuppressive agents, HIV infection, and death within four days of sepsis diagnosis. All complete blood cell counts during the first four days following diagnosis were recorded. Lymphopenia was defined as an absolute lymphocyte count (ALC) less than $1.2 \text{ cells}/\mu\text{l} \times 10^3$.

Results: 76 (22.7%) patients died within 28 days of sepsis diagnosis. Lymphopenia was equally present in survivors (median ALC $0.7 \text{ cells}/\mu\text{l} \times 10^3$ [IQR 0.4, 1.1]) and non-survivors (median ALC $0.6 \text{ cells}/\mu\text{l} \times 10^3$ [IQR 0.4, 1.1]) at the onset of sepsis ($p = .35$). By Day 4, the median ALC had increased significantly more in survivors than in non-survivors ($p = .0004$) to a median of $1.1 \text{ cells}/\mu\text{l} \times 10^3$ [IQR 0.7, 1.5] in survivors vs $0.7 \text{ cells}/\mu\text{l} \times 10^3$ [IQR 0.5, 1.0] in non-survivors. Using multivariable logistic regression to account for potentially confounding factors (including age, APACHE II, cirrhosis, congestive heart failure, chronic renal insufficiency, and hours until appropriate antibiotic coverage), an ALC less than $1.2 \text{ cells}/\mu\text{l} \times 10^3$ on Day 4 was significantly associated with 28-day mortality (adjusted OR 2.39 [95% CI 1.20, 4.76], $p = .02$).

Conclusions: Lymphopenia was present on the day of sepsis diagnosis in both 28-day survivors and non-survivors; however, persistent lymphopenia on Day 4 after diagnosis independently predicted death. Given the large number of animal studies showing that prevention of lymphocyte apoptosis improves survival in sepsis, a strong rationale exists for clinical trials of immunotherapeutic agents that reverse sepsis-induced lymphopenia.

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Division of Pediatric Hematology/Oncology

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Mentors: Philip Spinella, MD; Monica Hulbert, MD; Ron Jackups, MD, PhD

Red blood cell storage duration and outcomes for acute chest syndrome in children and young adults with sickle cell disease

Fields ME; Berlin A; Jackups R; Hulbert ML; Spinella PC

Introduction: Red Blood Cells (RBCs) undergo physical and metabolic changes during storage, but it is unknown how these changes pertain to outcomes in patients with Sickle Cell Disease (SCD). The objective of our study is to determine if there is an association between the storage age of transfused RBCs and clinical outcomes for pediatric SCD patients with acute chest syndrome (ACS).

Methods: In this retrospective cohort study, we included pediatric SCD patients with ACS that were treated with an RBC transfusion between January 2007 and May 2012. We excluded ACS episodes treated with exchange transfusion, and patients with a history of stem cell transplant or receiving chronic RBC transfusion therapy at the time of the ACS episode. The primary outcome measure was length of hospital stay (LOS) after transfusion. Secondary outcomes included duration of supplemental oxygen and IV opioid utilization after transfusion.

Anticipated Results: One hundred and forty-six episodes of ACS in 91 patients (49 male, 42 female, 81 HbSS, 3 HbSC, 4 Hb S β^0 , 1 Hb S β^+ , 2 HbFH) were included. Median (IQR) storage age of the oldest unit of transfused RBCs was 18.5 (12.0-27.0) days. In all 146 episodes of ACS, median (IQR) LOS after transfusion was 3.0 (2.0-5.0) days. Supplemental oxygen was required prior to transfusion in 109/146 (74.7%) of ACS episodes and for a median of 2.0 (0.0-3.0) days after transfusion. IV opioids were administered prior to transfusion in 93/146 (63.7%) of ACS episodes and for a median of 2.0 (0.0-4.0) days after transfusion. Future examination will include univariate and multivariate association of potential confounds with the three outcomes stated previously by Generalized Estimating Equations to account for multiple measurements within each patient.

Conclusions: Prospective, randomized, controlled trials are needed to determine if the common practice of transfusing RBCs of decreased storage age is beneficial in children with SCD. This retrospective study will provide the pilot data necessary to move forward with these trials.

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Hagemann, Andrea, MD

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Neoadjuvant chemotherapy in Stage IV uterine papillary serous cancer

Hagemann AR; Wilkinson-Ryan I; Frolova A; Liu J; Thaker PH; Massad LS; Powell MA; Mutch DG

Introduction: Uterine papillary serous cancers (UPSC) have similar tumor biology and prognosis to epithelial ovarian cancers, although the role of neoadjuvant chemotherapy (NAC) has not been explored among patients with UPSC. The goal of this study was to compare surgical and survival outcomes of women with stage IV UPSC who receive NAC and interval debulking to women with Stage IV UPSC who undergo primary debulking.

Methods: This retrospective dual cohort study included women diagnosed with stage IV UPSC from 1/2000-6/2013 at a single academic institution. Kruskal-Wallis and Fisher's Exact tests were used to compare demographics and surgical outcomes. Median progression-free (PFS) and overall survival (OS) were estimated using Kaplan-Meier methods. Comparison between study groups was tested by log-rank statistics.

Results: Ten women with stage IV UPSC who received NAC and 34 who received primary debulking surgery followed by adjuvant chemotherapy qualified for the study. NAC patients had a lower mean BMI (26.9 kg/m² v. 31.6 kg/m², p=0.042) and were more often black (70% v 30%, p=0.034) but otherwise were similar in demographics and comorbidities to the primary debulking cohort. Women who received NAC had shorter median operative times (116.5 min v. 183 min, p=.025) and were discharged from the hospital earlier (median length of stay 3 v. 5 days, p=0.002). There was no difference in rate of optimal debulking (<1cm residual disease) (100% of NAC patients v. 82% of primary surgery patients). Median follow-up time was 17.5 months. There was no difference in median PFS or OS (10.4 v 12 months PFS, p=0.29; 17.3 v. 20.7 months OS, p=0.23 for NAC v. primary debulking cohorts, respectively).

Conclusions: In this retrospective study, women who received NAC for Stage IV UPSC had shorter surgeries and hospital stays compared to those receiving up-front debulking, while overall and progression-free survival were similar. NAC may be an appropriate therapy for patients with advanced stage UPSC without compromising overall outcomes. Further research is needed on the utility of NAC in UPSC.

No
Poster

Levy, Philip, MD

Postdoctoral Mentored Training Program in Clinical Investigation (MTPCI), CRTC MSCI Degree Program
Division of Newborn Medicine
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Mentor: Aaron Hamvas, MD

Maturational changes of right and left ventricular longitudinal strain in premature infants

Levy P; Holland M; Sekarski T; Hamvas A; Mathur A; Lee C; Singh G

Introduction: The right ventricle (RV) and left ventricle (LV) are embryologically and structurally distinct and their functional roles change postnatally. The objective of this study was to discern the difference in cardiac mechanics between RV and LV reflective of structural distinction and maturational changes in premature infants.

Methods: Peak global longitudinal strain (GS), strain rate (GSR), and segmental strain (SS) in the RV free wall (RVFW), septum, and LV free wall (LVFW) were measured in 10 premature infants (<28 weeks at birth) enrolled through the Prematurity and Respiratory Outcomes Program (NIH 1U01 HL1014650). Measurements were obtained at four time points (24 hours, 72 hours, 32 weeks and 36 weeks) using standard and 2D speckle tracking echocardiography (GE EchoPac) and were compared.

Results: LV GS and GSR remained unchanged from birth until 36 weeks (p=0.6), whereas RV GS and GSR significantly increased (p=0.03) ≥10% every month of aging (figure 1). By 36 weeks, GS, GSR, and SS were significantly larger (p=0.01) in RVFW than in LVFW. A significant apex-to-base SS gradient (p=0.04) in LVFW existed throughout maturation, and a reverse base-to-apex gradient developed by 36 weeks (p=0.01) in RVFW (figure 2). Septal GS increased throughout maturation (p=0.04). A base-to-apex gradient existed for septal SS at 24 and 72 hours and significantly (p=0.003) *reversed* by 32 weeks. The ratio of minor to major axis of LV remained unchanged.

Conclusions: Our study suggests that longitudinal LV GS remains relatively unchanged with a stable apex to base gradient in the LVFW that may reflect the relative constant LV geometry with maturation. Conversely, RV and septal GS and GSR increase with maturation. Pertinently, septal SS reverses its gradient from an RV to LV dominant arrangement with maturation. All of these patterns may reflect the different developmental programming, structural anisotropy, postnatal loading conditions, and consequential developing cardiac mechanics of the RV, Septum, and LV in premature infants [NIH R21 HL106417].

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McAndrew, Christopher, MD

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Risk factors associated with rehospitalization after hip fracture

McAndrew CM; Gardner MJ; Binder EF; Ricci WM; Lenze EJ

Introduction: Unintended 30-day rehospitalization cost Medicare \$17.4 billion in 2004. Rehospitalization rate after hip fracture is 18%. This study of elderly hip fracture patients aims to identify risk factors for rehospitalization, directing future intervention and study.

Methods: Patients >60 years of age with a hip fracture treated surgically at 8 hospitals from 5/2008 to 11/2011 enrolled in a prospective cohort study. Subjects with cognitive impairment (Short Blessed Scale <14) that persisted for 1 week were excluded. At scheduled interviews, the enrollees and care-takers provided new diagnoses, medications, and hospitalizations. Reasons for rehospitalization came from self or family reporting. Five-hundred-ninety-one patients were screened. Sixty-three patients were excluded and 31 withdrew nearly immediately after initially enrolling, leaving 497 subjects in the study.

Results: Of 497 subjects, 32 (6.4%) patients died over 1-year, with 4 (0.8%) dying within 30 days and 13 (2.6%) dying within 90 days. Four-hundred-sixty-one (92.8%) subjects completed 4-week data, and 402 (80.9%) subjects completed 12-week data. Of these, 54 (11.7%) and 84 (20.9%) were rehospitalized at 30 and 90 days. Hip related complications and gastrointestinal complications were the most common reasons for rehospitalization, making up 17% each. At 90-days, hip complications and pulmonary complications were the most common, making up 15% and 13% of the cases, respectively. Cardiac complications (9% and 11%) and thromboembolism (9% and 8%) were also common.

Conclusions: 30-day rehospitalization (11.7%) and 1-year mortality (6.4%) rates in a cohort study of cognitively intact patients were lower than historical rates. Hip and GI complications were the most common reasons to be rehospitalized at 30 days. Hip complications remained the most common reason to be rehospitalized at 90 days. Targets for intervention include orthopaedic surgical treatment, prevention of GI and pulmonary infection, prevention of arrhythmia and myocardial infarction, and thromboembolic prevention and streamlined management.

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Mentors: Robert Hayashi, MD; Jeffrey Peipert, MD, PhD; Donna Jeffe, PhD; Allison King, MD, MPH; Matt Kreuter, PhD, MPH

Academic difficulties in childhood cancer survivors

Schapiro MS; Jeffe D; Hayashi R

Introduction: Central nervous system (CNS) treatment or prophylaxis is an essential part of therapy for leukemia and lymphoma. Unfortunately, studies have shown that some childhood cancer survivors who have received CNS-directed treatments go on to experience difficulties in school: as a group, they are more likely to be placed in special education programs and less likely to graduate from high school when compared to their siblings. However, the full scope of their academic difficulties is not well understood. The goals of this study are to describe parents' and survivors' concerns about academic difficulties in middle school and high school, to assess parents' and survivors' knowledge of school-related difficulties as they relate to cancer treatments, to examine parents' knowledge of and utilization of available educational resources, and to identify factors that influence access to educational resources.

Methods: Surveys and interviews are currently being administered to collect both quantitative and qualitative data. Eligible subjects include leukemia and lymphoma survivors 11-18 years of age who completed their cancer treatment at least one year ago, as well as their parents.

Results: Preliminary results are not yet available.

Conclusions: The long-term goal is to gain the knowledge needed to develop effective educational interventions for this patient population, enabling them to optimize their academic outcomes.

082 Schmidt, Elizabeth, MD

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Reasons for selection and continuation of the IUD among adolescents in the Contraceptive CHOICE Project

Schmidt EO; James AS; Peipert JF; Madden T

Introduction: The United States has one of the highest adolescent birth rates in the developed world. The most commonly used forms of contraception, oral contraceptive pills and condoms, have high failure rates. Adolescents need more effective contraception and the intrauterine device (IUD) offers an ideal option; however, uptake is low. Better understanding of adolescents' attitudes and experiences with the IUD is needed.

Methods: This is a qualitative analysis examining the reasons for selection, continuation and discontinuation of both the levonorgestrel intrauterine system (LNG-IUS) and the copper T380A IUD (copper IUD) by adolescent participants in the Contraceptive CHOICE Project. We will hold focus groups with groups of adolescent IUD users to explore attitudes toward the IUD including reasons for use, continuation, and discontinuation. The groups will be stratified by type of IUD chosen by the participant, LNG-IUS or copper. We will use a semi-structured focus guide to lead the focus groups; specific topics that will be explored include IUD knowledge, reasons for choosing an IUD, reasons for choosing the specific type of IUD, side effects experienced, and reasons for continuation and discontinuation. Groups will be audio-recorded and transcribed. We will create a codebook with themes and definitions to ensure consistent coding across groups. Transcripts will be independently coded by two researchers and interrater reliability will be calculated using a Kappa coefficient. Minor discrepancies will be resolved by discussion and consensus. If there are major discrepancies we will refine the codebook and recode the transcripts. Focus groups will be continued until thematic saturation is reached.

Anticipated Results and Conclusions: We plan to recruit a total of 60 adolescents; 30 copper IUD users and 30 LNG-IUS users. We anticipate that the results will provide information that will help tailor contraceptive counseling for adolescents and help increase IUD uptake in this population.

002 Sheshadri, Ajay, MD

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Division of Pulmonary and Critical Care Medicine

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Mentor: Mario Castro, MD, MPH

Ventilation defects with hyperpolarized helium MRI in severe asthma before and after bronchial thermoplasty

Sheshadri A; Thomen R; Kozlowski J; Gierada D; Tarsi J; Koch T; Burgdorf D; Sajol G; Yin-Declue H; Wilson B; Schechtman K; Quirk J; Castro M; Woods J

Introduction: Bronchial thermoplasty (BT) uses radiofrequency energy to decrease airway smooth muscle and improve asthma control. We investigate whether BT improves whole lung ventilation as detected by hyperpolarized helium MRI (³He MRI).

Methods: 7 healthy individuals and 7 subjects with severe asthma underwent baseline ³He MRI at a volume of FRC+1 L using a 2D gradient-echo sequence and 3x3 mm in-plane resolution with 10-mm slices that covered the entire lung. Subjects with asthma received BT and underwent a second ³He MRI scan at 135 ± 21 days after the initial scan. Ventilation defect percent (VDP) was calculated as the fraction of the ³He signal intensity below slice-specific threshold. Each subject had baseline spirometry pre/post bronchodilator (BD), questionnaires, health care utilization, serum IgE, blood and sputum eosinophils. A paired t-test was performed to detect change in VDP in subjects with severe asthma before/after BT.

Results: Healthy subjects were younger than asthmatics (26.4±9.1 years vs. 45.3±4.1 years, p=0.009). There was no significant difference in race or gender between groups. FEV₁% predicted (FEV₁%) was significantly higher post-BD in normals than in asthmatics (FEV₁% post-BD: 104.7±12.9% vs. 74.0±8.3%, p=0.008). Subjects with severe asthma had higher VDP at baseline (24.4±13.9%) compared to healthy subjects (3.5±1.6%) (p=0.003). After BT, subjects with severe asthma had a trend towards improvement in VDP: 17.6±13.5% (mean change -6.8±9.3%, p=0.10). FEV₁% inversely correlated with VDP at baseline in all subjects post-BD (FEV₁% postBD: r=-0.60, p=0.02). Sputum eosinophilia showed a trend towards correlation with change in VDP after BT (r=0.74, p=-0.056).

Conclusions: Subjects with severe asthma have significantly more lung ventilation defects at baseline than healthy subjects with a trend towards improved ventilation after BT. Sputum eosinophilia may predict an improvement in ventilation defects after BT and guide selection of subjects who may benefit from BT.

Smith, Matthew, MD

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Fast-pitch softball pitchers experience a significant increase in pain and fatigue during a single high school season

Smith MV; Yang JS; Stepan J; Dvoracek L; Davis R; Brophy RH; Wright RW

Introduction: The effect of fatigue on fast-pitch softball pitchers is unknown. We aimed to characterize the influence of pitch counts and games pitched on pain, fatigue, range of motion (ROM) and strength in high school fast-pitch softball pitchers during a single season. We hypothesized that increased pitch count and games pitched were associated with increased subjective and objective measures of pain and fatigue.

Methods: We used a cross-sectional study to evaluate shoulder and elbow strength, ROM, pain and fatigue in high school fast-pitch softball pitchers (ages 15-18) before and after a single game, during the first and last week of the high school softball season. We recorded the exact number of pitches thrown in each game and the total number of games pitched during the high school season.

Results: The average number of pitches thrown per player per game was 89 ± 25 (range 30-161). The average games pitched was 12 ± 5.7 (range 5-24). Supraspinatus, forward flexion strength, and external rotation strength in abduction decreased significantly post-game compared to pre-game ($p < 0.02$). Pain and fatigue were significantly higher post-game than pre-game ($p < 0.01$). Pre-game pain and fatigue increased, and flexion, supraspinatus, and external rotation strength, decreased with the number games pitched during the season ($r = 0.66-0.88$, $p < 0.006$). At the end of season, there was a significant increase in pre-game pain, fatigue, and decrease in forward flexion, supraspinatus, and external rotation strength between players who pitched more than 10 games versus players 35 who pitched less than 10 games through the season ($p < 0.033$).

Conclusions: Strength decreases significantly throughout the course of a game. Increase in games pitched during a season significantly increases pain and fatigue while significantly decreasing pre-game forward flexion and rotator cuff strength. There was a significant increase in pre-game pain and fatigue, and a significant decrease in forward flexion and rotator cuff strength from beginning to end of season between players who pitched more than 10 games.

CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program

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CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program; Dean's Fellowship
Summer Research Program

Division of Cardiothoracic Surgery

Department of Surgery, Washington University in St. Louis School of Medicine

Mentor: Varun Puri, MD

Associations of the conversion of a laparoscopic procedure during hiatal hernia repair

Adaralegbe OA; Bell MJ; Puri V

Introduction: Hiatal hernias are commonly repaired via a laparoscopic procedure with similar results, smaller incisions, and shortened hospital stays, when compared to an open one. However, they have a potential to convert to an open operation – for reasons that remain poorly understood – and it is not known which patients are at a high risk for conversion. We aim to retrospectively study patients who have undergone a hiatal hernia repair to elucidate risk factors for conversion, and study outcomes after such an event.

Methods: Data on participant demographics, comorbidities, and operative outcomes was extracted from Barnes-Jewish hospital databases, reviewed and then entered into an Access Database. Patients with at least a moderate sized hiatal hernia were considered. The data in the Access Database were then analyzed for comparisons among patient groups.

Results: Between 1/1/2000 and 4/30/2013, 275 patients underwent a hiatal hernia repair at Barnes Jewish Hospital. Of these, 180 underwent a completely laparoscopic procedure, 31 had to convert to an open one, and 64 had an elective open procedure. Comparing patients who underwent a successful laparoscopic, conversion, and elective open repair, members of all 3 groups were similar in demographics, comorbidities, and significant hiatal hernia characteristics. Patients in the latter 2 groups were more likely to be undergoing surgery for a recurrent hiatal hernia or have had multiple prior abdominal operations. Of the conversions, 5 were urgent, and the remaining 26 were non-emergent. Patients in the converted group had a longer hospital stay than the laparoscopic group; however, this was comparable to the open group. Other major perioperative morbidities were similar between the converted and laparoscopic groups; however, patients in the elective open group experienced a higher incidence of atelectasis, pneumonia, dysrhythmia, and respiratory failure than the other two groups.

Conclusions: Having a recurrent hiatal hernia or multiple prior abdominal operations are associated with conversion to an open approach during laparoscopic hiatal hernia repair. The major perioperative outcomes of conversions are similar to those of a minimally invasive procedure with the exception of a prolonged length of stay.

083

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CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program; Dean's Fellowship
Summer Research Program

Department of Obstetrics and Gynecology, Washington University in St. Louis School of Medicine

Mentors: Gina M Secura, PhD; Jeffrey F Peipert, MD, PhD; Jenifer E Allsworth, PhD

Racial disparities in contraceptive continuation: evidence from the contraceptive CHOICE project

Olufemi A; Allsworth J; Peipert J; Secura G

Introduction: Each year half of all pregnancies are unintended. The percentage of pregnancies that are unintended has decreased among white (40%), while remaining unchanged among Black (69%). Black women have unintended live birth rates double that of white women (37% vs. 18%). Correct and consistent use of contraception can dramatically reduce unintended pregnancy, yet significant barriers to consistent use of the most-effective methods exist for many women.

Methods: This was a substudy of the Contraceptive CHOICE Project, a prospective cohort study of 9256 women which provided no cost contraception for up to 24 months. Women included in our analysis (N=5678) were Black and White women who had continuation data through 24 months in December 2012. Our basic statistical approach was survival analysis. Specifically, we estimated rates of continuation at 12 and 24 months after contraceptive initiation through the construction of Kaplan-Meier survival curves. We evaluated the factors that are associated with faster discontinuation among white and black women using Cox proportional hazards regression. All statistical analyses were completed using Stata (version 12, StataCorp, College Station, TX). We hypothesize that Black women will have lower rates of contraceptive continuation at 12- and 24-months and that predictors of discontinuation will be modified by race.

Results: Most women discontinued non-LARC methods by 24 months. 80% of White women and 91% of Black women on non-LARC methods discontinued. However, there were no differences between Black and White women in rate of discontinuation [Adjusted HR = 1.06 (0.90 -1.25)]. Most women remain on LARC methods at 24 months (23% White women stopped; 30% Black women) [Adjusted HR = 1.33 (1.13 – 1.57)]. Black women stopped LARC methods significantly faster than White women.

Conclusions: Black women are discontinuing LARC methods slightly faster than White women. Moving forward, we will identify predictors of discontinuation particularly among Black women using LARC.

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Anderson, Kelsey

CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program

Doctor of Medicine Program, Saint Louis University

Department of Internal Medicine, Washington University in St. Louis School of Medicine

Mentor: Daniel Brennan, MD

Association of isolated JC viremia and protection from acute renal allograft rejection

Anderson, KL

Introduction: BK and JC polyomaviruses can reactivate after kidney transplantation, causing renal dysfunction or graft failure. JC can also cause progressive leukoencephalopathy (PML). Previously, we characterized BK and JC-reactivation in urine and blood samples collected serially through one-year post-transplant from 200 renal transplant recipients. Drug-compliant patients with isolated JC-viremia had less acute rejection than those without JC ($p=0.054$). The purpose of the present study was to increase the number of subjects to provide adequate power to determine whether isolated JC-viremia was associated with less acute rejection in compliant patients.

Methods: In the present study, sequential urine and blood samples were collected 6 times post-transplant: weeks 0, 4, 8, 12, 24 and 52 from 100 patients. Samples were assessed by PCR for JC virus. BK-viremia was assessed separately per standard clinical protocol at months 1-6, 9 and 12 and for cause. Follow-up occurred after study samples were collected during standard clinical visits through 7/2013. The data were analyzed with SPSS V.21.

Results: In the 100 patient cohort, 10 patients were excluded. In 90 patients, JC-viremia was detected in 15 (16.7%) patients and BK-viremia in 14(15.6%) patients, with a 2.2% co-incidence rate. In 12 (13.3%) with acute rejection, only 1 patient (8.3%) had JC-viremia ($p=0.405$) while 4 patients with rejection (33.3%) had BK-viremia ($p=0.068$). Isolated BK-viremia was associated with higher acute rejection ($p=0.029$) and graft loss ($p=0.028$). No significance was found between acute rejection or JC viremia with age, sex, race, HLA mismatch, repeat transplant, CMV serostatus, and delayed graft function. Including the 200 patient cohort from the previous study, isolated JC-viremia was associated with less acute rejection in drug-compliant patients ($p=0.032$).

Conclusions: The purpose of this study was to determine if a type II error occurred in the previous study or if JC-viremia is not a significant predictor of acute rejection in transplant patients. The incidence of BK and JC infection were similar in both groups. Although each individual study lacked significant power, when combined, compliant JC-viruric patients were significantly less likely to have an acute rejection.

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Bailey, Ryan, MS, OTR/L

CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program, CRTC MSCI Degree Program

Movement Science Program

Program in Physical Therapy, Washington University in St. Louis School of Medicine

Mentor: Catherine Lang, PhD

A quantitative method for measuring bilateral arm activity via accelerometry

Bailey RR; Klaesner JW; Lang CE

Introduction: Neurological injury (e.g. stroke) commonly results in motor deficits, such as hemiparesis. Recovery of bilateral arm function is important for the performance of many everyday tasks. Some assessments measure bilateral arm function inside the clinic, but do not assess real-world function. Additionally, existing assessments do not quantify the contribution of each arm to activity. If the goal of rehabilitation is functional restoration of the impaired arm, then this is an important construct to measure. Therefore, the purpose of this study is to examine the construct validity of a novel method for assessing bilateral arm activity during everyday tasks using wrist-worn accelerometers.

Methods: Neurologically intact adults ($N = 74$) wore accelerometers on both wrists while completing 10 everyday, unilateral and bilateral tasks (e.g. typing, writing, cutting, folding towels, stacking boxes). For each task, the magnitude of acceleration was determined for each arm, and also summed to determine the bilateral magnitude. The ratio of arm acceleration (magnitude ratio) in one arm vs. the other was calculated, such that values close to 0 indicate unilateral activity and values close to 1 indicate equal contributions from each side. Time spent in bilateral activity (i.e. simultaneous arm movement) was also calculated.

Results: Bilateral magnitude varied, with some tasks completed with low bilateral magnitudes (e.g. writing), some with high bilateral magnitudes (e.g. stacking boxes), and others with variable bilateral magnitudes (e.g. grooming). Only a few tasks were truly unilateral, as most magnitude ratios were greater than 0. There was considerable variability across tasks and across individuals. Time spent in bilateral activity and the magnitude ratio were strongly correlated ($r = 0.87, p < 0.001$).

Conclusions: During everyday activities, the contribution to bilateral activity from each arm varies across tasks and individuals. These results demonstrate construct validity of this assessment method for quantifying bilateral arm activity, and can now be used to assess recovery of real-world, bilateral arm function in patient populations.

009

Buchanan, Porsche N

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CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program; Dean's Fellowship
Summer Research Program

Mallinckrodt Institute of Radiology, Washington University in St. Louis School of Medicine

Mentor: Jie Zheng, PhD

Fast resting non-contrast MRI perfusion can detect myocardial ischemia with moderate sensitivity and specificity

Buchanan PN; Zheng J

Introduction: Arterial spin labeling (ASL) is a less extensively explored method to observe myocardial perfusion. Before ASL, the radioactive contrast agent gadolinium was used to determine tissue perfusion. ASL uses magnetically labeled water, which can be used repeatedly without causing adverse effects, unlike using a radiotracer. Patients with renal insufficiency cannot receive any radiotracer, which makes ASL a monumental development for those patients & others who have conditions that prevent them from receiving contrast. Previous projects explored cerebral blood flow using ASL. In cardiology, first pass perfusion is the gold standard to detect ischemia. The current project explores the use of ASL to identify poor perfusion throughout myocardium. ASL can be performed on patients with kidney failure, unlike first pass perfusion. ASL could greatly enhance the evaluation of transient ischemic attacks. We hypothesize that ASL perfusion MRIs can be used in a cardiological clinical setting to diagnose coronary artery stenosis & myocardial ischemia.

Methods: 14 patients with suspected myocardial ischemia were prospectively scanned. The imaging protocol included 3-slice pre-contrast ASL imaging & 3-slice first-pass perfusion imaging. Custom-made software was used to create ASL maps. Reviewers indicated presence/absence of ischemia in each segment of ASL & first-pass perfusion images. Sensitivity & specificity of the detection of myocardial ischemia were calculated.

Results: Most patients had evidence of myocardial ischemia as detected by first-pass perfusion. Sensitivity, specificity, positive predictive value, & negative predictive values were 63%, 76%, 60%, & 78%, respectively.

Conclusions: To our best knowledge, this is the first time a fast non-contrast ASL method was evaluated in patients with myocardial ischemia. While sensitivity is relatively low, the relatively high specificity may permit this method as a screening tool for suspected myocardial ischemia. Advancement in ASL technique is needed to improve spatial resolution & motion correction.

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Chambers, Ethan

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CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program; Dean's Fellowship
Summer Research Program

Department of Anesthesiology, Washington University in St. Louis School of Medicine

Mentor: Ben Julian Palanca, MD, PhD

Optical imaging of brain networks during sleep

Chambers E; Palanca BJ

Introduction: Sleep consists of altered states of consciousness that maintains both homeostasis of physiologic processes and cognitive function. The dynamics of spontaneous brain connectivity in these states remain poorly characterized. Functional magnetic resonance imaging (fMRI), a technique for imaging brain connectivity, has shown both strengthening and weakening of during sleep during sleep, but requires a specialized facility and likely disrupts natural sleep through loud noises and vibrations. Diffuse optical tomography (DOT) is a portable light-based technique that allows mapping of connectivity among superficial cortical regions in manner comparable to fMRI. This project will determine how intracortical connectivity differs during wakefulness and non-rapid eye movement (REM) sleep using DOT.

Methods: Fifteen healthy volunteers of 18-50 years of age will be recruited for overnight sleep studies. Exclusion criteria include MRI-incompatible implants, the use of psychotropic medications, and existing sleep disturbances. Structural and functional imaging will be obtained with fMRI. After fifteen minutes of baseline DOT data have been acquired during quiet wakefulness, participants will sleep in a soundproof chamber during simultaneous DOT and clinical polysomnography (PSG), including a standard EEG montage. Imaging data will be acquired during light NREM (N1 and N2) and deep NREM (N3) sleep and processed offline. Neural connectivity analysis of HbR time-courses will use Pearson correlation coefficients as a surrogate of connectivity between brain regions.

Results: Compared to wakefulness, we expect distinct patterns of brain connectivity within the different sleep stages with stronger connectivity during light N1/N2 sleep and weaker connectivity during deep N3 sleep.

Conclusions: These findings will assess the use of DOT as an alternative to fMRI and EEG for measuring cortical dynamics during sleep and lay the groundwork for future studies evaluating sleep in the perioperative period.

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Coney, Talia

CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program

Doctor of Medicine Program, Saint Louis University

Division of Emergency Medicine

Department of Internal Medicine, Washington University in St Louis School of Medicine

Mentor: Brian Fuller, MD

The effect of cardiac dysfunction on acute respiratory distress syndrome in mechanically ventilated patients with sepsis

Coney T; Fuller B

Introduction: Our main objective is to determine whether cardiac dysfunction had a negative or positive impact on patients with Acute Respiratory Distress Syndrome (ARDS) and where mechanically ventilated and presented with sepsis. Our secondary objective is to describe the effect of cardiac dysfunction on ARDS using the new definition of ARDS as described by the Berlin definition.

Methods: This is a retrospective chart review observational study of patients who presented with acute respiratory distress syndrome and sepsis and were mechanically ventilated. 251 of these patients fit the criteria for the study and were enrolled. To determine the effect of cardiac dysfunction right ventricular dysfunction, left ventricle ejection fraction, troponin level and BNP were recorded and analyzed for each patient. Three medical students conducted the retrospective chart review. Each medical student reviewed their findings twice before the junior investigators (emergency department residents) and the principal investigator reviewed the findings.

Results: Results are pending.

Conclusions: Data are still in the process of being analyzed thus conclusions cannot be made at this time.

No

Poster

Feely, Megan, MSW

CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program, CRTC MSCI Degree Program

Social Work Doctoral Program

George Warren Brown School of Social Work, Washington University in St. Louis

Mentor: Patricia Kohl, PhD

Comparing the prevalence of types of maltreatment between urban and rural children in a nationally representative child welfare sample

Feely MA; Kohl PL

Introduction: Timing and type of childhood maltreatment is important in understanding the immediate service needs and long-term impact. This study uses a nationally representative sample to compare the prevalence of types of maltreatment children were alleged to have experienced in rural and urban areas to better inform the provision of services.

Methods: Using the Second Cohort of the National Survey of Child and Adolescent Well-Being, the most serious type of maltreatment, child's age and urban and rural residence were analyzed. Four age categories were used: ≤ 1 year old, 2-5 years, 6-12 years and 13 years and older. Most severe type of maltreatment was identified by case-managers' assessment. If more than 50% of the county was urban using the 2000 Census definition, the county was urban.

Results: The sample was 77% urban, 23% rural. The most common types of most-severe maltreatment were: 33% neglect; 22% physical abuse; 13% parental substance abuse; 8% sexual abuse; 8% exposed to domestic violence; 5% emotional abuse; the rest were other forms of maltreatment. In this sample, 21% of rural children and 9% of urban ≤ 1 year were physically abused. More urban children 13 years and older were physically abused (27%) than rural children (22%). Less than 5% of rural children ages 5-and-under experienced domestic violence, versus 11%-13% of 5-and-under urban children. Parental substance abuse or exposure was the most severe problem for 23% of urban children one year-old and younger and 17% of children in rural areas. For 8% of urban teenagers versus 16% of rural teenagers, parental substance abuse or exposure was the most severe form of maltreatment. Sexual abuse was consistently higher in rural areas across all age groups except the youngest. Twice as many rural children ages 2-5 years were sexually abused (10% vs. 5%) as were more rural teenagers (13% vs 9%).

Conclusions: The clinically meaningful differences identified in this nationally-representative sample of the most severe types of maltreatment that children experience in rural areas compared to urban, have significant implications for preventative and treatment service needs and availability in rural areas.

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Frisse, Ann

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Summer Research Program

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Mentor: Jeffrey F Peipert, MD, PhD

Self-reported history of *Chlamydia trachomatis* compared to serologic status

Frisse A; Secura GM; Allsworth JE; Peipert JF

Introduction: Healthcare providers ask about previous CT infection while taking a medical history, but it is unclear to what degree a self-reported history of CT infection is a valid measure of past infection. The purpose of this study is to evaluate the validity of women's self-reported history of *Chlamydia trachomatis* (CT) infection compared to CT serology as the gold standard.

Methods: We analyzed baseline data from the Fertility After Contraception Termination (FACT) study. We compared participants' survey responses to the question, "Have you ever been told by a healthcare provider that you had Chlamydia" to serological test results indicating the presence or absence of antibodies to CT. We calculated sensitivity, specificity, predictive values and their respective 95% confidence limits.

Results: Thirty-one percent of participants reported having a history of CT infection, whereas 34% of participants had positive serological test results. The sensitivity and specificity of self-reported history of CT infection were 65.1% (95% CI, 50.2%, 77.6%) and 86.8% (95% CI, 77.8%, 92.4%), respectively. Positive predictive value of self-report was 71.8% (95% CI, 56.2%, 83.5%), and the negative predictive value was 82.8% (95% CI, 73.5%, 89.2%). The likelihood ratio was found to be 4.9. Agreement between self-report and serology was found to be only moderate ($\kappa = 0.53$, $P = 0.43$).

Conclusions: Self-reported history of CT infection is a reasonable measure of past infection status. However, when definitive status of past CT infection is needed, serology should be obtained.

No

Poster

Godzik, Jakub

CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program, CRTC MSCI Degree Program

Division of Spine Surgery

Department of Orthopaedic Surgery, Washington University in St. Louis School of Medicine

Mentors: Lawrence G Lenke, MD; Michael P Kelly, MD

Multiple lower extremity and pelvis fractures predict higher pulmonary embolus rates in trauma patients

Godzik J; McAndrew CM; Morshed S; Kandemir U; Kelly MP

Introduction: The incidence of venous thromboembolism (VTE) following major trauma has been estimated to be as high 60%, despite appropriate prophylaxis. Pulmonary emboli (PE) are associated with the occurrence of DVT, and are associated with significant morbidity and mortality. We sought to examine risk factors for PE among patients sustaining pelvic and lower extremity fractures in the National Trauma Databank (NTDB).

Methods: The NTDB v7.1 (2002-2006) was queried to identify patients sustaining pelvic, femur, and/or tibia fractures. Univariate analysis and multiple logistic regression were used to assess potential risk factors for PE during the index hospitalization period.

Results: A total of 199,952 patients with pelvic and lower extremity fracture were identified. There were 918 (0.46%) patients who developed PE in our study population, 117 (12%) of whom died during hospitalization. After adjusting for age and injury severity, the risk of pulmonary embolism was significantly increased in multiple fractures (OR: 1.89, 95% CI 1.58 - 2.253, $p < 0.001$), prior Coumadin therapy (OR: 2.09, 95% CI: 1.141-3.496, $p = 0.009$), obesity (BMI >40 OR: 3.38, 95% CI: 2.379-4.651, $p < 0.001$), disposition from ED (Surgery OR: 1.68, 95% CI 1.422-1.995, $p < 0.001$; ICU OR: 2.4, 95% CI 2.088-2.849, $p < 0.001$), and hospital setting (University OR: 1.36, 95% CI: 1.185-1.569, $p < 0.001$).

Conclusions: Multiple pelvic and lower extremity fractures, obesity, and prior Coumadin therapy were associated with PE in the NTDB. Those patients with more severe injury are also likely at risk, as seen by the associations with disposition from the ED and admitting hospital type. This study offers guidance in identifying patients with skeletal trauma that are at elevated risk for PE.

No **Godzik, Jakub**

Poster CRTCL1 Predoctoral Interdisciplinary Clinical Research Training Program, CRTCL1 MSCI Degree Program
Division of Spine Surgery

Department of Orthopaedic Surgery, Washington University in St. Louis School of Medicine

Mentors: Lawrence G Lenke, MD; Michael P Kelly, MD

Efficacy of structural allograft in occipitocervical fusion

Godzik J; Ravindra V; Ray W; Schmidt MH; Bisson EF; Dailey AT

Introduction: Although autograft provides the ideal substrate for bony fusion after posterior cervical arthrodesis, the rate of significant donor-site morbidity has been reported to be as high as 25%. The utility of structural allograft has been demonstrated in posterior atlantoaxial fixation, but limited data exist on the use of allograft for occipitocervical fixation.

Methods: The authors reviewed the records of 44 consecutive patients treated with occipitocervical fusions between 2003 and 2010.

Results: Thirty-three patients underwent occipitocervical arthrodesis using bicortical allograft, and 11 patients underwent fusion using iliac crest autograft. The mean follow-up for all patients was 20 months (range 1–108 months). Of patients with a minimum 12-month follow-up, 18/20 (90%) in the allograft group and 8/8 (100%) in the autograft group demonstrated evidence of bony fusion on flexion-extension radiographs or computed tomography. Patients in both groups demonstrated minimal deterioration of sagittal vertical alignment at final follow-up. Operative times were comparable between groups, but patients undergoing occipitocervical fusion with autograft demonstrated greater blood loss (317 mL vs. 188 mL). A single patient (9%) suffered a significant complication related to autograft harvesting.

Conclusions: The use of allograft in occipitocervical fusion allows for a high rate of successful arthrodesis, yet avoids the potentially significant morbidity and pain associated with autograft harvesting. The safety and effectiveness profile is comparable with previously published rates for posterior C1-2 fusion with evidence of minimal radiographic deterioration.

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CRTCL1 Predoctoral Interdisciplinary Clinical Research Training Program, CRTCL1 MSCI Degree Program
Division of Spine Surgery

Department of Orthopaedic Surgery, Washington University in St. Louis School of Medicine

Mentors: Lawrence G Lenke, MD; Michael P Kelly, MD

Relationship of syrinx size and tonsillar descent to spinal deformity in Chiari I Malformation with associated syringomyelia

Godzik J; Kelly MP; Radmanesh A; Kim D; Holekamp T; Smyth M; Lenke LG; Shimony JS; Park TS; Leonard J; Limbrick DD

Introduction: Chiari Type I Malformation (CIM) is a developmental abnormality often associated with a spinal syrinx. Patients with syringomyelia are known to be at increased risk of scoliosis, yet the influence of specific radiological features on the prevalence of scoliosis remains unclear. The goal of the present study was to identify associations between radiological parameters and the presence of spinal deformity in children with CIM and syringomyelia.

Methods: The authors conducted a retrospective review of pediatric patients evaluated for CIM with syringomyelia at a single institution from 2000 to 2012. Syrinx morphology and craniovertebral junction (CVJ) parameters were evaluated by magnetic resonance imaging (MRI), while the presence of scoliosis was determined using standard radiographic criteria. Multiple logistic regression was used to analyze radiological features that were independently associated with scoliosis.

Results: Ninety-seven subjects with CIM and syringomyelia were identified. Mean age was 10.5±5 years. A total of 40/97 (41%) patients were found to have spine deformity, of whom 23/40 (58%) were referred primarily for deformity and 18/40 (42%) were diagnosed during workup for other symptoms. Multiple regression analysis identified increasing maximum syrinx diameter (OR 1.536, CI_{95%} 1.318-1.709, $p < 0.001$), and moderate (5-12 mm) rather than severe (>12mm) tonsillar herniation (OR 4.79, CI_{95%} 1.521-15.10, $p = 0.007$) as significant predictors of spine deformity when controlling for age, gender, and syrinx location.

Conclusions: The current study further elucidates the association between CIM and deformity by defining specific radiographic characteristics associated with the presence of scoliosis. Specifically, patients presenting with moderate tonsillar ectopia (5-12mm) and greater syrinx diameter are at increased risk of scoliosis at presentation. The predictive value of MR imaging parameters may offer guidance for radiographic workup during the preoperative CIM evaluation.

Godzik, Jakub

CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program, CRTC MSCI Degree Program
Division of Spine Surgery

Department of Orthopaedic Surgery, Washington University in St. Louis School of Medicine

Mentors: Lawrence G Lenke, MD; Michael P Kelly, MD

Corrective spine surgery in Chiari Malformation with syringomyelia versus Idiopathic Spine Deformity

Godzik J; Holekamp T; Limbrick DD; Lenke LG; Park TS; Ray WZ; Kelly MP

Introduction: Chiari Malformation, Type 1, with syringomyelia (CMS) is often associated with spinal deformity. Aims of this retrospective matched cohort analysis were to evaluate the safety of spinal fusion and assess surgical outcome following spinal reconstruction for CMS-related deformities compared with Idiopathic Spinal Deformities (ID).

Methods: We matched 38 CMS subjects to ID subjects (ratio, 1:1) for age, gender, degree of major deformity, and extent of spinal fusion. All CMS patients underwent Chiari decompression prior to spinal reconstruction, with initial syrinx width $7.4\text{mm} \pm 3.2$. Demographics, deformity morphology, surgical details, neuromonitoring (NM) data, and pre- and postoperative SRS-22 scores were recorded.

Results: Mean age was 14.5 ± 5 years (CMS: 14.6 ± 5 , ID: 14.4 ± 5), and 45% of subjects were male. Preoperative mean major coronal curve angle measured 53 vs. 56 degrees ($p = 0.6$) with mean kyphosis 58 vs. 38 degrees ($p < 0.001$). An average number of 10.5 ± 2.5 vertebral levels were fused (10 vs. 10.5, $p = 0.82$). No significant difference existed in surgical approach ($p = .101$), estimated blood loss (690 vs. 740, $p = 0.39$), or duration of surgery (6.2 vs. 5.7 hours, $p = 0.748$). Complication rate was comparable between the two groups (32% vs. 18%, $p = 0.185$). CMS experienced more neurological complications (10% vs. 0%, $p = 0.04$), NM false positives (12% vs. 3%, $p = 0.185$), false negatives (6% vs. 0, $p = 0.185$), and NM difficulties (20% vs. 7%, $p = 0.103$). For CMS, NM difficulties were associated with larger syrinx diameter (10 mm vs. 7 mm, $p = 0.014$). Mean curve correction was comparable between the two groups at 2 years (65% vs. 66%, $p = 0.865$). At follow up (5 years vs. 4.3, $p = 0.39$), both groups demonstrated improved SRS-22 outcome subscores of self-image (CMS: 0.8, N=11, $p = 0.012$; ID: 0.6, N= 18, $p = 0.002$), mental health (0.4, $p = 0.054$; 0.2, $p = 0.106$) and satisfaction (1.2, $p = 0.005$; 0.7, $p = 0.007$). No difference in outcome subscores existed between CMS and ID subjects.

Conclusions: While CMS patients undergoing spine reconstruction can expect similar deformity corrections and outcomes scores to ID patients, they also experience higher rates of NM problems and neurological complications related to surgery. Surgeons should be prepared for such situations in this population, particularly in children with larger syrinx size.

No

Godzik, Jakub

Poster

CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program, CRTC MSCI Degree Program
Division of Spine Surgery

Department of Orthopaedic Surgery, Washington University in St. Louis School of Medicine

Mentors: Lawrence G Lenke, MD; Michael P Kelly, MD

Neurological safety and efficacy of vertebral column resection for severe deformity with myelopathy

Holekamp T; Lenke LG; Godzik J; Sun SQ; Dorward I; Kelly MP; O'Neill K; Neumann B; Kim S; Koester LA

Introduction: Vertebral column resection (VCR) is a highly invasive technique reserved for severe spinal deformities that can cause myelopathy. In these cases neuromonitoring (NM) may be unreliable and no reports exist of postoperative neurological status. We studied neurological changes in patients who presented with myelopathy and underwent VCR for severe deformity.

Methods: All pts with myelopathy who had VCR surgery by one surgeon from 2000-2012 were included. Demographics, radiographs, pre- and postop curve angles, NM data, and neurological status were collected. Neurological exams were stratified as (1) improved, (2) unchanged, or (3) deteriorated.

Results: 16 pts (11 females, 5 males) with mean age of $15\text{ yrs} \pm 9.7$ were included. All patients were myelopathic and 88% (14/16 pts) had overt weakness or sensory deficit. Eighty percent (8/10) of preop MRIs exhibited cord compression, 60% (6/10) demonstrated T2 signal change, and 30% (3/10) had a syrinx. Ten VCRs (63%) were revision surgeries, median 2-level VCR (Range 1-3), with two-staged approaches in 11 pts (69%). NM was used in all pts, with an inability to capture all modalities in 56% (9/16). There were 5 (31%) true positives, 1 (6%) false positive and 1 false negative NM readings. Mean major scoliotic curve correction was 67% (Range 0%-93%, $p < 0.01$), while major kyphosis improved 56% (Range 8%-83% $p < 0.01$). Seven pts (44%) improved neurologically, 38% (6/16) were unchanged, and 18% (3/14) worsened (mean preop Cobb= 54° , mean sagittal Cobb= 108°). Preop cord compression was associated with improved neurological exam after surgery ($p = 0.001$). Preop T2 signal change ($p = 0.5$), deformity correction ($p = 0.7$), age ($p = 0.3$), revision status ($p = 0.32$), number of VCR levels ($p = 0.23$), and NM difficulty ($p = 1$) were not associated with neurological status after surgery.

Conclusions: Acceptable correction with stabilized or improved neurological condition can be achieved in a majority of myelopathic severe deformity patients who undergo VCR. NM data should be considered unreliable in such patients with false results being relatively common. Preop cord compression predicts neurological improvement after VCR though no factor predicts deterioration.

No **Godzik, Jakub**
Poster CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program, CRTC MSCI Degree Program
Division of Spine Surgery

Department of Orthopaedic Surgery, Washington University in St. Louis School of Medicine

Mentors: Lawrence G Lenke, MD; Michael P Kelly, MD

Cost-effectiveness of surgical intervention in the setting of asymptomatic cervical lesions

Godzik J; Kelly MP; Cha TD; Riew KD; Carreon LY

Introduction: Despite the high prevalence of abnormal imaging findings of the cervical spine in asymptomatic individuals, treatment remains controversial. The purpose of the present study was to review and synthesize available evidence in order to explore the cost-effectiveness of surgical intervention for asymptomatic cervical lesions.

Methods: We developed a decision analytic Markov model to compare surgical intervention to observation in patients with abnormal imaging findings in a 20-year time horizon. Costs, utilities, and probabilities were abstracted from published literature. Base-case analysis and sensitivity analyses were conducted to determine cost-effectiveness from a payer's perspective. Monte Carlo simulation was performed to evaluate the impact of uncertainty on the results.

Results: With the use of a 4.8% annual symptomatic rate, surgical intervention was found to be a cost-effective strategy (\$7334/Quality Adjusted Life Year [QALY] vs. \$4478/ QALY) in the base-case analysis. Monte Carlo simulations produced an incremental cost-effectiveness ratio of \$70,300 per QALY. At a benchmark willingness-to-pay threshold of \$100,000 per QALY, observation was the more cost-effective strategy in 67% of simulations.

Conclusions: The decision for surgical intervention in the setting of abnormal imaging findings in an asymptomatic individual depends strongly on the likelihood of symptom development. Given the current reported rates in the literature, surgical intervention in patients with abnormal changes in the cervical spine is cost-effective under commonly accepted benchmarks.

058 **Gogineni, Swetha**
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Department of Internal Medicine, Washington University in St. Louis School of Medicine

Mentor: Brian Fuller, MD

Cardiac dysfunction and ARDS in mechanically ventilated patients with sepsis in the emergency department

Gogineni S; Fuller B

Introduction: Sepsis and acute respiratory distress syndrome (ARDS) are common and highly lethal. Cardiac dysfunction is a characteristic of sepsis but there is no research on its impact on mechanically ventilated patients with sepsis in the emergency department. There has also been little research about the event rate of ARDS under the new Berlin definition – an accurate event rate will aid in designing clinical trials on prevention of ARDS after ICU admission from the ED. The purpose of this study is to determine the effect of cardiac dysfunction on clinical outcomes in mechanically ventilated patients with sepsis and calculate the event rate of ARDS.

Methods: This is a retrospective observational cohort study. We are studying data from mechanically ventilated patients who were enrolled in a severe sepsis registry between June 2005 and May 2010. We are analyzing data that researchers at Washington University have previously collected and examined.

Results: Pending.

Conclusions: Pending.

064

Grant, Aubrey

Medical Student, Meharry Medical College

CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program; Dean's Fellowship

Summer Research Student

Division of Cardiology

Department of Internal Medicine, Washington University in St. Louis School of Medicine

Mentor: Phyllis K Stein, MD

Normal vs. abnormal sleep heart rate patterns and mortality in high risk cardiac patients: the cast

Grant AJ; Stein PK

Introduction: Identification of markers to recognize high-risk post-myocardial infarction (post-MI) patients is essential to improving survival rates in this population. Evidence suggests links between sleep difficulties and decreased cardiac function. This retrospective case-control study investigated the relationship between sleep-wake rhythms, sleep-disordered breathing heart rate (HR) patterns, and cardiac death in high-risk post-MI patients who were treated with anti-arrhythmic medications. We hypothesized that sleep/wake patterns, prevalence of sleep disordered breathing (SDB), and cyclic variation of heart rate (CVHR), as detected by changes in HR over 24-hours will be more abnormal in those who died.

Methods: 24-hour Holter recording data from the Cardiac Arrhythmia Suppression Trial (CAST) was used to determine apparent bed times, wake times, sleep periods and the presence of SDB HR patterns in a previously constructed cohort. Five-min HR and hourly power spectral heart rate variability plots were used to identify sleep/wake parameters and these were confirmed using tachogram plots of beat-to-beat HRs vs. time. Recordings for patients with a clear sleep/wake cycle and evidence for SDB were further analyzed, using novel software, to measure the number of cycles of all CVHR, SDB heart rate changes, and their magnitude and duration.

Results: Sleep patterns, as identified by Holter recordings, were not statistically different between survivors and non-survivors, and were otherwise normal. There was no significant difference between circadian patterns of survivors vs. non-survivors. Maximum change in heart rate during CVHR was greater in non-survivors than survivors indicating a possible variable to stratify post-MI patients. An increase in number of events was indicative of a higher mortality rate in post-MI patients.

Conclusions: The results of this study suggest that maximum change in heart rate during each cyclical change in heart rate and the total number of events could both be used to further stratify risk factors for post-myocardial infarction patients.

109

Greenstein, Daniel

Medical Student

CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program; Dean's Fellowship

Summer Research Student

Department of Ophthalmology, Washington University in St. Louis School of Medicine

Mentor: Lawrence Tychsens, MD

Gaze apraxia in children with cerebral palsy

Greenstein DS; Tychsens L

Introduction: Gaze apraxia is the difficulty in initiating and controlling saccades and appears to be common in children with cerebral palsy (CP), but its prevalence has yet to be determined empirically. Gaze apraxia is often overlooked and the broader diagnosis of cortical visual impairment (CVI) is commonly used instead. We plan to determine the prevalence and severity of gaze apraxia in children with CP and determine if optokinetic nystagmus (OKN) video testing is an adequate diagnostic tool.

Methods: A retrospective cohort of 131 children with CP ages 2-18 was followed from their first visit in St. Louis Children's Eye Center to their most recent. Gross Motor Function Classification System (GMFCS) level and gaze apraxia diagnosis was collected for every subject. Saccade data was collected for a second group of 19 children with CP who had also undergone OKN video testing and compared to a control group of 32 children.

Results: Chi square statistical analysis revealed a gaze apraxia prevalence of 55% and a positive association between GMFCS level and gaze apraxia diagnosis ($p < 0.001$). Average difference in OKN test scores between experimental group and control was 6.61.

Conclusions: The results of this study show that gaze apraxia is a common CP related visual impairment and has a higher prevalence in children with more severe forms of CP. Children with CP have lower scores on the OKN video test which gives the test promise as a potential diagnostic tool.

058

Gregory, Robert

CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program
Department of Internal Medicine, Washington University in St. Louis School of Medicine
Mentor: Brian M Fuller, MD

The effect of cardiac dysfunction on acute respiratory distress syndrome in mechanically ventilated patients with severe sepsis and septic shock: an observational study

Fuller BM; Cullison K; Coney T; Gogineni S; Gregory R

Introduction: Sepsis and acute respiratory distress syndrome are two syndromes that have a high mortality rate and are detrimental to the patient outcome in the critical care field. Cardiac dysfunction has been observed but never analyzed in patients afflicted with sepsis and ARDS. Our goal is to research the impact of cardiac dysfunction on clinical outcome in mechanically ventilated patients with severe sepsis and septic shock and to analyze the effect of cardiac dysfunction on the classification of ARDS diagnosis in regards to the New Berlin Definition.

Methods: This retrospective observational cohort study analyzes the impact of cardiac dysfunction on patient clinical outcome in 251 patients enrolled in the Severe Sepsis registry between June 2005-May 2010 at a University-affiliated, urban academic hospital. Two intensivists certified in perioperative echocardiography who were blinded to the study evaluated cardiac function.

Results and Conclusions: 16 additional patients were reclassified as having ARDS according to the New Berlin definition. Results for effect of cardiac dysfunction on clinical outcomes are pending.

No

Poster

Gunasinghe, Hashini

CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program
Doctor of Medicine Program, Saint Louis University
Division of Clinical Research
Department of Obstetrics and Gynecology, Washington University in St. Louis School of Medicine
Mentor: Gina Secura, PhD, MPH

Sexual behaviors and reproductive outcomes of young women enrolled in the Contraceptive CHOICE Project

Gunasinghe H; Secura G; Peipert J

Introduction: Fifty-two of every 1,000 reproductive-aged women will experience an unintended pregnancy in a year; teenagers (15-19 years) and young women (20-24 years) experience even higher rates (60/1,000 and 107/1,000 respectively) . Increased access to youth-centered sexual and reproductive health facilities may increase contraceptive use and continuation, and decrease unintended pregnancy in this at-risk population. We sought to identify differences in sexual behaviors and reproductive outcomes of young women that seek contraceptive services at a youth-centered clinic compared to university- and community based reproductive care clinics.

Methods: We analyzed baseline and 12-month follow-up data collected from women 14-24 years enrolled in the Contraceptive Choice Project. We compared demographic and reproductive characteristics across two clinic types: the youth-centered SPOT, and reproductive health clinics that included a university research clinic, community family planning clinics, and two abortion clinics. Differences across groups were examined using chi-square, t-test, and survival analysis.

Results: Participants recruited at the SPOT were more likely to be 14-19 years (53%) and African American (76%) compared to young women recruited at other sites (28%, 51%; $p < 0.05$). They reported lower baseline prevalence of sexual activity (94%), contraceptive use (87%), and pregnancy (36%) compared to young women enrolled at other sites (98%, 96%, 60%; $p < 0.5$). A greater proportion discontinued the pill, patch, ring, or injection (77%) and experienced higher unintended pregnancy rates (16%) compared to women enrolled at other sites (43%, 9%; $p < 0.05$). However, they reported greater dual contraceptive use at 12-months (59% vs. 40%; $p < 0.05$) and equally high uptake of an intrauterine device or implant and continuation at 1 year as women enrolled from other sites.

Conclusions: Women enrolled at the SPOT were at greater risk of discontinuing contraceptive methods that require daily, weekly or monthly adherence. Given teens and young women seeking care at youth-centered clinics were as likely to choose and continue a highly effective long-acting reversible contraceptive (LARC) method, youth-centered clinics should provide greater education and access to LARC methods at an affordable cost.

No
Poster

Kolody, Brianna

CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program, CRTC MSCI Degree Program
Department of Psychiatry, Washington University in St. Louis School of Medicine
Mentor: Tamara Hershey, PhD

Glycemic exposure and cortical brain thickness in type 1 diabetic youth

Kolody BC; Koller JM; Lugar HM; Hershey T

Introduction: Children with type 1 diabetes mellitus (T1D) display subtle brain compromise early in the disease, with qualitatively different effects from hypoglycemia (Hypo) and/or hyperglycemia (Hyper). Brain regions of the default mode network (DMN) may be preferentially vulnerable to glycemic extremes due to their high glucose metabolism. We retrospectively studied the association between glycemic exposure and altered cortical structure within the DMN of youth with T1D.

Methods: T1D subjects and non-diabetic sibling controls (NDC) underwent brain MRI. History of Hyper and Hypo was ascertained. Cortical thickness (CT) in DMN regions (cuneus, precuneus, medial prefrontal, posterior cingulate, medial temporal, and lateral temporal-occipital) was measured (N=111 T1D, 56 NDC), compared between groups, and correlated with glycemic exposure among T1Ds.

Results: The adjusted mean difference (AMD) in precuneus and cuneus gray matter CT ($p=0.030$ and $p=0.002$ respectively) differed by gender and hemisphere between T1D and NDCs. Compared to NDCs, T1D females had reduced CT, particularly on the right, whereas males were more affected on the left. Among T1Ds, greater Hypo exposure in females was associated with incrementally reduced CT in precuneus (1-2 episodes: AMD=0.107mm, SE=0.043; 3+ episodes: AMD=0.171mm, SE=0.045), and in males with increased precuneus CT (1-2 episodes: AMD=-0.058mm, SE=0.029; 3+ episodes: AMD=-0.197mm, SE=0.041). Compared to T1Ds without Hyper, 3+ Hyper episodes in females was associated with increased left cuneus CT (Left AMD=-0.083mm, SE=0.037), and in males with reduced cuneus CT bilaterally (Left AMD=0.123mm, SE=0.029; Right AMD=0.143mm, SE=0.031).

Conclusions: T1Ds demonstrate gender- and side-dependent differences in precuneus and cuneus CT compared to NDCs, and also T1Ds based on glycemic exposure. This may result from asymmetric and gender-unique developmental trajectories. Prospective, longitudinal investigation will further define susceptible regions and developmental phases, and will compare the destructive potential of opposing glycemic extremes. This may yield treatment regimens that proactively defend cognition during vulnerable ages by pre-emptively buffering against an injurious glycemic extreme.

028

Monseratte, Andrés

CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program
Doctor of Medicine Program, University of Puerto Rico School of Medicine
Department of Neurology, Washington University in St. Louis School of Medicine
Mentor: Randall Bateman, MD

Post lumbar puncture headaches on the Dominantly Inherited Alzheimer Network (DIAN) participants

Monseratte A; Bateman R; Ryman D

Introduction: The Dominantly Inherited Alzheimer Network (DIAN) performs lumbar punctures on autosomal dominant Alzheimer's disease patients to monitor the biomarker changes from the early asymptomatic stages to the clinically diagnosed stage. A possible risk of a lumbar puncture is developing post dural puncture headache (PDPH), defined as a postural headache caused by cerebrospinal fluid (CSF) leakage through the dural tear. The goal of this study is to identify specific procedure practices that more commonly lead to or protect against PDPH.

Methods: 392 DIAN participants who received a lumbar puncture were retrospectively analyzed. Univariate analysis was done on predictive variables (age, gender, position, needle size, collection method, insertion site, and volume of CSF collected) to test their link with three different outcomes (immediate headache, delayed headache, and blood patch). The variables that proved to be significantly linked with the outcome tested were included in a multivariate logistic regression model to assess their independent predictive value.

Results: On univariate analysis, lying down (OR 95%CI 0.167-0.982), L4-L5 insertion site (OR 95%CI 0.244-0.911), and collecting less CSF (OR 95%CI 1.069-1.222) were protective factors for immediate headaches. Multivariate tests revealed that only CSF volume was independently linked with immediate headache (OR 95%CI 1.051-1.213). Univariate analysis revealed that for delayed headaches, age (OR 95% CI 0.939-0.993) and collecting more CSF (OR 95%CI 0.887-0.992) were protective factors. Multivariate analysis independently linked age (OR 95%CI 0.938-0.993) with the outcome. CSF volume barely failed to reach independent significance (OR 95%CI 0.889-1.003). Blood patch risk was significantly reduced by age (OR 95%CI 0.903-0.994) in the univariate analysis. Volume of CSF revealed close to significant results (OR 95%CI 0.850-1.010).

Conclusions: To ensure better outcomes, this study suggests participants should be lying down rather than sitting during the lumbar puncture. An optimal range of CSF volume collection should be established to minimize adverse events. Further studies should be made with the needle sizes used in DIAN to assess their safety and viability for collecting samples.

046

Morley, Samantha

CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program
Doctor of Medicine Program, Indiana University School of Medicine
Department of Anesthesiology, Washington University in St. Louis School of Medicine
Mentor: Peter Nagele, MD, MSc

High-sensitivity cardiac troponin T elevation after cardiac stress testing: A pilot study

Morley SH; Nagele P; Davila-Roman VG

Introduction: Novel high sensitivity cardiac troponin (hs-cTn) assays allow for the detection of circulating cardiac troponin (cTn) levels even in the absence of acute cardiac events. We hypothesize that myocardial stress – for instance, stress induced by cardiac stress testing – will lead to a measurable increase in high sensitivity cardiac troponin T (hs-cTnT). However, the kinetics of hs-cTnT release is currently unknown. This prospective study aims to determine the kinetics of cardiac troponin release after cardiac stress testing using a novel hs-cTnT assay.

Methods: In patients already scheduled for cardiac stress testing, blood samples were obtained at five preset time points: before stress testing (baseline), immediately after stress testing, and 1, 2, and 3 hours after stress testing. Baseline hs-cTnT, peak hs-cTnT, change in hs-cTnT, and the time-point of peak hs-cTnT were determined for each patient in order to evaluate the kinetics of hs-cTnT release.

Results: Pending.

Conclusions: Pending.

No

Poster

Patel, Puja

CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program
Doctor of Pharmacy Program, St. Louis College of Pharmacy
Department of Internal Medicine, Washington University in St. Louis School of Medicine
Mentor: Mario Castro, MD, MPH

Steroid responsiveness in vitamin D sufficient vs. insufficient asthma patients

Patel P; Castro M

Introduction: Previous studies have shown reduced vitamin D levels are associated with decreased lung function in asthmatics, but few studies have examined the result of reduced vitamin D levels on response to oral corticosteroids. This study will focus on whether there is a difference in corticosteroid responsiveness, defined by a $\geq 5\%$ improvement in FEV₁, in asthmatic patients who are vitamin D sufficient vs. insufficient. In addition we will assess if there is a correlation between vitamin D levels in asthmatics and the change in FEV₁ after an oral corticosteroid challenge.

Methods: This retrospective cohort includes participants from Vitamin D Add on Therapy Enhances Corticosteroid Responsiveness in Asthma (VIDA), the Severe Asthma Research Program (SARP), and the Asthma and Allergic Diseases Cooperative Research Centers (AACRC). Participants will be divided into a vitamin D insufficiency group (serum vitamin D levels < 30 ng/ml) and Vitamin D sufficient group (serum vitamin D levels ≥ 30 ng/ml). Participants will then have their lung function assessed using spirometry before being administered oral corticosteroids, and once again after they have completed the regimen. Participants from VIDA will be on corticosteroids for one week, whereas participants on SARP and AACRC will be on the regimen for two weeks. A repeated measure t-test will be used to assess the corticosteroid responsiveness in patients after the data has been collected.

Results: Pending.

Conclusions: Pending.

087

Siller, Alejandro

Medical Student

CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program; Dean's Fellowship
Summer Research Program

Division of Pediatric Cardiology

Department of Pediatrics, Washington University in St. Louis School of Medicine

Mentors: Charles E Canter, MD; Kathleen P Simpson, MD; Joshua Sparks, MD

Neurological complications post-orthotopic heart transplant in a pediatric population

Siller A; Canter CE; Simpson KP; Sparks J

Introduction: Reversible Posterior Leukoencephalopathy (RPLE) syndrome is a dangerous neurological complication experienced by pediatric orthotopic heart transplant recipients. This syndrome has been linked, among other etiologies, to hypertension and to immunosuppression therapy with calcineurin inhibitors, both of which are risk factors seen in pediatric orthotopic heart transplant recipients. This study aims to determine the extent to which hypertension is associated with cases of RPLE in orthotopic heart transplant recipients at St Louis Children's Hospital since January 1, 2000.

Methods: This was an observational study of recipients of orthotopic heart transplants at St Louis Children's Hospital from January 1, 2000, to May 31, 2013. Retrospective chart review was conducted to find patients who, within 60 days of their heart transplant operation, developed RPLE and/or severe hypertension. Development of RPLE was based on clinical signs backed up by positive imaging studies, with two exceptions where the patients' condition precluded imaging, but clinical signs were very suggestive of RPLE according to the patient's chart. Patients were determined to have developed severe hypertension if they required antihypertensive therapy during the 60-day post-operative period.

Results: Between January 1, 2000 and May 31, 2013, 239 patients received orthotopic heart transplants at St Louis Children's Hospital. RPLE was observed in 9 patients. Of these 9 patients, 6 were treated for hypertension within our post-operative period of interest (60 days). Out of the 230 patients who did not develop RPLE, a total of 57 were treated for hypertension within the same period.

Conclusions: Moving forward, the same study should be performed on a larger scale. The available population is not quite large enough to power a valid statistical analysis, however the fact that a Fisher's Exact test on the proportion of RPLE patients with hypertension compared to non-RPLE patients with hypertension yields a p-value of $p=0.0116$ suggests that further study of the link between hypertension and RPLE is warranted.

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Sorensen, Christopher, MS

CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program, CRTC MSCI Degree Program
Movement Science Program

Program in Physical Therapy, Washington University in St. Louis School of Medicine

Mentor: Linda Van Dillen, PT, PhD

Differences in movement patterns during the active hip abduction test in low back pain developers and non pain developers

Sorensen CJ; Johnson MB; Callaghan JP; George SZ; Van Dillen LR

Introduction: Previous studies have used an induced-pain paradigm in back-healthy people (BHP) to understand risk factors for developing low back pain (LBP) during prolonged standing. Performance on a standardized clinical test, the active hip abduction test (AHAT), has shown promise for predicting who will develop LBP during standing. However, judgments of performance on the AHAT have been based on decision rules applied by a single clinician. The purpose of this study was to quantify hip and pelvic motion during the AHAT in BHP who develop pain (Pain developers, PD) and do not develop pain (Non pain developers, NPD). We hypothesized that PDs would show less symmetry (left vs. right) in onset of pelvic motion relative to hip motion (relative motion) compared to NPDs.

Methods: BHP completed the AHAT while their hip and pelvic motion was recorded using a motion capture system. Participants then stood for 2 hours while performing 4 different simulated light work tasks. At baseline and every 15 minutes during standing, participants rated their LBP intensity on a 100 mm visual analog scale (VAS). Participants with a ≥ 10 mm increase on the VAS were considered PDs. Independent samples t-tests were used to test for differences in symmetry of relative motion between PDs and NPDs.

Results: There were 20 (31%) PDs and 44 (69%) NPDs. PDs showed significantly less symmetry in relative motion compared to NPDs (Mean difference = 3.5%; 95% CI = 7.1 to 0.04).

Conclusions: PDs displayed less symmetry in relative motion during the AHAT compared to NPDs. We have identified similar patterns during clinical tests in subgroups of people with LBP. The similarity in movement pattern between PDs and subgroups of people with LBP suggests that PDs may have pre-existing altered movement patterns that increase their risk of LBP development during standing. Correction of altered movement patterns in people with LBP has been shown to decrease symptoms. Future research should examine whether correcting the altered movement patterns decreases LBP symptom development during prolonged standing.

No **Stepan, Jeffrey G**

Poster Medical Student; MSCI Candidate

CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program, CRTC MSCI Degree Program

Department of Orthopaedic Surgery, Washington University in St. Louis School of Medicine

Mentor: Ryan P Calfee MD, MSc

Elderly patient activity level does not affect wrist function after distal radius malunion

Stepan JG; Nelson GN; Osei DA; Calfee RP

Introduction: There is little consensus whether elderly patients with malunited distal radius fractures (DRF) have poorer outcomes than those with anatomically-united fractures. Prior clinical series report discordant results, however, they grouped all elderly patients by chronologic age without considering the range of patient activity level. This study was designed to determine if patient activity-level affected self-rated and objective upper extremity (UE) disability after distal radius malunion.

Methods: This cross-sectional investigation enrolled 102 patients 65 years of age and older at a minimum of 1 year following DRF. Patients returned for a study-related office evaluation at which the QuickDASH and VAS-pain & function questionnaires were administered to evaluate self-rated UE disability. A standardized bilateral wrist examination with wrist radiographs was also completed. The patient activity level was quantified with the validated Physical Activity Scale of the Elderly (PASE) to define high (n=40) and low activity (n=62) participants. A fellowship-trained hand surgeon, blinded to examination data, analyzed each radiograph to determine presence of a malunion using standardized criteria. Linear regression and the Mann-Whitney U test were used to compare outcomes between all high activity patients with malunion and anatomic unions and those undergoing operative vs. non-operative management.

Results: High-activity participants with malunions demonstrated equivalent QuickDASH scores, VAS function, strength, and wrist ROM compared to those with anatomic unions. These participants reported statistically but not clinically relevant increases in VAS pain scores (difference 0.5, p=0.02). Using linear regression, neither PASE score ($\beta = -0.003$, 95%CI: -0.006 to 0.000) nor malunion ($\beta = 0.31$ 95%CI: -0.16 to 0.78) predicted QuickDASH scores after accounting for age, sex, and treatment. Operative management was not associated with any superior outcome measures and resulted in decreased grip strength.

Conclusions: Distal radius malunion has minimal impact on elderly patients. Even in high-activity elderly patients, conservative management should be considered.

No **Sylvester, Peter, MSCI**

Poster CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program

Doctor of Medicine Program, Eastern Virginia Medical School

Department of Neurosurgery, Washington University in St. Louis School of Medicine

Mentors: Michael Chicoine, MD; Jeffrey Peipert, MD, PhD; Dan Marcus, PhD

Clinical implications of "atypical" pathology in GH-secreting pituitary adenomas

Sylvester P; Zohny Z; Thompson A; Dacey R; Kim A; Chicoine M

Introduction: Atypical pituitary adenomas are classified pathologically using the 2004 WHO criteria including Ki-67 labeling index > 3%, nuclear p53 reactivity, and frequent mitotic figures. Due to relatively rarity of classification, the prognostic influence of the "atypical" definition has not been rigorously analyzed clinically. Even fewer studies have evaluated the impact of atypical definition on GH-secreting pituitary adenoma.

Methods: Retrospective review of 58 GH-secreting pituitary adenoma resections performed at a single institution between 1998 and 2012. Analysis of atypical adenomas was performed on 42 cases remained after exclusion for resection before WHO definition in 2004 and inadequate tissue sample for histologic classification. Low case / event counts precluded progression-free survival analysis; however, prior studies informed the use of extent of resection (EOR) as a surrogate marker of post-operative effectiveness. Baseline patient and tumor characteristics were assessed for associations with EOR and atypical histologic definition. The threshold for significance on two-tailed testing was $p < 0.05$.

Results: Larger tumor size, tumor extension outside the sella turcica, and pre-operative IGF-1 levels were significantly associated with sub-total resection (STR) on analysis of the 58 total GH-secreting tumor resections. Atypical histology was identified in 12/42 (28.6%) non-excluded cases. Large tumor size was associated with atypical definition (mean 23.0 mm vs. 15.9 mm; $p = 0.03$); however, no difference in STR rate was noted (41.7% vs. 40.0%, respectively; $p = 0.61$). Of the 15/42 cases receiving post-operative adjuvant treatment for residual tumor (surgery, radiation, or hormone suppressive medication), none displayed subsequent progression / recurrence.

Conclusions: No difference in EOR was noted between typical and atypical GH-secreting adenoma, and adjuvant post-operative therapies were effective in controlling residual tumor regardless of histological definition. These results fail to support more aggressive post-operative treatment of GH-secreting atypical adenoma; however, a multi-institutional study may be needed to generate adequate statistical power to assess the importance of histologic definition on progression/recurrence rate.

Tinius, Rachel, MS

CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program, CRTC MSCI Degree Program
Movement Science Program

Department of Physical Therapy, Washington University in St. Louis School of Medicine

Mentor: W Todd Cade, PT, PhD

Increased maternal lipid oxidation in obese pregnancy is associated with higher infant birth weight

Tinius RA; Cahill AG; Cade WT

Introduction: In the United States, more than one half of all pregnant women are classified as overweight or obese. In obese pregnancy, an altered intrauterine metabolic environment may play a crucial role in fetal programming leading to unfavorable neonatal outcomes and long-term health implications. An impaired maternal ability to metabolize lipids may lead to increased fetal delivery of lipids in utero, resulting in increased neonatal fat deposition, higher birth weight, and other adverse outcomes. The purpose of this study was to compare lipid oxidation rates (basal and insulin-stimulated (IS)) between lean and obese women during late pregnancy. A secondary purpose was to examine the relationship between maternal lipid oxidation rate and infant birth weight.

Methods: 21 obese (BMI greater than 30 kg/m²) and 9 lean (BMI between 21 and 27 kg/m²) pregnant women participated. Indirect calorimetry was performed under fasted conditions (basal) and during a hyperinsulinemic-euglycemic (90mg/dL) clamp procedure (IS). Lipid oxidation rate was calculated from volumes of oxygen consumed (VO₂) and carbon dioxide produced (VCO₂). A two-way ANOVA was used to determine differences in lipid oxidation between groups (lean and obese) under both conditions (basal and IS). Pearson product-moment correlation coefficients were used to determine the relationships between maternal lipid oxidation rate and infant birth weight.

Results: Maternal lipid oxidation rate was higher in the obese group compared to the lean group in both conditions (basal: p=0.02, IS: p=0.05). Infant birth weight was associated with maternal lipid oxidation in both conditions (basal: R=.42, p=0.02, IS: R=.37, p=.05). The obese group had significantly larger babies (p=0.02).

Conclusions: Higher lipid oxidation rate may contribute to increased birth weight in obese pregnancy. Future research examining maternal lipid oxidation and generation of reactive oxygen species (known by-products of lipid metabolism) in obese pregnancy is needed to better understand the mechanisms of fetal programming, and therefore, design targeted interventions to improve neonatal outcomes.

No
Poster

Toure, Jamal, MS

CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program

Doctor of Pharmacy Program, St. Louis College of Pharmacy

Division of Infectious Disease

Department of Internal Medicine, Washington University in St. Louis School of Medicine

Mentors: Tom Bailey, MD; Anne Drewry, MD

The use of temperature patterns to predict sepsis in adult intensive care unit patients

Toure JN; Drewry AM; Bailey TC

Introduction: Sepsis in critically ill patients is challenging to diagnosis. When evaluating patients for possible infection, most physicians focus on the presence of fever rather than following body temperature trends. Previous work has shown slight changes in baseline body temperature precede clinical suspicions of sepsis. By using sophisticated machine learning techniques, an automated electronic monitoring system would be able to detect these subtle changes in critically ill patients.

Methods: To analyze this predictive program we must first establish and evaluate a standard to compare it by. Using the current diagnostic criteria of sepsis, a search algorithm was designed to designate patients in the ICU of Barnes Jewish Hospital from 1/1/2010 until 12/31/2011 as septic or non-septic (control). Patients with exogenous regulation or pathological disruption of basal body temperature were excluded. Power calculations were used to determine the number of patients needed for. Patients from the cohort were chosen in a randomly stratified manner and independently categorized as septic, control or excluded by a student pharmacist. The student pharmacist results were compared to the search algorithm and a physician would arbitrate any disagreements. Inter-observer kappa test, sensitivity, specificity, as well as (+) and (-) predictive value (NPV), (+) and (-) likelihood ratio were used to statistically evaluate usefulness and reliability of the program.

Anticipated Results: The results from the search algorithm were statistically similar to that of the student pharmacist with a kappa score of 0.8943, CI 95% (0.8443-0.9443) and a 0.025% standard error. The search engine has both high sensitivity (1.000) and high specificity (0.9875) and great predictive value with a PPV of 0.979 and a NPV of 1.000 and a (+) likelihood ratio of 39.659 and (-) likelihood ratio of 0.

Conclusions: We have demonstrated our search algorithm is in fact comparable to the current good standard. We can now use this program to analyze yet another. The next program will seek to determine if a patient is septic or not based solely on fluctuations in basal body temperature.

Turner, Lauren

CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program
 Doctor of Medicine Program, Saint Louis University
 Health Communication Research Laboratory
 George Warren Brown School of Social Work, Washington University in St. Louis
Mentors: Matthew Kreuter, PhD; Kim Kaphingst, MD

Health literacy INDEX evaluation of bowel prep materials

Turner L; Kreuter M

Introduction: Colorectal cancer is the third most common cancer and the second-most common cause of cancer death in the United States. Currently, colonoscopy is the gold standard for identifying colorectal cancer and colorectal surgery is a primary treatment for colorectal cancer. Bowel preparation for gastrointestinal procedures is markedly important for safe and effective execution of procedures, but execution of prep is often difficult for patients. The purpose of this study is to highlight the health literacy demands of colonoscopy and colon surgery prep materials as determined through an evaluation of materials with the Health Literacy INDEX.

Methods: This blinded, observational, pilot study evaluated fifty-one patient directed materials. Both colonoscopy and colon surgery materials were collected and compared for the presence of important health literacy predictors of patient adherence as determined by INDEX. INDEX is an evaluation tool built around 10 criteria and 63 indicators; INDEX passed stringent reliability and validity testing prior to this study. In this study, we analyzed the outcome of indicator and criteria scores assigned through INDEX based on each patient-directed prep material collected.

Anticipated Results: The majority of materials will meet the indicators within the criteria for Plain Language, Clear Purpose and Skill-Based Learning. Materials will demonstrate marked shortcomings in the criteria for Supporting Graphics, User Involvement, Audience Appropriateness, User Instructions and Development Details. The criteria, Evaluation Methods and Strength of Evidence will be inapplicable to all of the materials evaluated.

Conclusions: The results of this study suggest that more work must be done in the health literacy field to determine the best method of presenting information to patients. By characterizing the accessibility of materials, this study has the potential to make significant contributions toward limiting the problems associated with bowel preparation, ultimately making procedures safer and more efficient. This research should be followed by a comprehensive analysis of all bowel prep materials distributed, and efforts should be made towards simplification and uniformity.

VandenBerg, James

Medical Student
 CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program; Dean's Fellowship
 Summer Research Program
 Department of Internal Medicine, Washington University in St. Louis School of Medicine
Mentor: Christopher Carpenter, MD

Evidence-based diagnostics: blunt thoracolumbar spine trauma

VandenBerg JV; Carpenter C; Cullison K

Introduction: In contrast to patients with cervical-spine (c-spine) injuries, there are no well-developed decision rules for thoracolumbar (TL) spine injuries. Delayed diagnoses of unstable TL spine fractures can result in neurological deficits and excessive pain, so it is important to describe the sensitivity (SN) and specificity (SP) of different diagnostic modalities to improve decision making for these patients. The purpose of this study was to perform a systematic analysis to describe the diagnostic efficacy of the history, physical exam, and radiological studies for evaluating patients with blunt TL spine trauma.

Methods: A librarian launched a search strategy for studies including adult blunt TL trauma in PubMed, Embase, Scopus, CENTRAL, Cochrane Database of Systematic Reviews, and ClinicalTrials.gov. Then a scientific abstract hand search was independently performed by two authors. Inclusion criteria included papers studying patients with blunt TL trauma where 2x2 tables could be reconstructed. The Evidence was rated independently by two authors using the Quality Assessment Tool for Diagnostic Accuracy Studies (QUADAS) II tool. The data were then grouped by category of diagnostic test and location of injury, and meta-analyzed using Meta-DiSc software to create forest plots.

Results: Our current meta-analysis TL injury tests that were considered valid for meta-analysis were: computed tomography (CT) exams with a pooled SN of 99% ([CI]=0.93-1.00, $I^2=45.7%$) and SP of 99% ([CI]=0.97-1.00, $I^2=56.2%$) and motor bike crash with a pooled SN of 12% ([CI]=0.08-0.17, $I^2=0.0%$) and SP of 91% ([CI]=0.90-0.92, $I^2=56.4%$). Though it was not meta-analyzable, the x-ray data showed a range of SN of 22-73% and SP of 84-100%. Our data extraction is still ongoing, and we anticipate meta-analyzing MRI and clinical exam test results, as well as adding more data to existing meta-analyses.

Conclusions: CT is the best test for identifying TL injuries, but due to the high heterogeneity of our results, more accurate studies should be performed to assess TL diagnostic tests. MRI and clinical exam studies hold promise for offering diagnostic value to diagnosing TL spine injuries, and circumventing the need for CT scans.

145 **Vasiljevic, Davor**

CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program, CRTC MSCI Degree Program
Program in Physical Therapy, Washington University in St. Louis School of Medicine
Mentors: Gretchen Salsich, PhD, PT; Marcie Harris-Hayes, PT, DPT, MSCI, OCS

Three-dimensional movement pattern characteristics in people with pre-arthritis hip disease

Vasiljevic D; Salsich G; Harris-Hayes M

Introduction: Pre-arthritis hip disease (PAHD) is associated with hip joint pain and dysfunction and may precede osteoarthritis. Excessive hip adduction (ADD) and internal rotation (IR) during movement may contribute to PAHD by altering hip joint stresses. Medial collapse (MC), characterized by dynamic medial knee displacement, has been observed in people with PAHD. However, 3-dimensional (3D) hip characteristics have not been studied in this population. This preliminary study compared 3D hip kinematics of single leg squatting (SLS) in people with PAHD with two distinct movement patterns. We hypothesized that participants with MC would exhibit more hip ADD and IR compared to those with neutral (NT) movement.

Methods: Video and kinematic data of 3 SLS repetitions were captured during one session using a digital video camera and an 8-camera motion capture system, respectively. Two groups were based on frontal plane visual assessment of the SLS from digital video, with MC defined as a 10 degree difference between the starting (single leg stance) and ending (bottom of descent) frontal plane projection angles (FPPA). A deviation of less than 10 degrees was considered NT. Nine participants (age: 28.6+4.4, BMI: 23.0+2.9) were assigned to MC and 11 (age: 28.1+6.6, BMI: 23.8+1.9) to the NT group. We calculated average 3D hip angles (thigh relative to pelvis) at peak hip flexion for each participant. An independent samples *t*-test was used to evaluate hip angle differences between MC and NT groups. Significance set at a two-sided alpha level of .05.

Results: Participants in the MC group demonstrated greater hip adduction (21.7+3.3 versus 15.0+4.0 degrees, $p=.001$) compared to NT. There was no significant difference in hip internal rotation between groups (MC, 4.8+5.6 versus NT, 1.4+7.3 degrees, $p=.26$).

Conclusions: We found greater ADD in participants with medial collapse compared to neutral. However, no difference in hip IR was observed. It is plausible that hip adduction is the primary 3D component of observed medial collapse in the SLS. Understanding 3D kinematics will inform rehabilitation aimed at addressing dynamic malalignment and improving hip function.

038 **Walker, Katie**

CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program
Doctor of Pharmacy Program, St. Louis College of Pharmacy
Alzheimer's Disease Research Center, Washington University in St. Louis School of Medicine
Mentors: Catherine Roe, PhD; David Carr, MD

Effect of medications and supplements on cognition of adults over 65: A prospective study

Walker K; Yambert J; Carr D; Roe C

Introduction: Adults over age 65 account for the largest percentage of prescription medication use and polypharmacy in the US. This demographic is especially vulnerable to CNS effects. Many medications have the potential to influence the cognition of an older patient. Bupropion, oxybutynin, naproxen, calcium-vitamin D, ferrous sulfate, potassium chloride, flax, sertraline, and furosemide are medications associated with psychometric performance. It is possible that medications that interfere with cognition expose an underlying dementing disorder earlier than it would have been discovered otherwise. Conversely, medications that enhanced cognition may serve to delay diagnosis of an underlying dementing disorder. We are examining whether each medication is associated with the time to CDR>0 (mild cognitive impairment) when initial symptoms of dementia develop.

Methods: Participants were enrolled at Alzheimer's Disease Centers in the United States. Centers submitted data to the NACC which serves as a repository that codes and de-identifies data. This study adopts a prospective cohort study design using data that has been archived by NACC. Kaplan-Meier survival curves examined whether taking each drug at baseline was associated with time to incident cognitive impairment, defined as CDR>0. The Mantel-Cox log-rank test evaluated if there was a significant difference between the survival distributions of the participants taking the medications and the control group.

Results: Participants who reported taking calcium-vitamin D at baseline had a significantly longer time until CDR>0 conversion compared to those who were not taking the supplement. Participants who were taking furosemide, potassium chloride, and sertraline at baseline experienced a significantly shorter time until CDR>0 conversion compared to participants that were not taking the drugs.

Conclusions: In the future we will complete the following statistical analyses: Cox Proportional Hazard Model to incorporate important covariates (i.e. APOE, Education, Race, Gender) and treat each drug as a time dependent covariate as opposed to just if the participants were taking the drug at baseline.

Weyrauch, Stephanie

CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program, CRTC MSCI Degree Program
 Program in Physical Therapy, Washington University in St. Louis School of Medicine
Mentor: Linda Van Dillen, PT, PhD

Association between rotation-related impairments and activity type in people with and without low back pain

Weyrauch SA; Bohall SC; Van Dillen LR

Introduction: Activities requiring repeated and asymmetrical trunk movements are associated with an increased risk for low back pain (LBP). The use of repetitive movements is thought to contribute to tissue adaptations that eventually become impairments. The purpose of this secondary analysis was to determine if people with LBP who regularly participated in a rotation-related activity displayed more rotation-related impairments than people without LBP who did not participate in the activity. We hypothesized that people with LBP who participated in a rotation-related sport would display more rotation-related impairments and asymmetry of these impairments than people without LBP who did not participate in the sport.

Methods: Back healthy controls (BHCs) and people with LBP were recruited and matched based on gender, age, and activity level. Participants completed self-report measures and participated in a standardized clinical examination. The number of impairments exhibited during the clinical examination was calculated for each participant. Independent sample t-tests were conducted to compare the total number of rotation-related impairments and asymmetry of these impairments between the BHC and LBP groups.

Results: Data from 55 participants with LBP and 42 BHCs were analyzed. Compared to the BHCs, participants with LBP displayed a significantly higher number of rotation-related impairments (Mean difference = 2.35; 95% CI = 3.29 to 1.40) and asymmetry of rotation-related impairments (Mean difference = 0.97; 95% CI = 1.68 to 0.25).

Conclusions: Participants with LBP displayed a significantly greater number and asymmetry of rotation-related impairments than BHCs. These data suggest that although both groups display movement impairments, participation in an activity in which the movement impairments are used repetitively may increase the number and asymmetry, and potentially contribute to a LBP condition. Future research should include prospective investigation to better elucidate the relationships among impairments, activity type, and LBP with the goal of identifying the most relevant impairments to target for rehabilitative and preventative treatment.

Willingham, Mark, MSCI

CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program
 Doctor of Medicine Program, Saint Louis University
 Department of Anesthesiology, Washington University in St. Louis School of Medicine
Mentors: Michael Avidan, MBBCh; Arbi Ben Abdallah, PhD; Heiko Kaiser, MD

The association between intraoperative electroencephalographic suppression and postoperative mortality

Willingham M; Kaiser H; Abdullah A; Avidan M

Introduction: Low bispectral index values frequently reflect electroencephalographic (EEG) suppression and have been associated with postoperative mortality. This study investigated whether intraoperative EEG suppression was an independent predictor of 90-day postoperative mortality and explored risk factors for EEG suppression.

Methods: This observational study included 2,662 adults enrolled in the B-Unaware or BAG-RECALL trials. A cohort was defined with >5 cumulative minutes of EEG suppression, and 1:2 propensity-matched to a non-suppressed cohort (≤ 5 min suppression). We evaluated the association between EEG suppression and mortality using multivariable logistic regression, and examined risk factors for EEG suppression using zero-inflated mixed effects analysis.

Results: Ninety-day postoperative mortality was 3.9% overall, 6.3% in the suppressed cohort, and 3.0% in the non-suppressed cohort (Odds ratio (OR) [95% Confidence Interval (CI)] = 2.19 [1.48 to 3.26]). After matching and multivariable adjustment, EEG suppression was not associated with mortality (OR [95% CI] = 0.83 [0.55 to 1.25]), however, the interaction between EEG suppression and low mean arterial pressure (MAP) was (OR [95% CI] = 2.96 [1.34 to 6.52]). Risk factors for EEG suppression were older age, number of comorbidities, chronic obstructive pulmonary disease, and higher intraoperative doses of benzodiazepines, opioids, or volatile anesthetics. EEG suppression was less likely in patients with cancer, preoperative alcohol, opioid or benzodiazepine consumption, and those who received nitrous oxide.

Conclusions: Although EEG suppression was related to increasing anaesthetic administration and comorbidities, the hypothesis that intraoperative EEG suppression is a predictor of postoperative mortality was only supported if it was coincident with low MAP.

016

Zubovic, Ema

Medical Student

CRTC TL1 Predoctoral Interdisciplinary Clinical Research Training Program; Dean's Fellowship
Summer Research Program

Division of Plastic & Reconstructive Surgery

Department of Surgery, Washington University in St. Louis School of Medicine

Mentor: Albert Woo, MD

Cranial base asymmetry after open and endoscopic repair of isolated lambdoid craniosynostosis

Zubovic E; Woo AS; Skolnick GB; Naidoo SD; Smyth MD; Patel KB

Introduction: Premature fusion of the lambdoid suture results in deformity of the cranial base characterized by deviation of the foramen magnum, asymmetry of the petrous ridges and the external acoustic meatus, an ipsilateral mastoid bulge, and contralateral occipital bossing. Previous studies have shown that traditional open cranial vault remodeling does not fully address the endocranial deformity in patients with lambdoid synostosis. This study aims to compare endoscopic-assisted suturectomy with postoperative molding helmet therapy to traditional open reconstruction by quantifying changes in cranial base morphology.

Methods: Anthropometric measurements were made on pre- and 1-year postoperative three-dimensionally reconstructed computed tomography scans of 12 patients with unilateral lambdoid synostosis: 8 patients underwent open posterior cranial vault reconstruction and 4 received endoscopic-assisted suturectomy with molding helmet therapy. Cranial base asymmetry was analyzed using measures of posterior fossa deflection angle (PFA), petrous ridge angle (PRA), mastoid cant angle (MCA), and vertical and anterior-posterior (A-P) displacement of external acoustic meatus (EAM). Postoperative comparisons were made between the open and endoscopic groups.

Results: Preoperatively, patients in the open and endoscopic groups were statistically equivalent in PFA ($p=0.720$), PRA ($p=0.958$), MCA ($p=0.085$), and A-P EAM displacement ($p=0.591$). Postoperatively, open and endoscopic patients were statistically equivalent in all measures. Mean postoperative PFA for the open and endoscopic groups was 6.61 and 6.43 degrees ($p=0.939$), PRA asymmetry was 6.37 and 7.56 percent ($p=0.641$), MCA was 4.01 and 3.18 degrees ($p=0.387$), vertical EAM displacement was -2.28 and -2.25 millimeters ($p=0.974$), and A-P EAM displacement was 6.84 and 7.75 millimeters ($p=0.429$).

Conclusions: Patients treated with both open and endoscopic repair of isolated lambdoid synostosis show persistent postoperative cranial base asymmetry. Results of endoscopic-assisted suturectomy with postoperative molding helmet therapy are similar to those of open reconstruction.

CRTC Doris Duke Clinical Research Fellowship

007

Lin, Leanne Yuanci, MPHS

Medical Student, MD5 Candidate

Doris Duke Clinical Research Fellowship, CRTC Predoctoral Interdisciplinary Clinical Research Training Program
Mallinckrodt Institute of Radiology, Washington University in St. Louis School of Medicine

Mentors: Joshua S. Shimony, MD, PhD; Maruzio Corbetta, MD

Correlating fractional anisotropy in the corticospinal tract with stroke recovery

Lin LY; Ramsey L; Metcalf N; Callejas A; Baldassarre A; Rengachary J; Shulman G; Shimony JS; Corbetta M

Introduction: Patients who have suffered stroke damage in the corticospinal tract (CST) often have acute loss of motor function on the contralateral side that gradually recovers over weeks or months. The recovery varies greatly between patients, and predicting stroke recovery has always been challenging. Traditionally, in addition to baseline comorbidities and patient characteristics, prognosis is determined by initial neurological deficits.

Methods: Using fractional anisotropy (FA), a metric associated with axonal injury and is measured using diffusion tensor magnetic resonance imaging (DTI/MRI), we can quantify the damage to the CST outside of the lesion itself. The FA can then be correlated with clinical factor scores that measure patient motor function.

Results: With data from 31 ischemic stroke patients (13 with lesions involving CST), we are able to show that the FA of the ipsilesional CST in patients is statistically different at 12 months compared to 3 months post stroke ($p = 0.0042$), which is not seen in the contralesional CST ($p = 0.5987$). This difference is correlated to the improvement in clinical factor scores (a metric combining results of several motor tests), as ipsilesional CST FA values are significantly correlated with clinical factor scores of contralateral limbs ($p = 4.0189e-7$ at 3 months, $p = 7.8058e-8$ at 12 months); whereas contralesional CST FA values are not correlated with the corresponding contralateral limbs ($p = 0.1213$ at 3 months, $p = 0.22121$ at 12 months).

Conclusions: The results suggest that post stroke, FA values of damaged CST is correlated with motor function on the contralateral limbs, and the improvement in FA reflects the improvement in motor function during recovery. Since the FA values were taken in the CST outside of the lesion, this would suggest that beyond the lesion itself, a stroke causes damage to the CST that can be correlated with motor function.

Dames Fellowship

042

Chen, Ishita

Medical Student

Dames Fellowship; Dean's Fellowship

Summer Research Program

Department of Neurosurgery, Washington University in St. Louis School of Medicine

Mentor: Albert Kim, MD, PhD

Gene expression signature for low and high survival glioblastoma based on TCGA microarray analysis

Chen I; Kim A

Introduction: Glioblastoma is the most aggressive form of primary brain tumor, associated with a median survival of 15 months, even after multimodal treatment. Factors that have been associated with survival include age, Karnofsky performance score, degree of necrosis, enhancement on pre-operative MR images, and extent of resection in surgery. More recent papers have classified glioblastoma into molecular subtypes and elicited prognostic signatures using gene expression information. In this work we identify a unique gene signature based on differential expression in extremely low survival and high survival groups.

Methods: Using 481 patient cases from the cancer genome atlas (TCGA), we subdivided the data randomly into a training group (308) and validation group (157). The data in the training group was subdivided into two groups: a low survival group (<6 months) and high survival group (>2 years). Differentially expressed genes between the two groups were extracted and used for hierarchical clustering of patient gene expression profiles. Kaplan-Meier survival analysis and Cox proportional hazards model were used to study the survival differences between the clustered groups of patients.

Results: There were 46 genes that were found to be significantly different in their expression between the low and high survival groups. Hierarchical clustering divided both the training and validation sets into two distinct groups. Kaplan-Meier survival curves showed differences in survival in the clustered groups for the training set (log rank test $p < 0.05$), however the results were not significant in the validation set. The Cox proportional hazards method showed the two gene expression clusters to have prognostic value even after accounting for age and Karnofsky performance score.

Conclusions: The 46 gene expression signature predicted a significant difference in survival in the groups clustered. These findings were however weakened by the inability of that signature to predict survival in the validation group. This difference between the training and validation sets could be due to selection bias, and in future work a statistical jackknifing approach would be used to counter selection bias.

David F. Silbert Summer Fellowship

037

Ramsey, Kara

Medical Student

David F Silbert Summer Fellowship

Summer Research Program

Department of Neurology, Washington University in St. Louis School of Medicine

Mentor: Randall Bateman, MD

Optimization of an immunoprecipitation/mass spectrometry protocol for measurement of amyloid beta metabolism in human plasma

Ramsey KR; Bateman R

Introduction: Significant evidence supports the hypothesis of amyloid beta (A β) as the cause of Alzheimer's Disease (AD).

A β is a peptide that aggregates into plaques in the brains of individuals with AD. An immunoprecipitation/mass spectrometry (IP/MS) protocol was previously developed to study the metabolism of this peptide in the CNS. The purpose of this project was to optimize the IP/MS protocol for measurement of $^{13}\text{C}_6$ -leucine labeled and unlabeled A β from human plasma in order to study A β metabolism in the blood.

Methods: Cognitively normal age-matched controls and individuals with AD were intravenously labeled with $^{13}\text{C}_6$ -leucine to enable incorporation of $^{13}\text{C}_6$ into newly synthesized A β . Blood samples were taken at regular intervals from the participants and the plasma was frozen. Plasma samples were processed using an IP/MS protocol that detected 4 different A β isoforms (A β 38, A β 40, A β 42, and A β total) in both labeled and unlabeled form. Different conditions were tested to enhance the yield and purity of the samples for improved detection by MS.

Results: Overall, the best resuspension solvent for injection onto the LC/MS was found to be 10% ACN/5% MeOH/0.1% FA. This solvent enabled the solubilization and binding of all 4 isoforms to the LC column, and the MS chromatograms had significantly cleaner peaks, stronger signals, and higher signal:noise ratios than other solvent conditions tested.

Conclusions: The results of this study indicated that optimal solubilization of all 4 A β isoforms with concomitant binding to the LC/MS column required a finely tuned concentration of organic solvent. The two more hydrophobic species, A β 40 and A β 42, required higher concentrations of organic to become solubilized, but the less hydrophobic peptides, A β 38 and A β total, did not bind to the LC column if the organic component was too concentrated. 10% ACN/5% MeOH/0.1% FA balanced both of these considerations. By calculating the $^{13}\text{C}_6$: $^{12}\text{C}_6$ ratio for all four isoforms at each time point for a participant, a labeling curve with high signal:noise was generated demonstrating A β production and clearance in the blood.

061

Xiao, Qi

Medical Student

David F Silbert Summer Fellowship

Summer Research Program

Department of Internal Medicine, Washington University in St. Louis School of Medicine

Mentor: Michael Gross, PhD

The study of intrinsically disordered proteins (IDPs) using fast photochemical oxidation of protein (FPOP) protein footprinting

Xiao Q; Zhang H; Rempel D; Rohrs H; Gross M

Introduction: Intrinsically disordered proteins (IDPs) are involved in signaling and other biological functions. The lack of well-ordered structure in IDPs makes high-resolution methods difficult to apply. Thus, new techniques are needed to study this important class of proteins. To demonstrate the method and the utility of radical $\bullet\text{OH}$ -mediated labeling, Fast Photochemical Oxidation of Proteins (FPOP) was used to monitor the structural changes of two IDP samples: CBP (CBP_MOUSE, residues 2059–2117) and ACTR (NCOA3_HUMAN, residues 1018–1088).

Methods: A syringe containing 10 μM CBP or ACTR, glutamine, H $_2\text{O}_2$, PBS buffer, was infused through silica tubing contained a transparent window and intersected by a 248-nm pulsed KrF excimer laser beam (5 Hz) to photolyze H $_2\text{O}_2$ and label the protein. The flow rate was adjusted to give an exclusion volume of 15% and prevent over-labeling. The photolyzed sample was collected in an Eppendorf tube containing methionine and catalase for scavenging remaining H $_2\text{O}_2$ and radicals. Analysis of the modified protein was done with a Thermo LTQ FT mass spectrometer. Raw data from the experiment provided the input for the new software.

Results: The customized algorithm contains all known FPOP modifications and the data fitting process generates the all protein peaks based on the sequence. The calculated spectrum is used to fit the experimental data and the peak envelop of modification from fitting is used to generate the quantitative information.

Conclusions: This software demonstrated that it has the capability to quickly generate a quantitative report for protein footprinting experiment without the support of other proteomics searching engines. The new software was found to be a viable alternative to the traditional analysis method. The new software also provided a more straightforward data analysis workflow. The results of this study confirmed that FPOP can be used to rapidly obtain structural information for protein complexes. Altogether, 25 raw files were analyzed, each requiring about 10 minutes.

Dean's Fellowship

026

Agenor, Aouod

Medical Student

Dean's Fellowship

Summer Research Program

Division of Plastic and Reconstructive Surgery

Department of Surgery, Washington University in St. Louis School of Medicine

Mentors: Susan Mackinnon, MD; Matthew Wood, PhD

Peripheral nerve regeneration across a conduit embedded with Seprafilm compared to fibrin glue

Agenor A; Hunter D; Wood M; Mackinnon S

Introduction: There has been growing interest in using Seprafilm (hyaluronate/carboxymethylcellulose) to improve nerve regeneration since previous studies have demonstrated its ability to reduce scarring and adhesions, which are associated with poor axon regeneration, when used peripherally after nerve repair. This said, little is known about the direct effects of Seprafilm on the regenerating nerve when present between the nerve stumps. This study evaluates the direct effect of Seprafilm on nerve regeneration following nerve injury by comparing neuronal growth through a conduit embedded with either Seprafilm, fibrin glue or nothing.

Methods: Twenty-four rats were separated into three groups. Their sciatic nerve was transected and repaired using a 7mm empty silicone conduit (Group 1/control) or embedded with either sterile fibrin glue (Group 2/control) or Seprafilm slurry (Group 3). Rats were allowed to heal for four weeks after which Sciatic nerve proximal and distal to the conduit were harvested and evaluated by Histomorphometry.

Results: No regeneration was seen in 4 out of 8 rats in the Seprafilm group and poor regeneration was observed in the rest compared to the fibrin glue group, in which robust regeneration was seen in all rats. Nerve density distal to the conduit was higher in fibrin glue group, overall and when compared to the subset of rats in Seprafilm group that had shown some nerve regeneration. Despite the lower nerve density, no significant histomorphometric differences between groups were observed in the average axon, fiber and myelin area of the nerves when analysis was limited to rats in which at least one axon did cross the conduit.

Conclusions: The results of this study suggest that Seprafilm may disrupt axon migration and possibly act as a barrier when between nerve stumps, thereby preventing optimal regeneration. Although Seprafilm may reduce scarring, caution should be taken in its use for neuronal repair, particularly if it separates injured nerve stumps. Further studies are needed to better characterize the mechanism of the anti-regenerative barrier of Seprafilm to optimize its use in nerve repair and outcome.

039

Bruck, Brent

Medical Student

Dean's Fellowship

Summer Research Program

Department of Neurological Surgery, Washington University in St. Louis School of Medicine

Mentors: Wilson Z Ray, MD; Matthew MacEwan

A wireless nerve stimulator for monitoring functional recovery of the rat sciatic nerve

Bruck B; Gamble P; Rubenstein D; Stephen M; MacEwan M; Ray WZ

Introduction: The rat sciatic nerve model is widely used in peripheral nerve studies. It is particularly practical for monitoring peripheral nerve regeneration after injury. While a number of methods currently exist for assessing recovery of the rat sciatic nerve, these techniques often require the animal to be sacrificed at the time of data collection, reducing the amount of data that can be acquired per animal. Therefore, there is a demand to be able to monitor functional recovery of the sciatic nerve over time. Currently, using walking track analysis to calculate the Sciatic Functional Index (SFI) fills this void. However, some scientists dispute the validity of this measurement in assessing functional recovery. One possible, alternative is the use of Electromyography (EMG) which allows an experimenter to monitor the electrical activity of muscles innervated by the sciatic nerve and has the potential to provide a quantifiable indicator of nerve recovery. Still, there are challenges associated with executing EMG recordings over an extended time period, most notably accessing and selectively stimulating the sciatic nerve.

Methods: Here, we report the development of a novel and wireless peripheral nerve stimulator for chronic implantation into the rat hind limb. The device is surgically implanted under the skin, and its leads are wrapped around the sciatic nerve. An electromagnetic signal can then be used to induce stimulation of the sciatic nerve.

Results: This is an ongoing study with results pending further investigation.

Conclusions: Due to the ongoing nature of this study, conclusions cannot be drawn at this time.

119

Chen, Raymond

Medical Student

Dean's Fellowship

Summer Research Program

Department of Orthopaedic Surgery, Washington University in St. Louis School of Medicine

Mentor: Daniel A Osei, MD

Factors predictive of failure of non-operative treatment in lateral epicondylitis

Chen R; Knutsen EJ; Calfee RP; Osei DA

Introduction: Lateral epicondylitis often resolves after a course non-operative treatment. However, for a minority of patients, the symptoms persist beyond a year and are non-responsive to physical therapy, injections, medications or other non-surgical interventions. The primary aim of this study was to identify patient and disease factors that may predict the failure of non-operative treatment of lateral epicondylitis, defined as a progression to surgical treatment.

Methods: This case-control study analyzed 590 patients treated for lateral epicondylitis between 2007 and 2012 within our institution. Patient-specific and demographic characteristics were compared between patient groups (successful non-operative treatment versus surgery required). A forward entry multivariate logistic regression model was created based on preliminary univariate testing to determine which characteristics were associated with failure of non-operative treatment.

Results: Of the 590 patients treated for lateral epicondylitis, 94 (16%) failed non-operative treatment. Univariate analysis demonstrated a significant difference ($p < .1$) between the non-operative and operative groups for a number of characteristics. In our final multivariate model, the presence of radial tunnel syndrome (OR 3.1), workers' compensation claim (OR 9.0), prior injection (OR 2.0), treatment by a prior physician (OR 2.0), a history of previous orthopedic procedures (OR 3.1) and duration of symptoms greater than 12 months (OR 2.6) remained significant independent predictors of failure of non-operative treatment.

Conclusions: Patients being treated for lateral epicondylitis that present with prior injection, radial tunnel syndrome, a workers' compensation claim, prior treatment by a physician, a history of orthopedic surgery, or symptoms for greater than 12 months are more likely to fail conservative treatment for their lateral epicondylitis and may benefit from earlier surgical intervention. This information may be helpful when counseling patients regarding treatment options and the likelihood of successful non-operative treatment.

021

Chen, Simon

Medical Student

Dean's Fellowship

Summer Research Program

Section of General Thoracic Surgery

Department of Surgery, Washington University in St. Louis School of Medicine

Mentor: Traves D Crabtree, MD

Radiographic surveillance with chest X-Ray versus CT after resection for stage I lung cancer: impact on survival

Chen S; James B; Bell J; Gierada DS; Crabtree TD

Introduction: Controversy exists regarding appropriate radiographic surveillance following lung cancer resection. This work compares the impact of surveillance chest x-ray (CXR) vs. CT for patients that have undergone resection for stage I lung cancer.

Methods: A retrospective analysis was performed on patients who have undergone resection for pathologic stage I non-small cell lung cancer from January 2000 to April 2013. Patients were post-operatively followed with either routine CXR or CT imaging. Recurrences and survival were recorded.

Results: There were 554 evaluable patients with 232 receiving CT and 322 receiving CXR imaging for surveillance. Median follow-up was 2.5 years (range 0.28 – 9.93 years) for the CT group and 3.5 years (range 0.13 – 13.1 years) for the CXR group. Postoperative overall 5-year survival was 67.8% in the CT group vs. 74.8% in the CXR group ($p = 0.603$). Recurrence or new primary lung cancer were found in 27% (63/232) of patients in the CT group and 22% (72/322) patients in the CXR group ($p = 0.19$). Median relapse-free survival was 6.7 years for the CT group and 12.0 years for the CXR group ($p = 0.008$). Mean time to diagnosis of relapse was 1.93 years for the CT group vs. 2.56 years for the CXR group ($p = 0.046$). Regression analysis identified age, Charlson comorbidity index, and sub-lobar resection as significant predictors of overall survival, and indicated that imaging modality was not predictive of overall survival ($p = 0.958$). Overall 5-year survival for relapsed patients was 33.5% for the CT group vs. 40.2% for the CXR group ($p = 0.843$). For the CT group, 46% (29/63) of relapses were treated with curative intent vs. 43% (31/72) in the CXR group ($p = 0.728$). There was no difference in survival among patients treated with curative intent in the CT vs. the CXR group ($p = 0.389$).

Conclusions: For patients who have undergone resection for stage I lung cancer, surveillance CT results in earlier diagnosis of relapse without a demonstrable improvement in survival. A randomized controlled trial is needed to assess the impact of postoperative surveillance strategies on survival.

031

Chi, Tingying

Medical Student

Dean's Fellowship

Summer Research Program

Mallinckrodt Institute of Radiology, Washington University in St. Louis School of Medicine

Mentor: Michelle Lee, MD

Imaging features of solid palpable masses in women younger than 40 that may obviate the need for tissue sampling

Chi T; Lee M; Appleton C

Introduction: Each year, thousands of women under the age of 40 years undergo breast tissue biopsies to confirm suspected benign results. Given the discomfort and costs accompanying such procedures and the relatively low prevalence of breast cancer in this population, it would be beneficial to find reliable imaging features that could safely determine the malignancy of a palpable solid mass without the need of tissue biopsy. The purpose of this project is to identify ultrasound imaging features of palpable breast lesions that achieve a negative predictive value of 98% or greater to satisfy the probably benign classification (<2% chance of malignancy).

Methods: A retrospective study will be performed on 1,000 consecutively accrued lesions by using HIPPA compliant and institutional review board approved protocols in 1,000 patients under the age of 40 years who have undergone diagnostic imaging for the purpose of a palpable abnormality at Barnes-Jewish Hospital between years 2010 - 2012.

Results: It is anticipated that the findings of the retrospective analysis could demonstrate that patients could be safely followed by short-term interval imaging over two years rather than tissue biopsy.

Conclusions: This is an ongoing experiment; no conclusion will be available until all the data have been accrued and analyzed.

036

Fram, Brianna R

Medical Student

PI's Funding; Dean's Fellowship

Summer Research Program

Mallinckrodt Institute of Radiology, Washington University in St. Louis School of Medicine

Mentor: Delphine Chen, MD

Macrophage activation states in lung inflammation: in-vitro study of TSPO protein as a PET tracer target

Fram BR; Engle J; Chen DE

Introduction: Lung inflammation is part of disease states including COPD, sepsis and cystic fibrosis. Few effective treatment options exist for lung inflammation and we lack non-invasive methods to assess lung inflammation for the purposes of research and clinical care. The purpose of this study is to assess a PET tracer target and potential marker of lung inflammation, the TSPO protein, *in vitro* using human macrophages of various activation states.

Methods: Human peripheral blood monocytes were purified, matured, and differentially activated. Immunohistochemical staining and cell uptake assays of TSPO ligands were used to study differences between activation states. Lung tissue from COPD and control volunteers was also stained and analyzed regarding TSPO expression in macrophages and neutrophils.

Results: The histological results showed a higher percentage of highly TSPO co-stained macrophages in control lungs than in COPD lungs. This data requires inter-rater verification and further analysis regarding neutrophils. IHC staining showed no difference in TSPO staining between M1 and M2 activated macrophages. It showed increased staining for TREM2 protein in M2 macrophages. Uptake assays using H3-PK11129 ligand for TSPO had mixed results and may point toward changes in protein activation, as opposed to protein amount, in differentially activated macrophages. Uptake assay using C11-PBR28 ligand for TSPO showed increased uptake by M1 macrophages compared to M2, with even higher uptake by LPS activated macrophages.

Conclusions: The results of this study suggest possible differences in TSPO activation between subtypes of macrophages. Variation in IHC results also suggests that confirmation of the literature regarding the transience of these states *in-vitro*. Further protocol development is required to verify the phenotype of these activation states as achieved by our lab, and to assay their changes in protein expression over time. Overall, the hope is that TSPO-binding PET tracers can provide detailed information about the types of inflammatory process in the lungs of individual patients, allowing for the development of effective therapies for patient sub-populations.

055

Gallin, Hilary

Medical Student

Dean's Fellowship

Summer Research Program

Department of Anesthesiology, Harvard Medical School

Department of Anesthesiology, Washington University in St. Louis School of Medicine

Mentors: Douglas Raines, MD; Alex Evers, MD

The pharmacology of cyclopropyl-methoxycarbonyl metomidate: a comparison with propofol

Gallin H; Ge R; Pejo E; Jeffrey S; Cotton J; Raines D

Introduction: Cyclopropyl-methoxycarbonyl metomidate (CPMM) is a "soft" etomidate analogue currently being developed as a propofol alternative for anesthetic induction and maintenance.

Methods: We compared the potencies of CPMM and propofol by assessing their abilities to directly activate $\alpha_1(L264T)\beta_3\gamma_2$ gamma-aminobutyric acid type A (GABA_A) receptors and induce loss of righting reflexes in tadpoles. We also measured the rates of encephalographic recovery in rats following CPMM and propofol infusions ranging in duration from 5 to 120 minutes.

Results: CPMM and propofol activate GABA_A receptors and induce loss of righting reflexes in tadpoles with respective EC₅₀s of $3.8 \pm 0.4 \mu\text{M}$ and $3.9 \pm 0.2 \mu\text{M}$ (GABA_A receptor) and $2.6 \pm 0.19\mu\text{M}$ and $1.3 \pm 0.04 \mu\text{M}$ (tadpole). Encephalographic recovery after prolonged infusion was faster with CPMM and lacked propofol's context sensitivity.

Conclusions: CPMM and propofol have similar potencies in GABA_A receptors and tadpoles; however, CPMM provides more rapid and predictable recovery than propofol particularly after prolonged infusion.

122

Gefen, Ashley

Medical Student

Dean's Fellowship

Summer Research Program

Department of Orthopaedics, Washington University in St. Louis School of Medicine

Mentor: Robert Brophy, MD

Public understanding and expectations of meniscus injury and surgery

Gefen AM; Smith MV; Matava MJ; Wright RW, Brophy RH

Introduction: There is little literature evaluating public knowledge regarding the meniscus and its function, injury, or surgical treatment options. The objective of this study is to assess patient knowledge and perceptions about the meniscus and meniscal injury to improve patient-physician communication as well as patient education and perceptions of meniscus surgery.

Methods: This study used a 41-question survey designed to measure knowledge and perception of meniscus tears with regard to anatomy, function, indications, operative techniques, risks, overall benefits of repair or removal, and recovery times. Study participants between 18 and 60 years of age were recruited from an academic orthopedic sports medicine clinic.

Results: A total of 253 individuals were surveyed (132 males, 121 females) with a mean age of 38 years. Most (62%) respondents rated their knowledge about the meniscus as little or no knowledge and 50% of factual questions were answered correctly. There was no correlation between perceived knowledge and percent answered correct ($p=0.84$) and between level of knee injury/surgery exposure and percent answered correct ($p=0.57$). Forty-two percent understood catching is the most likely meniscus tear symptom while 47% thought it was weakness. Only 13% knew the meniscus can only be repaired, rather than removed, 15% of the time. Twenty-eight percent knew meniscectomy is the most common meniscus tear treatment. Just 13% knew the chance of more meniscus surgery after meniscectomy is <5%. The risk of developing osteoarthritis and the risk of needing more knee surgery were the biggest concerns about meniscus surgery.

Conclusions: Overall, public knowledge regarding the meniscus is poor, regardless of exposure, and patients do not have significant insight into how much they really know. There are deficits across the different areas of knowledge about the meniscus tested, suggesting a need for improved patient education. These findings can serve as a guide to patient-physician communication about meniscal injury and potential treatment. The risks of developing osteoarthritis and needing more knee surgery were the most important factors to patients when considering meniscus surgery and should be addressed with patients.

041

Han, Rowland

Medical Student

Dean's Fellowship

Summer Research Program

Departments of Neurosurgery and Pediatrics, Washington University in St. Louis School of Medicine

Mentors: Matthew D Smyth, MD; Chester K Yarbrough, MD

Characterization of temperatures achieved in human neocortex during intraoperative focal cooling

Han RH; Smyth MD; Rothman SM; Yarbrough CK; Patterson EE; Yang XF; Miller J; D'Ambrosio R

Introduction: Focal cortical cooling stops seizures and inhibits epileptogenesis in rodents. In order to investigate its potential clinical utility, we examined the thermal characteristics of canine and human brain undergoing surface cooling via active and passive methods.

Methods: Four patients with intractable epilepsy were treated in standard fashion. Prior to resection of a neocortical epileptogenic focus, multiple studies on active and passive cooling were performed intraoperatively. In addition, we actively cooled the neocortex of two dogs with temporarily implanted grids.

Results: Focal surface cooling of human brain causes predictable, depth-dependent cooling of underlying brain tissue. Cooling by 1.2 to 2°C was achievable to a depth of at least 10 mm from the cortical surface. The mechanism by which cooling occurs does not affect time to steady-state temperature. The perfused grid was able to produce comparable cooling of dog neocortex when the craniotomy was closed.

Conclusions: Cooling of human brain tissue is predictable and dependent solely on surface temperature and distance of tissue from the cortical cooling source. The technique used in these experiments could be used to safely cool human neocortex during prolonged invasive monitoring and provide pilot data for design of a permanently implantable thermoelectric device to control intractable epilepsy.

124

James, Michael

Medical Student

Dean's Fellowship

Summer Research Program

Department of Orthopaedic Surgery, Washington University in St. Louis School of Medicine

Mentor: Devyani Hunt, MD

The return to dance activity profile for hip preservation surgery

James MG; Hunt D

Introduction: Current research on hip preservation surgical outcomes largely focuses on patients engaged in sports that do not require the extreme hip range of motion essential for dancers. In addition, the majority of this research is on male athletes. This study focuses predominantly on female dancers with the intent to address the gap in the literature. The primary intent is to assess the ability of dancers to return to dance activity after hip preservation surgery including hip arthroscopies, surgical dislocations and periacetabular osteotomies and to identify correlates between pre-surgical factors such as hip pathology, dance style, and level of expertise to post surgical levels of activity.

Methods: The Joint Preservation Repository was searched for dancers between the ages of 13-40 who have had a hip arthroscopy, surgical dislocation or periacetabular osteotomy from 2007 – 2013 performed by Orthopedic Surgeon Dr. John Clohisy. A questionnaire assessing return to dance activity, the UCLA, HOOS, and SF12 were administered via a telephone conversation.

Results: 20 dancers were identified and contacted. Data collection is still in progress, but to date, 8 female dancers (representing 9 hips) have consented to take part in the study and 7 have completed the questionnaires.

Conclusions: At this juncture, there is not enough data to draw significant conclusions.

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Khan, Taleef

Medical Student

Dean's Fellowship

Summer Research Program

Department of Orthopaedic Surgery, Washington University in St. Louis School of Medicine

Mentor: Luke Zebala, MD

Long-term outcomes of transforaminal lumbar interbody fusion in spine surgery

Khan T; Zebala L

Introduction: Transforaminal Lumbar Interbody Fusion (TLIF) is a posterior based spine surgical technique that allows the surgeon to create structural support for the anterior side. The purpose of this study was to determine the effectiveness of this surgery after a number of years following operation.

Methods: The study conducted was a retrospective review of patients who had undergone the TLIF procedure at Barnes-Jewish Hospital. While not all patient data was utilized, since only 34 patients were reviewed in the limited time frame, many cases from Washington University were excluded. Those included in our database were adult patients, all above the age of 18, who underwent back surgery with at least 1 level of vertebrae having the TLIF being performed on it, along with at least 2 years of follow up.

Results: The results showed that of the 34 patient cases that were reviewed, 11 patients reported adjacent level degeneration following the procedure (32%). Additionally, if the 5 year follow up time was simply observed, only 1 patient would be observed to have complications with the TLIF at 3.6 years. With this individual, however, the TLIF procedure was carried out as a revisionary surgery as opposed to a primary surgery like for other patients. Furthermore, if only the TLIF was carried out in primary surgeries, the number of patients suffering from post-surgery complications would drop to 8, or 23%. Lastly, if only a 5 year follow up were observed for just the primary surgeries, our discovery would be that no patients suffered from significant post-operative complications.

Conclusions: The results of the study suggest that the TLIF surgery is a relatively safe procedure with most patients healing without any significant complications. Most operative complications were observed following at least a 10-year period. Future research is needed on the many other TLIF surgeries.

029

Liang, Zhe

Medical Student

Dean's Fellowship

Summer Research Program

Division of Diagnostic Radiology

Mallinckrodt Institute of Radiology, Washington University in St. Louis School of Medicine

Mentor: Susan Holley, MD, PhD

Utility of breast imaging for focal breast pain

Liang Z; Holley S

Introduction: Focal breast pain is a common breast condition that is responsible for large numbers of clinical visits. However, prior research has suggested that focal breast pain is rarely associated with breast malignancy. The aim of our study is to examine the predictive value of breast imaging in this clinical scenario, using a retrospective analysis of our experience with focal breast pain at the Breast Health Center at Washington University.

Methods: Approximately 6,000 cases of focal breast pain will be assembled from the Breast Health Center's imaging database that catalogues radiology reports from 2001-present.

Results: We predict that breast imaging has poor clinical values in predicting breast malignancy in patients with focal breast pain as the sole symptom. This agrees with the conclusions drawn from prior research.

Conclusions: Definite conclusion cannot be drawn at this point since the research is ongoing. Upon the successful completion of this research project, we may be able to limit the imaging performed for focal breast pain, and more efficiently target patients who will benefit from mammography, ultrasound, both, or neither. This could help reduce the overutilization of diagnostic imaging as well as improving the health care quality.

Lin, Kenneth M

Medical Student

Dean's Fellowship

Summer Research Program

Department of Orthopaedic Surgery, Washington University in St. Louis School of Medicine

Mentor: Robert Brophy, MD**Association of socioeconomic and occupational factors with shoulder activity level**

Lin KM; Brophy RH

Introduction: Activity level is recognized as an important outcome measure and prognostic factor in orthopaedics; however, patient variables associated with activity level have not been well studied. The purpose of this study was to assess the association of different socioeconomic and occupational factors to a patient's shoulder activity level.

Methods: Participants included adults aged 18 years and older in the United States, surveyed online by a marketing research firm. Participants completed the shoulder activity score and reported their age, sex, race, income, household size, employment type, and any history of shoulder symptoms or treatment. The survey was sent to 2773 people, with 2403 people completing the entire survey; from that group, 1625 participants were included as healthy controls.

Results: The mean shoulder activity score (SAS) of healthy controls was 8 ± 5 (range, 0-20). Mean SAS was significantly higher in individuals with income over \$50,000 than those with lower income (9.5 vs. 8.3 in males, 8.0 vs. 6.6 in females, $P < 0.001$ for both genders). By employment, mean SAS decreased from heavy to moderate to sedentary labor (12.1, 10.2, and 9.0, respectively for males, and 12.0, 8.8, 7.0, respectively for females, $P < 0.001$ for both genders). Mean SAS increased with household size (7.3, 8.0, and 8.6 for household sizes of 1, 2, and ≥ 3 , $P < 0.001$), but did not differ by race (8.2, 7.6, and 7.8 for White, African-American, and Other, $P = 0.190$). Higher income and larger household size were associated with increased participation in contact and overhead sports ($P < 0.001$ for both associations).

Conclusions: In healthy controls, shoulder activity level is related to socioeconomic and occupational factors such as income, employment type, and household size, but not race. These normative data help us understand the normal variance in shoulder activity level, and also suggest a possible link between socioeconomic variables and clinically relevant patient variables that may help us better predict and assess clinical outcomes of shoulder disorders.

Liu, Carol

Medical Student

Dean's Fellowship

Summer Research Program

Division of Immunology and Rheumatology

Department of Pediatrics, Washington University in St. Louis School of Medicine

Mentors: Anthony French, MD, PhD; Michel Sun**Sex differences in interferon-stimulated gene expression in human monocyte-derived macrophages**

Liu CW; Sun M; French AR

Introduction: Autoimmune diseases affect over 5% of the US population. Females are disproportionately affected by autoimmune diseases, with over 80% of autoimmune disease patients being women. However, the mechanisms leading to the sex bias in autoimmune susceptibility are not fully understood. Type I IFNs induce the transcription of thousands of interferon-stimulated genes (ISGs), which play crucial roles in the host defense against pathogens. The purpose of this study is to examine the sex-dependent differences in ISG expression following type I IFN stimulation in human macrophages.

Methods: We isolated monocytes from the peripheral blood of age- and race-matched male and female donors. We differentiated the monocytes into macrophages and stimulated the cells with IFN- α . We then compared the relative gene expression changes of eight ISGs between male and female samples.

Results: We found that five of the eight ISGs had a higher fold change in gene expression in females than in males upon IFN- α stimulation.

Conclusions: The results of this study suggest that sex-dependent differences in ISG expression may partially explain the sex disparities in immune response. Once determined, the mechanism for the sex disparities in immune responses may help elucidate the sex bias in autoimmune susceptibility, and may lead to the improvement of autoimmune outcomes in females.

025

Overschmidt, Bo

Medical Student

Dean's Fellowship

Summer Research Program

Division of Plastic and Reconstructive Surgery

Department of Surgery, Washington University in St. Louis School of Medicine

Mentor: Terence Myckatyn, MD

Correlation of patient satisfaction with 3D imaging use in consultation and mammometric parameters

Overschmidt BT; Tenenbaum MM; Myckatyn T

Introduction: In breast augmentation surgery, result simulation from 3D imaging allows patients to participate in the preoperative planning and selection of cosmetic breast implants. It also allows measurement of breast parameters, termed mammometrics. Using mammometric analysis, parameters correlating with improved satisfaction per a validated patient reported outcomes instrument are identified, but first it is necessary to determine a standardized, reproducible method to define and measure these. Recognizing mammometrics and simulated results that correlate with high satisfaction will improve the patient experience with breast augmentation surgery.

Methods: All patients receive pre- and postoperative 3D imaging. They are randomized into two groups. The experimental group receives consultation using their 3D images to simulate results and aid in planning. The control group receives a standard consultation without simulation. Mammometric data is calculated for all patients. Breast border, quadrant, and landmark definitions were standardized using software comparing pre- and post-operative images. Satisfaction is assessed using the Breast Q, a validated questionnaire that measures patient reported satisfaction and yields an overall Q-score of 0-100 as well as scores in six separate core areas.

Results: Use of 3D imaging in preoperative consultation will correlate with higher patient satisfaction, especially in the "Satisfaction with care" core area. The mammometric parameters "superomedial pole fullness", "central nipple position", and "nipple to inframammary fold distance" will be positively correlated with patient satisfaction, particularly in the "Satisfaction with breasts" core area.

Conclusions: Using 3D images in consultation helps with managing patients' expectations and provides a simple, visual forum for expressing their vision for their breasts. Identifying parameters correlated with higher satisfaction will allow easier preoperative planning and directly affect intraoperative management. Together these will improve patient-surgeon communication and the patient's overall experience.

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Rodriguez, Jocelyn

Medical Student

Dean's Fellowship

Summer Research Program

Department of Orthopaedic Surgery, Washington University in St. Louis School of Medicine

Mentor: Rick W Wright, MD

Multicenter studies concerning the pathological knee joint

*Rodriguez JM; *Weese JR; Wright RW

Introduction: The multicenter ACL (anterior cruciate ligament) Revision Study (MARS) affords the opportunity to examine pathophysiology of the knee joint radiographically and arthroscopically at the time of revision ACL reconstruction. Existing knee osteoarthritis (OA) classification systems lend to suboptimal inter-observer reliability and it is unclear whether recurvatum knee alignment can predict outcomes of revision ACL reconstruction. The purpose of these studies is to assemble a reliable OA classification system, to determine if recurvatum knee alignment influences operative outcomes, and to determine inter-rater reliability when determining meniscal tear length.

Methods: *Study 1:* Six different OA classification systems were systematically deconstructed and compared for similarities and differences. The criteria were then converted to binary questions. Experienced surgeons will rate 30-40 Rosenberg X-rays on a 1-4 scale (zero, mild, moderate, severe) to determine the most reliable criteria for the rating of OA severity. *Study 2:* Extension angle from lateral full extension (LFE) x-rays from MARS patients was measured to divide the patients into two groups in relation to the degree of hyperextension (HE). *Study 3:* Videos of torn menisci were assembled into a DVD for distribution to determine inter-rater reliability of the tear length.

Results: *Study 1:* After testing, the most reliable criteria for determining OA severity will be determined. These criteria will then be used to construct a new, more reliable classification system for determining the severity of OA by radiograph. *Study 2:* The two-year follow-up data associated with the two cohorts divided by knee HE angle on LFE x-ray will be compared to determine if recurvatum is a predictor for outcome. It is hypothesized that a HE angle greater than 5 degrees will be a predictor of less favorable surgical outcome. *Study 3:* Assuming inter-rater reliability of meniscal tear length is adequate, the study will continue to the next phase.

Conclusions: The results of all three studies will affect clinical decisions when examining treatment of OA, revision ACL reconstruction, and meniscus tears.

*Both contributed equally to this work

014

Russell, Aaron

Medical Student

Dean's Fellowship

Summer Research Program

Division of Plastic and Reconstructive Surgery

Department of Surgery, Washington University in St. Louis School of Medicine

Mentor: Albert Woo, MD

Path of the superior sagittal sinus in unicoronal synostosis

Russell AJ; Skolnick G; Smyth MD; Woo AS

Introduction: The sagittal suture of the skull is frequently utilized as a landmark designating the location of the superior sagittal sinus (SSS). However, when significant asymmetry exists, as in the case of unicoronal synostosis, the relationship between the sagittal suture and the SSS cannot be presumed. This study investigates the anatomical relationship between the SSS and the sagittal suture in infants with uncorrected unicoronal synostosis. The morphology of the SSS is also evaluated postoperatively to assess whether normalization of intracranial structures occurs following reconstruction.

Methods: The study sample consisted of 20 computed tomography scans (10 preoperative, 6 postoperative, and 4 unaffected controls) obtained at St. Louis Children's Hospital between 2001 and 2013. The SSS and the sagittal suture were outlined using Analyze imaging software. These data were used to measure the maximum discrepancy between the SSS and sagittal suture and to assess for any change in the morphology of the SSS pre- and postoperatively.

Results: In children with uncorrected unicoronal synostosis, the SSS deviates to the side of the patent coronal suture posteriorly and tends to follow the path of the sagittal and metopic sutures. The discrepancy between the SSS and the sagittal suture ranged from 5.0 mm to 11.8 mm, with a 99.9% upper prediction bound of 14.4 mm. The curvature of the SSS was statistically smaller following surgical intervention but remained significantly greater than unaffected controls.

Conclusions: The SSS follows a predictable course relative to surface landmarks in children with unicoronal synostosis. When creating burr-holes for craniotomies, the SSS can be avoided in 99.9% of cases by remaining at least 14.4 mm or farther from the outer edge of the sagittal suture. Postoperative changes in the path of the SSS provide indirect evidence for normalization of regional brain morphology following fronto-orbital advancement.

001

Shankar, Vikram

Medical Student

Dean's Fellowship

Summer Research Program

Center for Health Policy, Washington University in St. Louis

Mentor: William Peck, MD

The Health Care Handbook at One Year

Shankar VA; Peck W

Introduction: *The Health Care Handbook* was published in September 2012, and to date has sold more than 10,000 copies through digital and paperback editions. Since the publication of the first edition, our focus has been directed in three areas-- marketing the book to health professions programs and students, creating curricular materials to accompany the book, and identifying revisions to make for the second edition. Washington University received a \$75,000 grant from the Missouri Foundation for Health to support the 2nd edition of the Handbook, to be released in the summer of 2014.

Curriculum: The *Handbook* is now being used as curricular material by 51 health professions training programs around the country, including over a dozen medical schools. We are in the process of developing case studies, quizzes, online videos, and lecture aids to supplement the content in the book. Some of these materials have already been produced in conjunction with programs like UT-San Antonio and SUNY-Albany, and are published on the website MedEDPORTAL.

Marketing: Primary marketing efforts for the *Handbook* have involved email outreach to a variety of health professions programs, businesses, and universities. These efforts are part of an ongoing process to expand the use of the book as an educational tool to teach health policy, business, and delivery. In July, we began our first targeted advertising campaign and also launched an entirely redesigned website. Our longer-term vision for our website includes a curriculum hub where instructors can access and share the curricular materials we are developing around the book.

Revisions and Future Directions: Revisions to the book will address new developments and policy research since the previous update, while expanding on topics that were underemphasized in the first edition. Most of these changes are relevant to Chapters 4 and 5, addressing medical research, the Affordable Care Act, and health reform; it is expected that these chapters will change the most. As our team and project have grown in scope, we have recognized a need for a formal business and marketing plan to guide successive editions. Integral in this effort is the identification of new markets for the book, particularly medical device, insurance, and technology companies.

Shen, Tony S

Medical Student

Dean's Fellowship

Summer Research Program

Department of Orthopaedic Surgery, Washington University in St. Louis School of Medicine

Mentors: Matthew Silva, PhD; Jennifer McKenzie, PhD**The role of hedgehog signaling in determining the osteogenic response to mechanical loading of bone**

Shen TS; McKenzie JA; Silva MJ

Introduction: Following injury, numerous molecular systems regulate the formation of woven or lamellar bone. Recent bone dynamic histomorphometry studies in the Silva laboratory demonstrated that inhibition of the hedgehog pathway via the inhibitor GDC-0449 resulted in decreased bone formation in the unloaded limb (left ulna) in rats mechanically loaded on the right ulna. We sought to further characterize this result by (1) analyzing bone formation in the tibias and (2) analyzing vasculature formation in the ulnas.

Methods: Samples obtained from GDC-0449 treated rats (N=18) and control rats (N=19) were analyzed by bone dynamic histomorphometry. Samples were imaged by fluorescent microscopy and analyzed using BIOQUANT OSTEO. Vascular analysis was performed by counting vessels positively stained for Von Willebrand's factor.

Results: We analyzed vascular differences between inhibited (GDC-0449) and control (vehicle) rats. At both day 3 and day 7 following loading, control rats showed a two-fold greater number blood vessels surrounding the callus than inhibited rats ($p < 0.05$). To explore the effect of hedgehog inhibition in other limbs, we measured bone formation in the right and left tibias of loaded rats. Compared to control, rats treated with GDC-0449 showed no statistically significant difference in bone formation as measured by mineralizing surface, bone formation rate, and mineral apposition rate.

Conclusions: The difference in vascular formation shows that Hh inhibition affects both angiogenesis and osteogenesis. The lack of any difference in bone formation in the tibias suggests that Hh inhibition does not lead to a global decrease in bone formation. While other studies suggest that Hh signaling may affect osteogenesis by disrupting angiogenesis, further genetic studies would be necessary to elucidate the precise mechanism by which Hh inhibition affects both of these systems.

No

Simien, Adrian A

Poster

Medical Student, Des Moines Medical College

Dean's Fellowship

Summer Research Program

Department of Surgery, Washington University in St. Louis School of Medicine

Mentors: William Chapman, MD, FACS; Richard Chen, MD, PhD**An agarose-albumin phantom for evaluating image guided radiofrequency ablation**

Simien AA; Chen R; Chapman W

Introduction: Radiofrequency Ablation (RFA) is a minimally invasive procedure that is used for the treatment of liver tumors, especially for those that are unable to meet requirements for surgical resection. Although there is increasing use of RFA, it is difficult to predict the therapeutic result because of uncertainties in the spatial extents of the ablation zones and in electrode placement. The purpose of this study is to develop a reproducible ex vivo model for evaluating image guided RFA and demonstrate that ablations are reproducible in phantoms with respect to its geometry.

Methods: A 1% agarose mixture with an albumin source was poured into a mold for a total of 10 phantoms. The imbedded tumors were composed of 2% agarose for ultrasound visibility. After the construction of the phantoms with the imbedded tumors, ultrasound was used to visualize the tumor placement and obtained measurements of the tumors for consistency in the first five phantoms. Image guidance was utilized in the first five ablations as well. The next five ablations consisted of free-hand placement. A clinical ablation system (RITA XL from Angiodynamics) was used for ablations.

Results: Phantom dimensions of five phantoms were measured and calculated (mean \pm SE in cm): From the surface to the top of the tumor (D top-surface): 4.27 \pm 0.17; Tumor diameter: 2.54 \pm 0.05; From the surface to the center of the tumor (D center-surface): 5.03 \pm 0.44; Tumor center to the left screen (D center-left): 5.95 \pm 0.09; Tumor center to the right screen (D center-right): 5.97 \pm 0.04. With comparing the various methods of RFA, Image-guided ablations resulted: 0.33 \pm 0.08. US guidance resulted: 0.58 \pm 0.148. Our T-test: P (T<=t) reveals information that our two groups are not significantly different (0.170>0.05), with respect to the most effective modality.

Conclusions: The results of this study suggest reproducibility with respect to the created phantoms. However, the comparison and calculations between ultrasound and image guidance was not able to show a significant difference with regards to effectiveness in treating our reproducible, tumor embedded phantoms.

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Skillington, S Andrew

Medical Student

Dean's Fellowship

Summer Research Program

Department of Orthopaedic Surgery, Washington University in St. Louis School of Medicine

Mentors: Robert Brophy, MD; Matthew Smith, MD

Shoulder activity level in normal and pathological shoulders and its relationship to shoulder dominance

Skillington SA; Brophy RH

Introduction: Activity scales have become increasingly prevalent in orthopedics in recent years. The Shoulder Activity Scale that Brophy et al. created is a reliable, valid, and responsive tool that may have some utility as a prognostic factor or an outcome measure. The purpose of the present study was to investigate shoulder activity level of a large cohort that included both healthy individuals and individuals with shoulder disorders. Additionally, shoulder dominance and its relationship to activity level were also investigated.

Methods: Study participants were drawn from the research marketing firm TNS Global's Lightspeed Research Panel (London, United Kingdom). A total of 2773 individuals over the age of 18 were contacted by email, and 2403 participants completed a survey that included the Shoulder Activity Scale, the Simple Shoulder Test, demographic information, and health history information.

Results: A total of 1625 people reported no current or past history of shoulder pathology and their mean activity score was 8.2 ± 4.7 (95% CI = 7.9-8.4). There were 778 respondents who reported either current or past shoulder pathology, and their mean shoulder activity score was 8.0 ± 4.8 (95% CI = 7.6-8.3). There was no significant difference between these groups ($P=0.36$). Of the 778 individuals who reported having a shoulder disorder, 594 had shoulder pathology in their dominant shoulder and 184 had shoulder pathology in their non-dominant shoulder. The mean shoulder activity scores for these groups were 8.0 ± 4.9 (95% CI = 7.6-8.4) and 7.9 ± 4.6 (95% CI = 7.2-8.5) respectively. There was no significant difference between these two groups ($P = 0.70$).

Conclusions: There is no significant difference in shoulder activity between individuals with non-specific shoulder pathologies and healthy controls. In patients with shoulder pathology, there is no significant difference in activity level between patients with a disorder in their dominant versus non-dominant shoulder. In general, having a non-specific shoulder disorder does not predispose one to having a higher or lower activity level.

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Weese, Jonathan

Medical Student

Dean's Fellowship

Summer Research Program

Department of Orthopaedic Surgery, Washington University in St. Louis School of Medicine

Mentor: Rick W Wright, MD

Multicenter studies concerning the pathological knee joint

*Weese JR; *Rodriguez JM; Wright RW

Introduction: The multicenter ACL (anterior cruciate ligament) Revision Study (MARS) affords the opportunity to examine pathophysiology of the knee joint radiographically and arthroscopically at the time of revision ACL reconstruction. Existing knee osteoarthritis (OA) classification systems lend to suboptimal inter-observer reliability and it is unclear whether recurvatum knee alignment can predict outcomes of revision ACL reconstruction. The purpose of these studies is to assemble a reliable OA classification system, to determine if recurvatum knee alignment influences operative outcomes, and to determine inter-rater reliability when determining meniscal tear length.

Methods: *Study 1:* Six different OA classification systems were systematically deconstructed and compared for similarities and differences. The criteria were then converted to binary questions. Experienced surgeons will rate 30-40 Rosenberg X-rays on a 1-4 scale (zero, mild, moderate, severe) to determine the most reliable criteria for the rating of OA severity. *Study 2:* Extension angle from lateral full extension (LFE) x-rays from MARS patients was measured to divide the patients into two groups in relation to the degree of hyperextension (HE). *Study 3:* Videos of torn menisci were assembled into a DVD for distribution to determine inter-rater reliability of the tear length.

Results: *Study 1:* After testing, the most reliable criteria for determining OA severity will be determined. These criteria will then be used to construct a new, more reliable classification system for determining the severity of OA by radiograph. *Study 2:* The two-year follow-up data associated with the two cohorts divided by knee HE angle on LFE x-ray will be compared to determine if recurvatum is a predictor for outcome. It is hypothesized that a HE angle greater than 5 degrees will be a predictor of less favorable surgical outcome. *Study 3:* Assuming inter-rater reliability of meniscal tear length is adequate, the study will continue to the next phase.

Conclusions: The results of all three studies will affect clinical decisions when examining treatment of OA, revision ACL reconstruction, and meniscus tears.

*Both contributed equally to this work

085

Wondmeneh, Sarah

Medical Student

Dean's Fellowship

Summer Research Program

Division of Genetics and Genomic Medicine

Department of Pediatrics, Washington University in St. Louis School of Medicine

Mentor: Beth Kozel, MD

Role of inflammatory response in modifying the vascular phenotype in elastin insufficient mice

Wondmeneh S; Kozel B

Introduction: Elastin haploinsufficiency is the cause of cardiovascular complications associated with Williams-Beuren syndrome and isolated supraaortic stenosis. Affected individuals demonstrate significant variability in the presentation of these symptoms. *Rag1* and *Ncf1* have been identified as modifier genes of interest, interacting with the elastin defect to enhance the degree of vascular pathology. However, further research is required to determine the specific pathways involved. The purpose of this study is to identify the specific immune cells involved in the pathological response to elastin insufficiency and determine variations in oxidative stress between *Eln*^{+/-} and WT mice.

Methods: Elastin and di-nitrotyrosine antibody staining was used to determine vascular morphology and ROS activity. Flow cytometry was used to identify immune cell variations between genotypes.

Results: Overall, elastin haploinsufficient mice had a higher lamellar number than WT. Knocking out the *Rag1* gene resulted in a decrease in lamellar number, indicating a buffering effect against the elastin insufficient vascular phenotype. Aorta of *Eln*^{+/-} mice displayed an increase in ROS activity. It was anticipated that *Rag* knockout mice would have decreased oxidative stress. However, further trials are required to confirm this result. Preliminary flow cytometry experimentation showed promising variations in immune cell populations between *Eln*^{+/-} and WT. However, further investigation is required.

Conclusions: Identification of specific components of immune response will allow us to better understand the role of inflammation in modulating cardiovascular disease severity in elastin insufficiency. Currently, there is no therapy that can restore normal elastin to those with elastin insufficiency due to the dynamic and complex nature of elastic fiber assembly. By suggesting new targets for immunotherapy of affected individuals, physicians will be provided a way to minimize risk for those with the life-long risk of vascular disease.

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Zhao, Johnny

Medical Student

Dean's Fellowship

Summer Research Program

Department of Orthopaedic Surgery, Washington University in St. Louis School of Medicine

Mentor: Jacob Buchowski, MD

Neuromuscular scoliosis and trigeminal neuralgia

Zhao J; Buchowski J

Introduction: Neuromuscular scoliosis is a condition marked by an unnatural bending of the spine in the coronal plane. The disease can be caused by disorders of the central nervous system or by pathology in muscles and peripheral nerves. Trigeminal neuralgia is a debilitating disease in which patients suffer from episodes of intense pain across the distributions of the trigeminal cranial nerve. This case report discusses one patient who reported to our institution with significant neuromuscular scoliosis following implantation of a motor cortex deep brain stimulator (DBS) as treatment for trigeminal neuralgia.

Case Report: The patient presented to our institution with complaints of severe lumbar back pain. Three years prior to presentation she had a DBS placed at an outside facility. Radiographs revealed she had a 53-degree lumbar scoliosis and 47-degree kyphosis of her spine. Given the patient's condition, she underwent a posterior spinal fusion with instrumentation from T4 to the sacrum and ilium, posterior column osteotomies from T10-L1, and transforaminal lumbar interbody fusion from L5-S1. At eight months postoperatively, the patient felt "85 percent" better compared to her preoperative condition. Her scoliosis was reduced to 20 degrees and kyphosis was reduced to 19 degrees. She also took the SRS-22, ODI, and SF-36 questionnaires pre- and postoperatively. Her SRS-22 score increased from 43 to 77, her SF-36 from 29 to 31, and her ODI decreased from 29 to 19.

Conclusions: This is a novel report in the literature of a patient developing neuromuscular scoliosis secondary to DBS placement for trigeminal neuralgia. The deep brain stimulator is directed to the motor cortex, which is responsible for regulating motor control. The stimulator could have changed the efferent innervation of the paraspinal muscles to cause neuromuscular scoliosis. Also, the primary somatosensory cortex, which lies adjacent to the motor cortex, could have been affected as well. Incorrect processing of sensory information could alter the subsequent paraspinal muscle activity. Clinically, this case report is important because it contributes to the understanding of possible side effects of motor cortex deep brain stimulator use and furthers knowledge of the possible mechanisms of scoliosis.

DeNardo Education and Research Foundation Grant

097

Essuman, Kow

Medical Student

DeNardo Education and Research Foundation Grant

Summer Research Program

Division of Pediatric Gastroenterology

Department of Pediatrics, Washington University in St. Louis School of Medicine

Mentor: David Rudnick, MD, PhD

Biomarker discovery in acute liver failure (ALF)

Essuman K; Rudnick D

Introduction: ALF is a serious, frequently fatal condition in which patients without previously unrecognized liver disease present with profoundly impaired liver function of diverse (often undefined) etiology. Although some patients recover spontaneously, many do not survive without liver transplantation. Thus, various algorithms have been developed to identify which ALF patients are most likely to die without (and, therefore, benefit from) liver transplantation. However, such prognostication remains challenging. Thus, an effort to develop more reliable tools for predicting ALF outcomes is a major goal of the NIH-supported multi-center ALFSG. With this in mind, our lab recently discovered that serum levels of alpha-NH₂-butyric acid (Aab) correlated with likelihood of spontaneous survival in a pilot study of pediatric ALF (PALF) patients. The current study was conducted to determine if serum Aab also correlates with clinical outcome in a pilot study of adults with ALF.

Methods: Serum Aab was determined on samples collected at enrollment into the ALFSG from 24 adults with acetaminophen-induced ALF, who either spontaneously survived or died.

Results: In our previous study, the mean serum Aab level across 40 pediatric ALF patients was 22±22 and the range 0-95 micromol/L. Spontaneous survivors exhibited a mean level of 29±27 micromol/L while those who died or were transplanted showed a level of 14±14 micromol/L (p<0.05). In the current study, de-identified sera from adult ALF patients were provided by the ALFSG, and serum Aab was quantified by the St. Louis Children's Hospital Clinical Laboratory without knowledge of clinical outcome. Preliminary results show a mean Aab of 58±56 and range of 12-270 micromol/L across all 24 samples. Comparison of Aab levels between outcomes groups will be performed once such outcomes data are provided by the ALFSG.

Conclusions: The current study will determine if serum Aab levels, which correlated with outcome in our PALF pilot study, exhibit similar correlation with outcomes in a small group of adult ALFSG patients. If this is the case, future studies should test whether incorporation of this biomarker improves ALF and PALF outcomes prediction algorithms.

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Jalalizadeh, Bayan

Medical Student

DeNardo Education and Research Foundation Grant

Summer Research Program

Department of Ophthalmology and Visual Sciences, Washington University in St. Louis School of Medicine

Mentors: Susan Culican, MD, PhD; David Vollman, MD

Developing a screening test to identify macular dysfunction

Jalalizadeh B; Culican S; Vollman D

Introduction: Although morbidity related to visual deficits is significant in individuals over 65, these individuals often do not receive comprehensive eye examinations annually as recommended by the American Academy of Ophthalmology. To minimize morbidity and healthcare costs, we developed a simpler, inexpensive computer-based tool that can screen for age-related macular degeneration (AMD) and other retinal dysfunctions in older adults. The purpose of this study is to perform the screening task on patients with and without AMD to establish a sensitivity of 0.90 or better.

Methods: Eighty adults aged 50 and older with visual acuity of 20/70 or better and no neurological history are participating in the study: forty individuals with AMD, and forty control patients without AMD. Empirical results from the screening tool will be compared with ocular diagnosis to determine parameters for the program's user feedback.

Results: It is anticipated that nearly all individuals in the maculopathy group will respond incorrectly to dynamic stimuli at least one or two times during the test, and most individuals in the control group will make no errors. The actual number of these errors in each arm of the study will be assessed to establish accurate positive or negative test results at the end of the screening task. Based on a former pilot study, it is assumed that the sensitivity will be at least 0.90, with a high specificity as well.

Conclusions: The establishment of the program's sensitivity in detecting AMD will allow for its use as a clinically efficacious screening tool. As an inexpensive, portable program, this tool could have profound implications for the early detection of visual impairment in the elderly throughout the community, allowing diagnosis by physicians and limiting the progression of debilitating diseases such as AMD.

034

Vyhmeister, Ross

Medical Student

DeNardo Education and Research Foundation Grant

Summer Research Program

Mallinckrodt Institute of Radiology, Washington University in St. Louis School of Medicine

Mentor: Adam Wallace, MD

Evaluation of low dose protocol for cerebrospinal fluid shunt head CT

Vyhmeister R; Wallace A

Introduction: Over 30,000 cerebrospinal fluid (CSF) shunts are placed annually in the United States, the majority of which are for the treatment of hydrocephalus. These shunts have a high complication rate which necessitates repeated non-contrast computed tomography (NCCT) scans to assess for malfunction, and consequently predisposes patients to high levels of radiation. A low dose protocol using automatic exposure control and automated tube potential selection has been implemented at St. Louis Children's Hospital (SLCH) to address this issue. The purpose of this study is to evaluate the reduction in radiation dosage achieved by this protocol compared to the standard protocol using fixed parameters.

Methods: A sample of 60 NCCT scans assessing for CSF shunt malfunction were identified, with 30 scans using the standard protocol and 30 using the low-dose protocol. The radiation exposure of the two protocols was compared using the CT dose index ($CTDI_{vol}$) and dose length product (DLP).

Results: The use of the low-dose protocol was found to reduce the average $CTDI_{vol}$ by 39% +/- 11%. All scans were found to be of diagnostic quality by two independent readers.

Conclusions: A low dose pediatric shunt NCCT protocol using technology that automates the selection of both the tube potential and the tube current reduced patient radiation dose compared to a prior protocol performed with fixed parameters. Wider adoption of this protocol may reduce the risks posed to members of this population.

045

Wang, Pengcheng

Medical Student

DeNardo Education and Research Foundation Grant

Summer Research Program

Department of Neurosurgery, Washington University in St. Louis School of Medicine

Mentor: Eric Leuthardt, MD

Modulation of electroencephalography with emotional state of a comatose patient

Wang P; Leuthardt EC

Introduction: The level of consciousness of patients who survive severe acute brain injury is a key prognostic factor for future outcome. Preferential response to family members has been documented in various coma staging systems; however, objective measures of this phenomenon are severely limited. Electroencephalography (EEG) has shown promise as a noninvasive tool to assess brain activity. Here, we attempted to find correlations between a preferential response to a family member and EEG activity in a case study of one comatose patient.

Methods: A pediatric traumatic brain injury (TBI) patient was asked to perform simple motor tasks. Instructions were first provided by his physician and subsequently, in a separate sequence, by his mother. EEG activities were recorded from each interaction and from rest. Spectral analyses of the signals were used to compare both interactions with each other and with baseline to ascertain significant differences in patient response.

Results: Comparison of each trial to its respective baseline revealed no significant amplitude change in the β frequency band typically associated with movement. While spectral comparisons between the mom and physician speaking revealed broadband changes in most electrode channels, this result could not be replicated after normalizing for baseline data taken immediately prior to each trial. Z-score filtering of each trial to narrow the search time-window for significant activity was unsuccessful at improving detection of preferential EEG activity. Overall, differences between EEG activities show low correlation with the particular individual giving instructions.

Conclusions: The apparent manifestation of preferred response could not be correlated with changes within the EEG power spectrum compared to rest. While broadband differences between the two trial conditions could represent an overall change in emotional state, nonspecific activation of multiple frequencies are difficult to extricate from noise generated from slight deviations of electrode position. Additional studies must be conducted to improve the power of this analysis and establish a concrete relationship between the emotional state of a comatose patient and EEG activity.

005

Witt, Jacob S

Medical Student

DeNardo Education and Research Foundation Grant

Summer Research Program

Department of Radiation Oncology, Washington University in St. Louis School of Medicine

Mentor: Clifford G Robinson, MD

A study of the anatomic distribution of brain metastases in HER2 positive breast cancer

Witt J; Robinson C

Introduction: While HER2 positive breast cancer represents approximately 20% of all breast cancer, it is responsible for the majority of CNS metastases related to the disease, and represents a significant source of mortality. Up to half of patients who develop HER2 positive brain metastases will die from these tumors. Despite significant advances in the management of HER2 positive disease outside of the CNS, treatment for intracranial metastases remains difficult. Therefore, prevention of CNS disease is an important consideration for patients with advanced HER2 positive disease. One well established strategy for killing microscopic disease is prophylactic cranial irradiation (PCI), where the brain is irradiated upon discovery of metastatic disease anywhere in the body. However, this often leads to memory and cognitive deficits, which recent research suggests may be associated with damage to the hippocampal region of the brain in particular. With current radiological technologies, it is possible to avoid this region when delivering PCI, and if incidence of metastasis to this region is low, then it should be considered for patients who wish to avoid cognitive and memory deficits associated with PCI.

Methods: Patients with both breast cancer and brain metastases were culled from the OQA tumor registry and Mosaiq from January 2004 through February 2012. HER2 status was determined by diagnostic report of FISH or Herceptest when appropriate. MRIs were then acquired for HER2 positive patients with brain metastases, and distance from the hippocampal zone was determined using the contouring atlas for RTOG 0933. Tumors closer than 1 cm were deemed positive.

Results: At this time we have analyzed 52 patients with HER2 positive breast cancer and brain metastases. While the vast majority of them do not have hippocampal metastases, we would like to add more patients to the set in order to make a more confident recommendation about the feasibility of this treatment option.

Conclusions: We expect to find a low incidence of hippocampal brain metastases in patients with HER2 positive breast cancer with brain metastases. This study is ongoing and final analysis will be presented in the future.

Forum for International Health and Tropical Medicine

019 Benzoni, Nicole

Medical Student

Forum for International Health and Tropical Medicine Fellowship; Dean's Fellowship
Summer Research Program

Department of Surgery, Washington University in St. Louis School of Medicine

Mentor: Joaquin Barnoya, MD, MPH

Congenital heart surgery outcomes at a Guatemalan surgical center's intensive care unit between 2009 and 2013

Benzoni N; Barnoya J; Mazate E

Introduction: Unidad de Cirugia Cardiovascular Pediatrica de Guatemala (UNICARP) was founded in 1997 to improve the access to high-quality care for an estimated 2,000 Guatemalan children born with congenital heart defects each year. To measure this center's performance over time and to determine areas for quality improvement, we compared annual surgical outcome rates between 2009 and 2013.

Methods: A retrospective analysis was conducted using UNICARP's ICU database and medical records. Patients less than 18 years old who underwent cardiac surgery for congenital heart defects between January 2009 and June 2013 were eligible for inclusion. The risk adjustment for congenital heart surgery (RACHS-1) was applied to adjust for annual differences in case mix. Annual mortality, adverse event and nosocomial infection rates were calculated. Infection rates were subdivided into pneumonia, surgical site and other infections rates. ANOVA tests were used to determine P-values for rate differences.

Results: A total of 972 procedures were analyzed. Overall, the adverse event rate was 48.4%, infection rate was 21.6% and mortality was 10.0%. When individual years were compared, annual mortality rates showed no obvious trend or significant difference ($p = 0.2$). Adverse events steadily declined from 60.2% in 2009 to 34.4% in 2013 ($p < 0.001$). Infection rates increased and peaked at 28.4% in 2012, but had decreased to 15.6% by June of 2013 ($p = 0.03$). Pneumonia rates displayed a similar trend and reached 13.8% in 2012 before decreasing to 7.44% in 2013 ($p < 0.001$).

Conclusions: Overall this study shows that while adverse event rates improved significantly, mortality and nosocomial infections rates increased over the same time period and provide area for quality improvement. Further research will be necessary to designate which programs could be best implemented.

079 Ma, Lisa S

Medical Student

Forum for International Health and Tropical Medicine Fellowship; Dean's Fellowship

Department of Medicine, University College London

Department of Internal Medicine, Washington University in St. Louis School of Medicine

Mentors: Alastair O'Brien, MD, PhD; Jeffrey Crippin, MD

An investigation of the anti-inflammatory effects of prostaglandin E2 on leukocytes

Ma L; Crippin J; O'Brien A

Introduction: The incidence of critical illness is on the rise and mortality has been persistently high. Patients that survive the systemic inflammatory response often have suppressed immune function and are vulnerable to nosocomial infections. This is believed to be a result of prolonged pro-resolution and anti-inflammatory processes. One such mediator, PGE2, has been found elevated in patients with liver cirrhosis and acute liver failure, who have increased susceptibility to secondary infection. PGE2 has been shown to have immunosuppressive effects on neutrophils and macrophages and reduces phagocytosis and NADPH oxidase-mediated killing of bacteria. A better understanding of the action of PGE2 may allow us to modulate its concentrations and restore immune function. The current use of MDMs from healthy volunteers has inadequate sample purity, low cell yield, and wide inter- and intra-personal variability in response.

Methods: We hoped to develop a more reliable model using the Mono Mac 6 cell line. The cells were stimulated with LPS, LTA, and PGN and the immune response was measured in terms of TNF- α production. Neutrophil bacterial killing was assessed by NADPH oxidase activity following stimulation by fMLP.

Results: PGN was determined as the best stimulant, but no clear response was seen in the undifferentiated or differentiated Mono Mac 6 cells when incubated with PGE2 while a decrease in TNF- α production was seen in the MDMs. A time course showed that PGE2 is fast-acting varying incubation times does not make significant difference. We noticed that the undifferentiated and differentiated Mono Mac 6 cells consistently produced much less TNF- α than their MDM counterparts. The neutrophils also showed no change in NADPH oxidase activity with the addition of PGE2, however the unexpected inhibitory effect of cytochalasin B suggests there may be experimental error.

Conclusions: While the immunosuppressive effects of PGE2 on MDMs was successfully reproduced, further work needs to be done before the effects of PGE2 on the Mono Mac 6 cells and neutrophils can be determined. Taking the greatly decreased TNF- α production in mind, the Mono Mac 6 cell line may not be an ideal model.

081

Ma, Yuntong

Medical Student

Forum for International Health and Tropical Medicine Fellowship; Dean's Fellowship
Summer Research Program

Department of Epidemiology and Molecular Microbiology and Immunology, John Hopkins Bloomberg School of Health
Department of Obstetrics and Gynecology, Washington University in St. Louis School of Medicine

Mentors: Patti E Gravitt, PhD; Jeffrey F Peipert, MD, MPH, MHA

Development of culturally tailored educational leaflets on HPV and cervical cancer for a multiethnic population in Malaysia

Ma Y; Gravitt PE

Introduction: Cervical cancer is the second most common cancer among women worldwide. In Malaysia, poor knowledge of HPV and a lack of understanding of its connection to cervical cancer have been identified as major reasons for the persistent low vaccine uptake and screening prevalence. However, little has been done to systematically address the issue. We have developed culturally tailored educational materials on HPV and cervical cancer for a multi-ethnic Malaysian population.

Methods: A review of literature on women's HPV and cervical cancer information needs was conducted. Research into existing educational materials developed for ethnic populations in other countries provided guidance in developing the content of our educational material.

Results: Educational prototypes were created in three languages—English, Bahasa Malaysia, and Chinese—to target each of Malaysia's three main ethnic groups. The prototype was piloted, reviewed, and revised based on feedback to create a final product.

Conclusions: We have developed educational leaflets to provide information to a multi-ethnic Malaysia population regarding HPV, cervical cancer, and prevention. When distributed in clinics, they should increase awareness of HPV and cervical cancer in women and encourage behavioral change to pursue HPV vaccination and Pap screening. They contribute to the body of literature on education for a multi-ethnic Malaysian population useful to both patients and the health professionals whom serve them.

033

Moses, Lindsey

Medical Student

Forum for International Health and Tropical Medicine Fellowship; Dean's Fellowship
Summer Research Program

Victoria Hospital, Cape Town, S. Africa

Department of Neurology, Washington University in St. Louis School of Medicine

Mentors: David Clifford, MD; Claudine Fermin, MD; Avril Whate, RN NP

Healthcare challenges and managing the HIV epidemic in South Africa

Moses L; Clifford D; Fermin C; Whate A

Introduction: The first case of HIV infection in South Africa was reported in 1982 and marked the beginning of what would later become one of the most devastating epidemics in the world. In 1990 the prevalence of HIV in South Africa was just below 1%, in 1995 it had risen to 10.4% and in 2000 to 22.4%. The current prevalence is estimated at 17% but in some regions, such as KwaZulu-Natal it is as high as 1 in every 3 adults in the population. The country has made great strides in reducing the spread of HIV through multiple countrywide campaigns and the rate of new infections has dropped 41% since 2001.

Methods: My goals during my time in South Africa were to explore the social factors that led to such a rapidly growing epidemic, to learn about how the country responded to the epidemic and how ongoing efforts to control and reduce the burden of disease are being carried out, and to learn about how HIV currently impacts everyday life and interactions as well as the health care system.

Results: A multitude of opportunities and experiences allowed me to fulfill the goals I had set for the summer and come back with a much deeper understanding of the impact of HIV on South Africa's people and health care system. Several of these opportunities included learning about the protocols for HIV treatment and how they have changed over time, particularly with the introduction and then withdrawal of PEPFAR funding, through working with patients who have HIV in the setting of both a clinic and a support group, and through working at several hospitals and observing the high prevalence of HIV and TB, specifically among Zulu people and other subgroups of the population who suffered the greatest inequities under the apartheid regime.

Conclusions: The combination of a high prevalence of HIV with increasing incidence of chronic diseases and other co-morbidities has left South Africa with the highest per capita health burden of any middle-income country in the world. Though faced with many challenges including a shortage of resources, both human and technological, the country is working to reduce the burden of HIV through multiple means including mass media and education of the public.

Xu, Wen

Medical Student

Forum for International Health and Tropical Medicine Fellowship; Dean's Fellowship

Summer Research Program

Immunological Regulation and Vaccinology Unit, Pasteur Institute, Paris

Department of Pathology and Immunology, Washington University in St. Louis School of Medicine

Mentors: Richard Lo-Man, PhD; Andrey Shaw, MD**The role of IL-19 and IL-20 in the modification of naïve CD4+ T cell polarization**

Xu WZ; Lo-Man R

Introduction: IL-19 and IL-20 are members of the IL-10 family of cytokine based on structural similarities. They both act on the heterodimeric IL-20 receptor 1 that is highly expressed in normal skin, testis, and lung, but their overexpression have been associated with psoriasis and asthma. The main source of IL-19 and IL-20 is monocytes, but neonatal dendritic cells also express them when stimulated by certain viruses and bacteria. In addition to IL-19 and IL-20, dendritic cells secrete various other cytokines (e.g. IL-1, IL-6, IL-10, IL-12, and IL-23) that polarize naïve T cells to Th1, Th2, Th17, or Treg depending on the immunological environment. Since newborns are especially susceptible to viral infections in the first several months of life due to the bias of their immune system toward Th2 response and the difficulty of eliciting a Th1 response, we aim to investigate the potential link between the influence of IL-19 and IL-20 when neonatal DCs are priming CD4+ T cells.

Methods: Peripheral blood mononuclear cells (PBMC) are isolated from adult donors by density gradient centrifugation. Naïve T cells are isolated through magnetic enrichment and sorting based on the presence of CD4 and CD45RA on the cell surface. Cells are activated in anti-IgG coated wells with medium containing anti-CD3, anti-CD28, and cultured with cytokines that polarize T cells with or without the addition of IL-19 or IL-20. Extent of polarization was determined by sandwich ELISA of the levels of IFN γ (Th1), IL-13 (Th2), IL-9 (Th9), and IL-17 (Th17) in the supernatants.

Results: The polarization of naïve T cells into Th1, Th2, Th9, and Th17 using the cytokine combinations was successful. The presence of IL-19 and IL-20 did not significantly alter the levels of secreted IFN γ , IL-13, IL-9, or IL-17 by the adult and neonatal T cells in the supernatant under the appropriate polarizing conditions compared to the control group without IL-19 and IL-20. Dose effect of IL-19 and IL-20 on the concentration of secreted cytokines by adult T cells was not observed.

Conclusions: These data suggest that IL-19 and IL-20 do not influence the polarization of naïve adult and neonatal T-cells.

Howard Hughes Medical Institute Summer Medical Fellows Program

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Yu, Jenny

Medical Student

HHMI Summer Medical Fellows Program

Summer Research Program

Division of Rheumatology

Department of Internal Medicine, Washington University in St. Louis School of Medicine

Mentors: Dorothy Sojka, PhD; Wayne Yokoyama, MD

Liver-resident natural killer (lrNK) cells are developmentally distinct from conventional splenic natural killer (csNK) cells

Yu JL; Sojka DK; Pak-Wittel MA; Yokoyama WM

Introduction: Historically, researchers have focused on csNK cells and attributed all NK functions to the csNK cells. However, the Yokoyama laboratory found two subsets of NK cells in the liver: a CD49a-DX5⁺ population, which are also found circulating in the blood and in the spleen, and a liver-resident CD49a-DX5⁻ population. Ongoing research in two transcription factor knockout (KO) mouse lines, referred to as KOA and KOB suggests that the lrNK population is a different NK cell lineage from csNK. In KOA, the csNK cells do not develop, while the KOB mouse lacks lrNK cells. To further characterize the phenotype and development of lrNK cells, we have analyzed cell surface markers and cytokine production in wildtype and KOA mice.

Methods: Mouse liver and splenic cells were labeled with antibodies which were detected by flow cytometry and functional assays were performed.

Results: lrNK cells display an immature NK cell phenotype and more activated state markers. Many conventional Ly49 receptors, which are responsible for self-recognition, are downregulated in CD49a-DX5⁻ cells. Upon cytokine stimulation, lrNK cells have higher expression of certain cytokines than CD49a-DX5⁺ despite their immature phenotype. Expressions of analyzed cell surface markers and cytokines in CD49a-DX5⁻ cells are not significantly different between wildtype and KOA mice. Proper development of CD49a-DX5⁻ cells is therefore not dependent on this specific transcription factor expression while CD49a-DX5⁺ development is.

Conclusions: The results suggest that the liver-resident CD49a-DX5⁻ NK cells are phenotypically distinct from conventional CD49a-DX5⁺ NK cells and are a separate lineage from the traditionally studied NK cells. Further research into the function of this recently defined NK cell population may reveal new information regarding the immune system's role in certain diseases.

MD5

108

Williams, Alton

Medical Student, MD5 Candidate

Department of Psychiatry, Washington University in St. Louis School of Medicine

Mentor: Kevin Black, MD

Morphometric analysis of the basal ganglia and thalamus in children with Tourette Syndrome

Williams AC; Black K

Introduction: Prior brain imaging and autopsy studies have suggested that structural abnormalities of the basal ganglia (BG) nuclei may be present in Tourette Syndrome (TS). These studies have focused mainly on the volume differences of the BG structures and not their anatomical shapes. Shape differences of various brain structures have been demonstrated in other neuropsychiatric disorders using large-deformation, high dimensional brain mapping (HDBM-LD). A previous study of a small sample of adult TS patients demonstrated the validity of the method, but did not find significant differences from control subjects. Since TS usually begins in childhood and adult studies may show structure differences due to adaptations, we hypothesized that etiologically relevant differences in BG and thalamus geometry and volume might be better characterized in children.

Methods: T1 weighted MR scans were collected in 13 children with TS and 16 healthy, tic-free controls. The primary outcome measures were the first 10 eigenvectors for each structure that are derived using HDBM-LD methods and represent the majority of the geometric shape information. We also investigated the volumes of each structure adjusted for whole brain volume, and compared hemispheric right/left asymmetry.

Results: We found no statistically significant differences between the TS subjects and controls in volume, shape, or right/left asymmetry.

Conclusions: This study fails to replicate some previous studies that found reduced caudate volume or other BG structural differences in TS. This study represents one of the first efforts to study shape as opposed to volume of the BG in TS, but power was limited by sample size. We are currently analyzing imaging from a much larger study population ($n > 400$) from which we expect to have some preliminary results soon.

Movement Science Program (MSP)

120

Cherry, Kendra, PT, DPT

Movement Science Program

Program in Physical Therapy, Washington University in St. Louis School of Medicine

Mentor: Catherine E Lang, PT, PhD

Does combining a partial NMDA receptor agonist with motor training result in greater learning?

Cherry KM; Lenze EJ; Lang CE

Introduction: Neurological rehabilitation involving intensive motor training leads to clinically meaningful improvements in function, but rehabilitation alone is unable to eliminate many of the impairments associated with neurological injury. Thus, there is a growing need for interventions that combine modalities, such as a pharmacological agent and behavioral therapy, in order to optimize recovery. D-cycloserine (DCS) is a pharmacological agent thought to enhance learning and memory via its action as a partial *N*-methyl-D-aspartate receptor (NMDAR) agonist. The purposes of this study were to determine if: 1) DCS, in combination with motor training, promoted learning of a primary motor task; 2) DCS augmented learning of a secondary motor task; 3) DCS enhanced generalization to a similar, unpracticed task.

Methods: Forty-four neurologically intact adults participated in this two-session, double-blind study. Session one consisted of baseline motor assessment, subject randomization, and oral administration of DCS or placebo (250mg). Subjects then participated in motor training consisting of massed practice of a balance task and a simulated feeding task. Subjects returned the following day for posttest motor assessment.

Results: Using repeated measures ANOVAs, we found that all subjects had improved performance from pretest to posttest on the balance task ($p < 0.001$) and the simulated feeding task ($p < 0.001$). Subjects who were given DCS prior to motor training did not show enhanced motor learning on either the balance task ($p = 0.784$) or the simulated feeding task ($p = 0.344$) compared to subjects given placebo. Moreover, the learning that occurred as a result of training on the primary balance task did not generalize to a similar, untrained balance task ($p = 0.09$).

Conclusions: While our findings in healthy adults were negative, this combination therapy might be efficacious in individuals with neurological injury who are known to have diminished NMDAR function. Future research should examine the effects of combining DCS and motor training in people with neurological injury. This methodology could also serve as an assay for testing different agents intended to promote motor learning.

No

Poster

Cheuy, Victor, MS

Movement Science Program

Program in Physical Therapy, Washington University in St. Louis School of Medicine

Mentor: Michael Mueller, PT, PhD

Intrinsic foot muscle deterioration and metatarsophalangeal joint angle in people with diabetes and neuropathy

Cheuy VA; Hastings MK; Commeyan PK; Ward SR; Mueller MJ

Introduction: Metatarsophalangeal joint (MTPJ) deformity is associated with increased skin breakdown and amputation. The aims of this study were to compare intrinsic foot muscle (IFM) deterioration (ratio of adipose to lean muscle volume), and physical performance in subjects with diabetes mellitus and peripheral neuropathy (DMPN) to controls, and determine their associations with MTPJ angle.

Methods: 23 DMPN subjects (59 ± 10 years) and 12 age-matched controls (57 ± 14 years) were studied. Radiographs and MRI were used to measure second MTPJ angle and IFM volume and deterioration through segmentation of tissue types by image signal intensity. The Foot and Ankle Ability Measure (FAAM) evaluated physical performance.

Results: The DMPN group, compared to controls, had almost half the lean muscle volume (18.2 ± 11.0 vs. 31.6 ± 12.8 cm³, $P = 0.003$) and twice the adipose tissue infiltration into the IFMs (17.9 ± 10.5 vs. 9.3 ± 3.8 cm³, $P = 0.001$). IFM deterioration (ratio of adipose to lean muscle volume) was almost 5 times higher in the DMPN group (1.58 ± 1.20 vs. 0.32 ± 0.15 , $P < 0.001$), and FAAM scores were decreased (65.1 ± 24.4 vs. 98.3 ± 3.3 %, $P < 0.001$). The correlation between IFM ratios and MTPJ angle was $r = -0.51$ ($P = 0.01$) for all DMPN subjects, but increased to $r = -0.81$ ($P < 0.01$) when only DMPN subjects with IFM ratios > 1.0 were included. No significant correlation was found between second MTPJ angle and FAAM scores.

Conclusions: This study shows DMPN subjects have almost 5 times as much IFM deterioration and lower physical performance than controls; and muscle deterioration is associated with second MTPJ angle, an important risk factor for skin breakdown and amputation. Additional research is required to understand how IFM deterioration interacts with other impairments leading to forefoot deformity and skin breakdown.

Marich, Andrej, PT, DPT

Movement Science Program

Program in Physical Therapy, Washington University in St. Louis School of Medicine

Mentor: Linda Van Dillen PT, PhD**Lumbar movement pattern displayed during a clinical test and a functional activity in people with and people without low back pain**

Marich AV; Bohall SC; Sorensen CJ; Zou D; Van Dillen LR

Introduction: Repetitive lumbar movement patterns used during functional activities are a potential mechanism for the development and course of mechanical low back pain (LBP). Lumbar movement patterns assessed during clinical tests are assumed to reflect those used during functional activities. The relationship between lumbar movement patterns during clinical tests and functional activities, however, has not been examined systematically. Our purpose was to examine, in people with and without LBP, the relationship between the lumbar movement pattern used during a clinical test (forward bending) and a functional activity test (picking up an object). We hypothesized that the pattern used during the 2 tests would be positively related.

Methods: Kinematic data were collected using an 8-camera motion capture system as participants performed forward bending and picking up an object. Starts and stops of segment movements were identified and segment movement times were calculated. The movement pattern variable was the difference in time between the start of pelvic segment motion and lumbar segment motion, normalized to total movement time (t-diff). A bivariate correlation was calculated between the t-diff variable for forward bending and picking up an object.

Results: 9 people with LBP (LBP group; age 33 ± 11 yrs, 6 men) and 7 people without LBP (NoLBP group; age 29 ± 7 yrs, 3 men) participated. For the entire group, the t-diff variables for forward bending and picking up an object were significantly related ($r = .71$, $p < .01$). The relationship between the t-diff variables for the 2 tests also was significant for the LBP group ($r = .66$, $p = .05$), and the NoLBP group ($r = .87$, $p = .01$).

Conclusions: The lumbar movement pattern during the clinical test of forward bending and the functional activity test of picking up an object were moderately related in both people with, and people without LBP. Our findings support the use of the forward bending test during an assessment to gain insight into the lumbar movement pattern a person may use repetitively during daily functional activities.

NIDA T32 Training Program in Epidemiology, Services and Prevention Research

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Balan, Sundari, PhD

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Mentors: Rumi Kato Price, PhD, MPE; Sarah Gehlert, PhD

Couple dyad modeling of post-traumatic stress symptoms and drinking levels among National Guard service members and their partners: Role of life/family disruption concerns

Balan S; van den Berk-Clark C; Widner G; Shroff MV; Scherrer J; Price RK

Introduction: Post traumatic symptoms (PTSS) and drinking levels may be high among National Guard service members who recently returned from deployment. Partners may also be affected. We examined the role of family disruption concerns (e.g., concerns about employment, relationships) because of deployment and depression in relation to PTSS symptoms and drinking levels.

Methods: National Guard service members (Men =171) and their partners (Women=171) attending a National Guard reintegration event were recruited to participate in an in-depth telephone interview at approximately 2-4 months post deployment. Only heterosexual dyad couples currently cohabitating with a partner are included (n=171 couples) and were separately interviewed. The outcome measures are sum of PTSS and Alcohol use disorder identification test items (AUDIT). Predictors of interest are life concerns, PTSS (for drinking levels) and AUDIT (for PTSS) for self, gender, depressive symptoms, combat deployment, pre-deployment negative life events, and demographic covariates. Initial analysis examined types of concerns associated with service members and partners' PTSS and drinking levels. Couple level analysis using multi-level modeling techniques to account for non-independence covered relationships between various predictors in relation to PTSS and drinking levels. Additional analysis examined the relation between concerns, depressive symptoms and PTSS/ drinking levels.

Results: Drinking was higher among service members but no differences in PTSS were observed. Similar concerns were associated with PTSS for service members and their partners. Individual's own concerns exacerbated both PTSS and drinking levels. Drinking levels were higher among couples with similar levels of concerns.

Conclusions: Concerns over family disruption present an important ecological factor that exacerbates both PTSS and drinking levels. Programs should consider utilizing active problem solving for such concerns when providing mental health services among both service members and their partners.

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Comparison of Attention-Deficit/Hyperactivity Disorder (ADHD) subtypes, substance use and use disorders

De Alwis D; Lynskey MT; Reiersen AM; Agrawal A

Introduction: Individuals with Attention-Deficit/Hyperactivity Disorder (ADHD) are more likely to report substance use and misuse. However, the relationship between DSM-5/DSM-IV ADHD subtypes (Predominantly Inattentive, Predominantly Hyperactive-Impulsive and Combined), substance use, and DSM-IV abuse/dependence is not clearly understood. This study utilizes nationally representative data to explore the relationship between ADHD subtypes, substance use and SUD.

Methods: Data were obtained from the National Epidemiological Survey of Alcohol and Related Conditions (NESARC) which is a nationally representative sample of adults aged 18 years and older (N=34,653). Face-to-face surveys were used to obtain information related to ADHD symptom criteria and lifetime use and DSM-IV abuse/dependence of alcohol, nicotine, cannabis, cocaine, sedatives, stimulants and heroin/opiates. Comparisons were made between the three ADHD subtypes and inattentive and hyperactive-impulsive symptom counts.

Results: The ADHD-combined subtype showed stronger associations with substance use and misuse, but statistically significant differences were not apparent across the three ADHD subtypes. Nicotine use (odds ratios ranging from 1.46-1.60) and nicotine dependence (odds ratios ranging from 1.42-1.92) showed elevated associations with all three ADHD subtypes.

Hyperactive/impulsive symptoms were associated with the initiation and SUD across all of the substances (for all substances, $p < .05$). Inattentive symptoms were associated with initiation, but progression to SUD was limited.

Conclusions: Results suggested ADHD to be correlated with substance use and misuse. There were no differences in the rates of substance use and SUD across the three ADHD subtypes. Hyperactive/impulsive symptoms were associated with initiation and misuse, suggesting that hyperactive/impulsive symptoms before age 17 years may be an important precursor for substance use initiation and SUD.

Office of the Provost, Diversity & Inclusion Grant

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Cloning and expression of ESR1-AKAP12 fusion protein involved in hormone insensitivity in ER+ breast cancer patients

Chimezie OS; Ellis MJ

Introduction: The Cancer Genome Atlas (TCGA) discovered an in-frame fusion event between the ESR1 (encoding the alpha isoform of Estrogen Receptor (ER α) and AKAP12 (encoding A Kinase Anchor Protein 12). This fusion was detected in an ER+/HER2- luminal B breast cancer patients who have developed resistant to endocrine treatment. This ESRI-AKAP12 fusion gene is very similar to another fusion gene (ESRI- YAP1) that has been previously discovered and studied. In this fused gene, the hormone-binding domain and activation function 2 (AF2) of ER α and the class type 1 Src Homology (SH3) is lost in AKAP12. In this study, we hypothesize that the fusion between ESRI that lacks the hormone binding domain and AKAP12 without SH3 domain could lead to the production of ER that can confer resistance to estrogen therapy.

Methods: We generated three constructs: ESR1 (1-365aa), AKAP12 (107-1782aa) and ESR1-AKAP12 using the pEGFP-n3 vector. The generated constructs will be transferred into a lentiviral vector (pFLRu-FH) that will be transfected into ER+ breast tumor cell lines to determine if forced ESR1-AKAP12 expression can confer hormone-independent growth of ER+ cells.

Results: Using primer design and PCR amplification of (ESR1 (1-365aa), AKAP12 (107-1782aa) and ESR1-AKAP12), we generated these 3 constructs. We sequenced the construct and confirmed that there were no mutations. We were able to successfully insert the generated gene constructs into a transformation vector (pEGFP-n3) that contains a Green Fluorescent Protein (GFP) tag. A Western blot analysis was performed on these constructs which showed that the proteins were being expressed.

Conclusions: The transformation constructs were successfully cloned. Future experiments would focus on the 3 constructs into a pFLRu-FH vector and stably expressing them in ER+ cell lines. This will be followed by growth analysis to monitor their response in the presence and absence of estrogen.

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Growth of mouse intestinal crypts is controlled by myofibroblast secretion of growth regulatory factors

Obi J; Rubin DC

Introduction: Stromal-epithelial interactions are required for normal morphogenesis and have a critical role in regulating proliferation of epithelial tissues. The intestinal crypt contains gut stem cells that differentiate into the four major intestinal cell types. These stem cells are rapidly dividing and appear to play a role in intestinal homeostasis and epithelial regeneration. Stromal myofibroblasts surround the crypts and have been thought to play a role in maintaining the normal intestinal stem cell niche. The niche regulatory factors secreted by myofibroblasts have been incompletely characterized. The overall goal of these experiments is to determine whether myofibroblast conditioned media can support the growth of intestinal crypts into organoids and to compare crypt growth in conditioned media vs. standard growth factor (GF)-enriched media.

Methods: Mouse crypt cells were isolated from the proximal segment of the jejunum, placed in matrigel and grown in crypt media consisting of supplements and antibiotics, for three days. On day 4, crypt cells were grown in either wild-type conditioned media or control GF media. On days 6-8, photographs of the organoids were taken and cyst diameter, crypt bud length, bud number, and the area of the entire organoid were measured.

Results: Crypts survived and grew into organoids in myofibroblast conditioned media. Cyst diameter, bud length, bud number, and organoid area were significantly increased in crypts grown in conditioned vs. GF media (*p< 0.05).

Conclusions: Secreted factors from myofibroblasts are sufficient to support crypt growth into organoids. Myofibroblast conditioned media further enhances growth of crypts compared to GF enriched media. Myofibroblasts play a role in the stem cell niche by secreting biologically significant concentrations of growth regulatory factors to support crypt growth, budding and stem cell expansion, and differentiation. Future studies will focus on identifying the specific secreted factors that contribute to the niche.

072 Osafo, Nina D

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Is the Rivermead Post-Concussion Questionnaire a valid tool for diagnosing traumatic brain injury in the acute setting?

Osafo N; Lewis L

Introduction: The Rivermead Post-Concussion Symptoms Questionnaire (RPQ) is a 16-item, 5-point Likert scale survey, which measures severity of symptoms of traumatic brain injury (TBI). The objective of this study is to determine if the RPQ can differentiate between TBI and non-TBI subjects in the acute setting. A previous study split the RPQ into two separate scales, RPQ 3 and RPQ 13. Taken separately, the RPQ 3 appeared to be a more reliable determinant of acute TBI.

Methods: We compared RPQ scores between patients presenting to the Emergency Department with TBI and those presenting for any complaint with no history of TBI (control subjects). Patients were excluded for the following: Degenerative neurologic disorders, psychiatric disease, recent (in the past 3 months) TBI, organ failure, severe pain, pregnancy, incarceration, or unable to understand English. The RPQ was administered by trained study personnel to 57 consenting subjects with TBI and 68 without TBI who met the remaining selection criteria. Mean total RPQ scores, as well as mean scores for the RPQ 3 and RPQ 13 were calculated for both groups and compared using a two-sided t-test.

Results: The mean total RPQ score was not significantly different between TBI and controls (13.6 vs. 11.0; $p=0.2$), nor was the RPQ 13 (10.4 vs. 9.0; $p=0.41$). However, RPQ 3 mean scores were significantly different between groups (3.26 vs. 2.02; $p=0.03$).

Conclusions: The RPQ score did not differentiate between subjects with and those without acute TBI, however the RPQ -3 showed significantly higher scores in subjects with acute TBI than in non-TBI controls. Our results suggest that a better and simpler discriminator would be to simply use the RPQ -3 alone to differentiate between those suffering from TBI and those who are not.

010 Rodgers, Ariel J

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The utility of pre-operative biopsy for suspicious lung nodules

Rodgers A; Puri V

Introduction: It has been questioned whether or not preoperative lung biopsies are necessary in the care of the lung cancer patient. We aimed to compare the outcomes of patients who had preoperative lung biopsies and those who did not have preoperative lung biopsies before surgical resection.

Methods: A retrospective study was conducted reviewing patients who had undergone lung resection for known or suspected early stage lung cancer at Barnes-Jewish Hospital between 1/1/2000 and 12/31/2012. Data on participant demographics, preoperative, intraoperative and postoperative variables were reviewed from medical records, hospital databases and surgeons' clinical charts. Statistical comparisons were performed using t-test for means, χ^2 test for categorical variables and Wilcoxon's rank-sum tests for medians.

Results: 152 patients from the database had pre-operative lung biopsies. Of the 152 patients who had preoperative biopsies, 34 had biopsy-related complications. The majority of these complications were pneumothoraces. Comparing the patients who had a preoperative pulmonary biopsy with the patients who did not, the demographics and co-morbidities were similar, but on average, the patients who had a preoperative biopsy were older than the patients who had not. Across the two groups, the incidence of postoperative complications was similar. Patients who had preoperative biopsies had longer hospital stays compared to the patients who had not (6.64 days – preoperative biopsy vs 4.09 days – no preoperative biopsy, $p=0.000$).

Conclusions: Having a preoperative pulmonary biopsy prior to lung resection for suspected lung cancer is associated with older age and longer hospital stays for the eventual lung resection. The incidence of biopsy-related complications is acceptable. Patients who did not have biopsies previous to lung resection were found to have a higher likelihood of benign pathology. It is possible that preoperative lung biopsies can avoid unnecessary lung resection for benign pathology.

Salib, Christopher G

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Mentor: Scott J Luhmann, MD

Radiographic outcomes of patients treated with shilla growth guidance system and definitive posterior spinal fusion

Salib CG; Luhmann S

Introduction: The purpose of this study is to evaluate the outcome of patients who had undergone the SHILLA™ GROWTH GUIDANCE SYSTEM (SGGS) procedure for management of scoliosis of the growing spine and subsequently underwent definitive posterior spinal fusion (PSF).

Methods: This was a retrospective study from a single center, of pediatric (skeletal-immature) patients who initially underwent SGGS for management of scoliosis $\geq 50^\circ$, and later underwent PSF as definitive treatment (at or near skeletal maturity). The study population consisted of 10 patients whose mean ages at SGGS was 9.0 y (3.5 to 11.9 y) and at PSF 13.4 y (10.3 to 15.9 y).

Results: The initial major curve was 61.0° (51° to 85.3°) and decreased post-SGGS to 24.5° (59.1% improvement). During the interval between SGGS and definitive PSF (mean 4.3 y) the major curve increased to 56.6° (31.7% increase), which then decreased to 30.6° (45.9% improvement) at the definitive PSF. Overall the major curve from initial (pre-SGGS) to final postop PSF improved 55.9% (61.0° to 26.9°). Initial T1-S1 length was 33.0 cm and 40.5 cm at final follow-up, a 7.4 cm increase. There were minimal changes in sagittal alignment over the study period: T5-T12 a 2.4° decrease, T10-L2 a 4.3° decrease, and L1-S1 a 4.2° increase. Of the 10 patients, 2 developed proximal junctional kyphosis during the study period. During treatment with the SGGS, 7 of the 10 patients underwent revision of the SGGS, with a mean of 1.7 revisions. Hence the overall revision rate for all 10 patients was 1.2. The mean length of time between PSF and final follow-up was 1.3 y (0.1 y to 2.5 y). Nine of the ten patients had a SGGS utilizing Shilla set plugs and one had a modified construct using CMAS fixation for dynamic fixation.

Conclusions: The conversion to a definitive fusion from the SGGS procedure is a safe and effective alternative treatment for skeletally immature patients, allowing them to grow with guidance to skeletal maturity without repeated surgical intervention.

Otolaryngology NIH T32 Physician Scientist Program (PSP)

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Blonski, Allison

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Otolaryngology NIH T32 Physician Scientist Program; Dean's Fellowship

Summer Research Program

Program in Occupational Therapy, Washington University in St. Louis School of Medicine

Mentor: Allison King, MD, MPH

Hearing loss in children treated with platinum-based chemotherapies – a systematic review

Blonski A; King A; Hayashi S; Fowler S; Stoll C

Introduction: The drugs cis- and carboplatin are common chemotherapies used in pediatric populations. One side effect of these drugs is high-frequency hearing loss. Though this toxicity is considered particularly severe in children, previous studies show vast variation in attempts to quantify its incidence. Understanding this ototoxicity more precisely would allow for improved assessment of the risks associated with these therapies. This systematic review of literature on this topic aims to determine the reason for this wide range of incidence and establish a more precise estimate of the occurrence of this ototoxicity.

Methods: Using methods established for conducting systematic reviews, inclusive search terms were generated and run through multiple databases. Citations were excluded if they did not contain quantifiable data, the population of interest, exposure to platinum-based chemotherapies, or properly defined measures of hearing loss. Included studies were reviewed by two researchers who extracted data pertaining to patient age, diagnosis, platinum drug dosage, follow up length, types of hearing tests performed, and hearing test outcomes. Following data extraction, the two researchers verified their results and corrected any discrepancies by consensus.

Results: In this ongoing study, early results show a wide range of reported incidences, due in part to the variety of audiometric measures used to define hearing loss. Currently, the Brock grading scale is the most commonly used measure and reports an incidence of hearing loss ranging from 0 to 79.4% with a mean of 33.1%. Further work is anticipated to show similar variation in other measures of hearing loss due to a lack of standard for "significant" hearing loss.

Conclusions: The wide range of reported incidences reflects the need to better define hearing loss in this population. Newer grading scales for hearing loss may provide a way to better standardize assessment of high-frequency hearing loss in children. Further research should attempt to incorporate long-term effects of this hearing loss on language development, which could be a factor in academic, social, and vocational outcomes in these cancer survivors.

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Fischer, Caroline

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Summer Research Program

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Mentors: Judith Lieu, MD, MSPH; Jay Piccirillo, MD, FACS

Unilateral hearing loss is associated with a negative effect on language scores in adolescents

Fischer C; Lieu J

Introduction: Unilateral hearing loss (UHL) has been associated with a significant negative effect on standardized language tests in children. Adults with UHL have reported significant hearing-related disability. However, little is known about how this delay in children translates into adolescence. This is the first study to compare language scores of adolescents with UHL to controls with normal hearing (NH).

Methods: We conducted a case-control study of 12-17 year-old adolescents with UHL (n=20) compared with sibling controls with NH (n=13). Scores on the oral portion of the Oral and Written Language Scales (OWLS) and the Clinical Evaluation of Language Fundamentals (CELF) were the primary outcome measures. Standardized intelligence scores were used as a secondary outcome measure.

Results: Adolescents with UHL demonstrated worse overall and expressive language scores than controls, (97 vs. 114; $P = 0.002$ and 99 vs. 114; $P = 0.004$) and had significantly lower full (98 vs. 111; $P = 0.016$), verbal (101 vs. 117; $P = 0.029$), and performance IQ (95 vs. 107; $P = 0.035$).

Conclusions: These findings suggest that UHL in adolescents is associated with a negative effect on standardized language scores and IQ. They also demonstrate that the developmental gap between children with UHL and children with NH does not resolve as the children progress into adolescence and may even widen as the children grow older. Therefore, these results strongly encourage implementation of early intervention for children with UHL to prevent speech-language delays. More studies in adolescents are warranted to evaluate educational outcomes.

Mishra, Shruti

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Otolaryngology NIH T32 Physician Scientist Program; Dean's Fellowship

Summer Research Program

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Mentor: Timothy E Hullar, MD**The role of head movements in sounds localization**

Mishra S; Hullar T

Introduction: Sound localization is critical for living. The ability to localize sound is very different among people. In particular, sound localization is a critical deficit among people with unilateral hearing loss. Sound localization depends on many factors, including binaural and spectral cues. The purpose of the present work was to determine the presence of a non-auditory input contributing to sound localization by testing the influence of head movement on sound localization.

Methods: We tested the benefit of head movement when sound was either presented in front of the subject (centered around zero degree azimuth) or to the side of the subject (centered around 90 degree azimuth) on 12 young, normal-hearing individuals. In both experimental conditions, we tested the effect of head-free vs. head-fixed listening, bilateral vs. unilateral listening, and one-second vs. three-second stimulus duration.

Results: We found that head-free vs. fixed and bilateral vs. unilateral listening significantly affected resolution of front/back ambiguity, while only the bilateral vs. unilateral listening condition significantly affected resolution of left/right ambiguity. We additionally found that head movement was useful in resolving front/back ambiguity when the stimulus was at least one second for bilateral listeners or three seconds for unilateral listeners.

Conclusions: The results of this study suggest that head movement is useful when the sound is presented to the side of the listener and not when it is presented to the front of the listener. This implies that head movement can be a critical cue to improve sound localization, and factors that contribute to head localization accuracy (including efferent, vestibular, proprioceptive, visual cues) are previously unrecognized, critical factors in sound localization.

Rehabilitation and Participation Science (RAPS) Doctoral Program

118

Babulal, Ganesh, MOT, OTR/L

Rehabilitation and Participation Science (RAPS) Doctoral Program
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Mentors: Lisa Connor, PhD; Carolyn Baum, PhD

The impact of cognition and emotion on performance after a first stroke

Babulal GM; Huskey T; Connor LT

Introduction: During stroke rehabilitation, emotional sequelae and cognitive impairments are not salient as physical impairments, yet they also limit functional progress. Cognition and emotion play crucial roles in post-stroke recovery; however, the literature is unclear as to the degree to which impairments in both domains impacts performance and the resulting impact on clinical treatment.

This study will obtain an estimate of the effect of emotion, cognition, and their interaction on performance during the early recovery period after stroke.

Methods: Measure the extent to which emotion, cognition and their interaction 1-week post-stroke predicts performance 3-months for first stroke survivors (n=40) via linear regression. Compare the relationship between post-stroke survivors and healthy controls (n=40) via linear regression.

Anticipated Results: We hypothesize that cognition, emotion, and their interaction one week post-stroke will predict performance in daily activities at 3 months post-stroke. We anticipate, patients with mood disruptions and impaired cognition will perform significantly worse at 3 months than patients with a deficit in cognition or mood ($p < .05$). The multiplicative effect of deficits in both emotion and cognition will lead to poor performance. Further, stroke survivors will have a different predictive relationship from age, gender, race and education matched controls.

Anticipated Conclusions: The results of this study will show that emotion and cognition can predict performance and should be considered as important as physical consequences in stroke recovery. The combined effect of impairments in both emotion and cognition leads to increased performance deficits, thus, demonstrating the strong relationship between these two constructs. More importantly, goals and treatment could be directed to helping alleviate these impairments and in turn, increase the efficacy of rehabilitation.

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Foreman, Matthew

Rehabilitation and Participation Science (RAPS) Doctoral Program
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Mentor: Jack R Engsborg, PhD

The role of compensation during virtual reality motor rehabilitation for persons with stroke

Foreman MH; Engsborg JR

Introduction: Virtual reality (VR) is being used for motor rehabilitation for persons with stroke due to its ability to (1) increase repetitive, task-oriented practice required for neuroplastic change, (2) provide immediate feedback, and (3) enhance motivation for therapy. Extensive use of compensatory strategies during VR therapy may inhibit improvements in performance by interfering with mechanisms of motor recovery. The purpose of this project is to develop a VR tool capable of measuring, inhibiting, and shaping compensatory movement involved in the performance of upper extremity tasks during VR therapy for persons with stroke.

Methods: The Microsoft Kinect sensor is used along with The Flexible Action and Articulated Skeleton Toolkit (FAAST) to convert bodily movement into the control of nearly any virtual environment (VE). Actions such as forward and lateral reaching are defined and scaled within the software based on a client's abilities, and VEs can be chosen based on a client's interests. Custom-written software facilitates the monitoring, recording, and feedback related to targeted and compensatory movement along with any post-processing related to joint kinematics. Algorithms for the assessment, restraint, and shaping of compensation are the main aspects of the control software. A virtual event is suppressed or negative feedback is provided according to compensatory movement at the trunk or shoulder beyond an adjustable threshold.

Results: Preliminary results show that it is feasible to use this system for shaping compensation during upper extremity movement. Healthy controls are able to successfully interact with VEs of their choosing within defined and adjustable thresholds of compensatory movement. Participants achieve high numbers of repetitions during short sessions, are receptive and motivated to use the device, and indicate that it would be useful both in the clinic and in the home.

Conclusions: While further development is needed, it is feasible to use the Microsoft Kinect and supporting software to provide a VR interface that can automatically address compensation during the performance of upper extremity VR therapy tasks.

Society of Nuclear Medicine Molecular Imaging Grants and Awards

054

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Society of Nuclear Medicine Fellowship; Dean's Fellowship
Summer Research Program

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Department of Cell Biology and Physiology, Washington University School of Medicine

Mentors: Umar Mahmood, MD, PhD; Koong-Nah Chung, PhD

¹⁸F-fluoroestradiol imaging guides dosing of estrogen receptor targeted therapy

Deng F; Heidari P; Esfahani S; Leece A; Shoup T; Vasdev N; Mahmood U

Introduction: Estrogen receptor (ER) is a key therapeutic target in breast cancer. Fulvestrant, the prototypical selective ER degrader, delays progression of metastatic breast cancer in a subset of patients. However, there are no current methods to account for interpatient pharmacodynamic variability and the optimal dosing regimen is unclear. The effect of fulvestrant on ER functional availability may be evaluable by positron emission tomography (PET) using 16 α -[¹⁸F]-fluoroestradiol (¹⁸F-FES). To assess the potential utility of ¹⁸F-FES-PET in therapeutic dose optimization, we used preclinical models to compare ¹⁸F-FES uptake with other measures of ER expression in response to different doses of fulvestrant.

Methods: ER+ MCF7 human breast cancer cells were incubated with fulvestrant for 24 h. ¹⁸F-FES cellular uptake was compared to semiquantitative assays of ER α protein expression (ELISA) and *ESR1* mRNA expression (qPCR). MCF7 tumors were also grown in nude mice. Two days after fulvestrant treatment (n=5-7 mice per dose group), PET/CT was performed using ¹⁸F-FES and, 24 h later, using ¹⁸F-FDG to assess downstream metabolic changes. ER expression was assayed by immunohistochemistry, ELISA, and qPCR on resected xenografts.

Results: *In vitro*, fulvestrant was equipotent at reducing ¹⁸F-FES uptake as ER protein expression (nanomolar-level IC₅₀), despite stimulating mRNA expression several fold. Tumors resected from mice demonstrated decreased ER staining with increasing fulvestrant dose. ER protein expression significantly decreased in tumor lysate from mice given high-dose (0.45 or 5 mg) versus low-dose (0.05 mg) fulvestrant or vehicle, despite similar mRNA expression. *In vivo*, high-dose fulvestrant significantly reduced tumor ¹⁸F-FES-PET standardized uptake value means and maxima compared to low-dose fulvestrant or vehicle. In comparison, differences in ¹⁸F-FDG-PET parameters were not yet apparent.

Conclusions: ¹⁸F-FES uptake showed dose-responsiveness to fulvestrant treatment consistent with changes in functional ER expression. Quantitative ¹⁸F-FES-PET may be useful for tracking early efficacy of ER blockade and guiding ER-targeted therapy dosing in breast cancer patients.

Summer Medical Education Research Fellowship (SMERF)

048

Qi, Owen

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Summer Medical Education Research Fellowship (SMERF); Dean's Fellowship

Summer Research Program

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Mentor: David Murray, MD

High-fidelity patient simulator cardiovascular laboratory: the new dog lab?

Qi O; Murray DJ

Introduction: Animal "dog labs" were used extensively before the 1980s to teach undergraduate medical students heart physiology. These labs have declined precipitously in recent years with nothing to replace the interactive and hands-on experience. Our goal is to determine if High-fidelity patient simulators (HFPS) can replace the role of animals in cardiovascular laboratory course offered concurrently to the core undergraduate cardiovascular physiology curriculum. We are analyzing results from an elective course called Cardiac Control Mechanisms (CCM) offered at Washington University in St. Louis School of Medicine to first-year undergraduate medical students.

Methods: Two sets of data were obtained, qualitative results from a paper survey and quantitative results from an online exam. A paper survey was administered to students enrolled in the 2011 and 2012 CCM courses containing questions on a Likert scale and free-response sections. To measure retention of cardiac physiology between students who did and did not take the CCM course, a 20-question online exam on cardiac physiology was distributed to all 2011 and 2012 matriculates.

Results: From the survey data we found that the selective course improved student's understanding of cardiovascular physiology (4.5/5), was an efficient use of student time (4.25/5), and that students believed that the course would benefit all first year medical students (4.51/5). The online exam data showed that within the 2011 matriculates, those who took CCM answered 11.83 (95% CI, 10.98-13.59) correct, and those who didn't answered 10.17 (95% CI, 8.13-12.20) correct. Within the 2012 matriculates, those who took CCM answered 10.08 (95% CI, 7.56-12.60) correct, and those who didn't answered 8.08 (95% CI, 6.65-9.51) correct.

Conclusions: Due to small sample sizes, the quantitative online exam data did not show any statistical significance. However, due to such an overwhelmingly positive response in the paper survey we believe that HFPS should be considered as a tool to bring back concurrent cardiovascular laboratory courses.

T32 NIH Cardiopulmonary Surgery Training Grant

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Janjua, M Burhan, MD

T32 NIH Cardiopulmonary Surgery Training Grant

Division of Cardiothoracic Surgery

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Mentor: Jennifer S Lawton, MD, FACS

The cardioprotective benefits of K_{ATP} channel opener diazoxide are lost with administration after the onset of stress in mouse and human myocytes

Janjua MB; Makepeace CM; Anastacio MM; Schuessler RB; Nichols CG; Lawton JS

Introduction: Adenosine triphosphate sensitive (K_{ATP}) potassium channel opener diazoxide maintains myocyte volume and contractility during stress via an unknown mechanism when administered at the onset of stress. This study was performed to investigate the cardioprotective potential of diazoxide when added after the onset of stress.

Methods: Isolated mouse ventricular or human atrial myocytes were exposed to control Tyrode's solution (TYR) for 20 min, test solution (hypothermic hyperkalemic cardioplegia (CPG), CPG + 100uM diazoxide (CPG+DZX) added after 10 or 20 min stress, followed by 20 min re-exposure to TYR (+/- DZX). Volume (human + mouse) and contractility (mouse) were compared.

Results: Mouse myocytes demonstrated significant swelling during exposure to CPG that was not prevented by DZX when administered either at 10 or 20 min after the onset of stress +/- administration during re-exposure to TYR (mean % change from baseline volume +/- SEM, Table). Contractility significantly declined when DZX was administered 20 min after the onset of stress ($p < 0.05$ vs. TYR). Contractility significantly improved in all groups between 10min and 20min re-exposure to TYR. Human myocytes demonstrated return to baseline volume at the end of stress only in the group with DZX administration after 10 min stress + throughout re-exposure to TYR (Table). Human myocytes also demonstrated a rapid return to baseline volume upon re-exposure to TYR.

Conclusions: To maintain myocyte volume homeostasis and contractility during stress (hyperkalemic cardioplegia), K_{ATP} channel opener diazoxide requires administration at the onset of stress. These data have implications for the clinical application of diazoxide.

T32 NIH NIDDK Diabetes Training Grant

093

Jacobi, Celina

Medical Student

T32 NIDDK Diabetes Training Grant; Dean's Fellowship

Summer Research Program

Division of Pediatric Hematology/Oncology

Department of Pediatrics, Washington University in St. Louis School of Medicine

Mentor: Robert Hayashi, MD

Patients with hereditary cancer predisposition syndromes have defined phenotypes specific to their syndrome

Jacobi C; Gettinger K; Henry J; Druley T; Kozel B; Shinawi M; Hayashi R

Introduction: Hereditary Cancer Predisposition Syndromes (HCPS) are hereditary conditions that are associated with malignancies that develop in diverse organ systems at any age. There are several well described conditions, such as Beckwith Wiedemann Syndrome, Hemihypertrophy, Pleuropulmonaryblastoma, Familial adenomatous polyposis, and Li-Fraumeni syndrome that are associated with a restricted scope of malignancies. However, the scope of nonmalignant conditions characteristic of each HCPS is varied and frequently poorly described. We hypothesize that patients with cancer predisposition syndromes have a defined phenotype with a range of specific physical, cognitive, and psychological difficulties that correlate to their diagnosis.

Methods: In order to characterize each syndrome, we designed a longitudinal database and are currently enrolling pediatric patients with a HCPS diagnosis. Participants' parents will complete a health history questionnaire each year until their child turns 18, assessing their child's physical, cognitive, emotional, and psychosocial health and noting the age of occurrence for each positive symptom. Additionally, the child's medical record will be reviewed to collect information, such as height and weight, limb measurements, and genetic testing.

Results: We anticipate that these tools will depict the specific phenotype of each HCPS and demonstrate the evolution of patients' symptoms over time.

Conclusions: The current standard of care for most HCPS with poorly defined phenotypes is surveillance for malignancy with frequent screenings until the patient ages out of the high-risk population. However, greater knowledge of each syndrome's phenotype will encourage holistic treatment that extends beyond tumor monitoring to improve patients' quality of life and long term wellbeing.

T35 NIH NHLBI Training Grant

129

Altenhofen, Brannon

Medical Student

T35 NHLBI Training Grant

Summer Research Program

Program in Occupational Therapy, Washington University in St. Louis School of Medicine

Mentor: Lisa Connor, PhD

Determining factors that predict listenability of auditory materials in people with aphasia

Altenhofen B; Mandozke V; Connor LT

Introduction: Auditory comprehension deficits are a possible post-stroke impairment, and a common chronic symptom of persons with aphasia (PWA). Impaired ability to understand affects many levels of patient management, consent, and research into the efficacy of interventions. The goal of this study is to identify additional syntactic and non-syntactic features of discourse that affect auditory comprehension, firstly in perceived difficulty, and later in actual performance.

Methods: 7 persons with Aphasia and 9 healthy controls listened to 37 passages of varying length and composition. Participants rated each passage in difficulty on a 5-point Likert scale. Subjective difficulty was compared to 8 variables generated through passage analysis through SALT transcription software to identify significant correlations.

Results: All of the hypothesized variables were significantly correlated with subjective difficulty, to varying degrees. The most highly correlated values were Mean Length of Utterance in Words ($r = .731, p < 0.001$), followed by number of different words ($r = .697, p < 0.001$), total utterances ($r = .669, p < .001$), and number of total words ($r = .646, p < 0.001$). The type token ratio was less correlated, but still significant ($r = .430, p = .008$). Duration of passages was also highly correlated with subjective difficulty ($r = .661, p < 0.001$). The two measures of syntactic complexity, Complexity Index and Preposition Density, were both correlated to approximately the same degree of significance ($r = .459, p = .004$ and $r = .493, p = .002$ respectively).

Conclusions: The results of this study uncovered many potential variables that affect discourse comprehension. Our data support the assertion that both syntactic and lexical variables influence perceived difficulty in auditory comprehension. By better understanding the factors that mediate auditory comprehension, we can work to provide better resources to caretakers and family members to foster better communication with aphasic patients, design better experiments and more accurately test potential interventions and therapies, and ultimately improve the quality of life of those with language disorders.

011

Bansal, Anchal

Medical Student

T35 NHLBI Training Grant

Summer Research Program

Division of Plastic and Reconstructive Surgery

Department of Surgery, Washington University in St. Louis School of Medicine

Mentor: Susan E Mackinnon, MD

Evaluation of inter-rater reliability of the scratch collapse test

*Bansal A; *Groves AP; *Sacks G; Davidge K; Poppler L; Mackinnon S

Introduction: The scratch collapse test is a novel test, which employs a spinal reflex mechanism to evaluate compression neuropathy. The test has previously been validated for ulnar and peroneal compression neuropathies with reported sensitivities of 69% and 77% respectively and specificities of 99%. The objective of this study is to evaluate the inter-rater reliability of the scratch collapse test as a tool for assessing compression neuropathy

Methods: The scratch collapse test was studied prospectively in 101 sites of potential nerve entrapments among 26 patients. Each patient was separately examined by the senior author and three medical students. All examiners were blinded to the results of the other raters at the time of the examination. The three medical students were blinded to the patient's chief complaint and health history. The results from each examiner were then used to determine the inter-rater reliability of the scratch collapse test.

Results: Among all scratch collapse raters the correlation coefficient (ICC) was 0.59, or "good" reliability. In comparing each medical student rater to the senior author there was 86.1% agreement between rater 1 and the senior author, 96.04% agreement between rater 2 and the senior author, and 90.10% agreement between rater 3 and the senior author.

Conclusions: With the proper teaching methods, the scratch collapse test can be performed with good inter-rater reliability. It is therefore a reliable provocative test for examining compression neuropathy and can be used in conjunction with other clinical findings to make a diagnosis.

*All contributed equally to this work

012

Bansal, Anchal

Medical Student

T35 NHLBI Training Grant

Summer Research Program

Division of Plastic and Reconstructive Surgery

Department of Surgery, Washington University in St. Louis School of Medicine

Mentor: Susan E. Mackinnon, MD

Evaluation of common peroneal nerve compression in high fall-risk patient populations

*Bansal A; *Groves AP; *Sacks G; Davidge K; Poppler L; Mackinnon S

Introduction: To determine the prevalence of peroneal nerve compression in high risk hospital patients.

Methods: Peroneal nerve compression was evaluated using two “provocative tests”: Tinel’s test and the more recent Scratch Collapse test. Muscle strength (dorsiflexion, plantar flexion, inversion, eversion) was also tested using Medical Research Council (MRC) grading.

Aim 1: A prospective cross-sectional study was conducted on patients identified as “moderate” to “high” risk for falling.

Aim 2: A prospective cohort study was conducted on patients undergoing elective cardiac surgery.

Results: *Aim 1:* The prevalence of peroneal nerve compression was found to be 42%, as evidenced by the presence of either provocative sign. Peroneal muscle weakness was found to be 35% in this population. Both provocative signs were found to be significantly correlated to muscle weakness, and to falling, tripping, or stumbling. Demographic data including age, heart disease, past joint replacement surgery, and foot numbness were significantly correlated to provocative signs.

Aim 2: In this population, 53% of patients experienced a change in provocative sign testing, and 26% developed peroneal muscle weakness.

Conclusions: This study confirms that peroneal nerve compression is common in patients at high risk for falls, and in patients undergoing elective cardiac surgery.

*All contributed equally to this work

056

Benjamin, Lawrence

Medical Student

T35 NHLBI Training Grant

Summer Research Program

Division of Cardiology

Department of Internal Medicine, Washington University in St. Louis School of Medicine

Mentor: Ari Cedars, MD

Clinical predictors of hospitalization in patients with transposition of the great arteries

Benjamin L; Cedars A

Introduction: Transposition of the great arteries (TGA) is a congenital heart defect in which the 2 large arteries leaving the heart are switched, leading to the aorta arising from the morphologic right ventricle and the pulmonary artery arising from the morphologic left ventricle. This often must be corrected surgically. Few studies have comprehensively followed individuals with TGA and correlated various clinical markers with their likelihood for hospitalization, and no studies have performed cost analysis associated with these hospitalization.

Methods: This single-center retrospective analysis utilized a database of 164 patients with TGA seen at the Centers for Adults with Congenital Heart Disease at Barnes Jewish Hospital in St. Louis, MO.

Results and Anticipated Results: The top 5 discharge diagnoses were AICD implant/generator change, congestive heart failure, atrial flutter, pacemaker implant/generator change, and supraventricular tachycardia. These data confirm previous studies findings of likely complications of patients with TGA. We will perform statistical analysis of the data collected to identify clinical predictors of hospitalization based on left ventricular, right ventricular, and valvular function as assessed by echocardiogram, chest CT, and cardiac MRI, and on baseline kidney and hepatic function. We also will conduct cost-analysis based on hospitalization duration and total numbers of outpatient visits, nuclear stress tests, echo stress tests, VO2 max tests, EKG stress tests, Holter monitors, event monitors, emergency department visits, hospitalization days, echocardiograms, chest CT’s, and cardiac MRI’s performed. These analyses will hopefully elucidate potential clinical predictors of hospitalization and correlations between various clinical markers and treatment cost.

Conclusions: This research provides an important diagnostic tool to better equip physicians in their treatment and management of patients with this complex congenital defect. Furthermore, the results of the cost analysis of this patient database has the potential for offsetting future healthcare costs by providing the basis of establishing the most cost-effective treatment regimens for these patients.

095

Berlin, Ari

Medical Student

T35 NHLBI Training Grant

Summer Research Program

Division of Neurocritical Care Research

Department of Pediatrics, Washington University in St. Louis School of Medicine

Mentor: Jose Pineda, MD

Predicting cardiac arrest in the pediatric intensive care unit using aggregate physiological data

Berlin A; Pineda J

Introduction: Despite advances in pediatric critical care over the last several decades, in-hospital cardiac arrest (CA) events are still associated with poor survival. Abnormal physiological trends are observed to precede patient deterioration, including CA events. However, real time physiological trend analysis is not currently available in the critical care environment. The purpose of this study is to employ nonlinear analysis of aggregate high-resolution physiological data to develop a model that reliably assesses the relative risk of CA in pediatric patients in the intensive care unit, enabling enhanced monitoring and potentially earlier intervention to improve outcomes.

Methods: To define how and when abnormal physiological trends become clearly distinguishable in children who decompensate to cardiac arrest, patients under 22 years of age who arrested after admission to the intensive care units at St. Louis Children's Hospital since October of 2012 were identified. Patients for whom less than 30 minutes of high-resolution physiological monitoring was available prior to their arrest were excluded, as were arrests that resulted from external (unpredictable) perturbations, such as accidental extubation. Relevant laboratory values (lactate, CO₂, etc.) were included in the aggregate data set.

Results: 22 patients were identified as having arrested in the cardiac or pediatric intensive care units while high resolution data was archived using BedMaster, a component of the electronic medical record that records aggregate physiologic trends (including both time series and waveform data for among other physiological variables, heart and respiratory rates, pulse oximetry, and premature ventricular contractions). We are partnering with Etiometry, an industry collaborator that specializes in analysis of large volumes of real time data to create clinical decision support systems.

Conclusions: A reliable model to assess the risk of CA in the pediatric intensive care unit will alert clinicians to patients at risk of acute decompensation, potentially enabling corrective courses of treatment and preventing poor outcomes.

098

Bichanich, Miles

Medical Student

T35 NHLBI Training Grant

Summer Research Program

Department of Pediatrics, Washington University in St. Louis School of Medicine

Mentor: Charles Canter, MD

Outcomes after referral for heart transplant in the pediatric population

Bichanich MJ; Sparks JD; Simpson K; Canter CE

Introduction: Heart transplantation is a validated treatment option for children with end-stage heart failure. However, there has been very limited investigation into the competing potential outcomes of patients following their referral to a heart transplant center. We postulate that early referral correlates with favorable outcome. We recorded data from pediatric patients referred to a high volume heart transplantation center for a heart failure evaluation in order to examine outcome.

Methods: Patient characteristics and outcome data were recorded retrospectively from all patients referred to the St. Louis Children's Hospital transplant team. A competing risk analysis for the data from these patients is currently ongoing.

Anticipated Results: 281 patients were referred for evaluation. Of these, 34% underwent orthotopic heart transplantation. Upon referral, 54% of patients had undergone a previous cardiac surgery, 76% were on inotropic therapy, 30% required mechanical ventilation, and the average time between primary disease diagnosis and referral was 3.6 years. 57% of referred patients carried a diagnosis of congenital heart disease, and 40% had been diagnosed with a cardiomyopathy. After referral, 66% of patients were listed for transplantation, 4% received alternative treatment instead of being listed, and 21% were found to be unsuitable transplant candidates. Of those listed, 80% received a transplant and 11% died on the waitlist. Upon completion of the competing risk analysis, we expect outcomes with referral in the earlier stages of disease to be favorable in comparison to late referrals.

Conclusions: If transplant referral timing in pediatric heart failure correlates with patient outcomes as predicted, this study will support the recommendation for early referral of these patients to heart transplant centers for evaluation. The low transplantation rate in referred patients suggests that referral to a large tertiary or quaternary health center might provide benefits beyond transplantation. Further analysis of our data should provide more insight into these hypotheses.

053

Cai, Alice

Medical Student

T35 NHLBI Training Grant

Summer Research Program

Department of Anesthesiology, Washington University in St. Louis School of Medicine

Mentor: Michael Avidan, MD

Memories of the postoperative period study

Cai A; Chen Y; Fritz B; Escallier K; Dexter F; Avidan M

Introduction: Although there have been numerous efforts to develop and validate instruments for assessing patient satisfaction with various components of anesthesia care, there has been a paucity of investigation into the patient memories which serve as the informational foundation for these satisfaction instruments. In order to address this gap in the field, we investigated the extent and variability of perioperative memories of patients undergoing general anesthesia.

Methods: We conducted a sub-study of two clinical trials (n=8100) which were focused on preventing intraoperative awareness. Patient responses to modified Brice questionnaires delivered face-to-face within 72 hours and over the telephone at 30 days after surgery were analyzed. Patient responses to the questions, "What is the last thing you remember before falling asleep?" and "What is the first thing you remember after waking up?" were categorized by preoperative and postoperative location. Patient responses within 72 hours and at 30 days after surgery were compared to assess the variability of perioperative memories between the 2 time points.

Results: Within 72 hours after surgery, 45% of patients reported remembering being in the operating room (OR) before their procedure, and 4% of patients reported remembering being in the OR after their procedure. Comparing all patient responses within 72 hours after surgery with all patient responses at 30 days after surgery, 40% of patients reported remembering a different last preoperative location, and a similar finding was found with respect to the first postoperative locations. In an analysis of only patients who remembered the OR at least 1 of the 2 time points (within 72 hours after surgery and 30 days after surgery), 47% of these patients reported remembering different last preoperative locations at the 2 time points, and 82% of these patients reported remembering different first postoperative locations at the 2 time points.

Conclusions: A majority of surgical patients do not remember being in an operating room either before or after their surgery. Moreover, even if they do remember being in the OR when questioned within 72 hours after their surgery, they often do not remember when questioned at 30 days after their surgery. Satisfaction assessments related to patient perioperative experiences may be hampered by limited and variable patient memories.

133

Chiu, Ami

Medical Student

T35 NHLBI Training Grant

Summer Research Program

Department of Pathology & Immunology, Washington University in St. Louis School of Medicine

Mentors: Aki Yoneda Kau, PhD; Gautam Dantas, PhD

Plasmid-size bias in the transformation of the cyanobacteria *Synechocystis* sp. PCC 6803

Chiu AC; Kau AY; Dantas G

Introduction: Natural transformation in the model cyanobacterium *Synechocystis* sp. PCC 6803 occurs through foreign DNA uptake and homologous double recombination into the genome. While previous optimization studies have explored various DNA effects on transformation efficiency, the impact of DNA molecule size has not been well characterized. This study seeks to (1) identify the maximum size of circular and linear DNA molecules capable of naturally transforming *Synechocystis*, (2) investigate the correlation between exogenous DNA length and homologous sequence length in transformation, and (3) test whether deletion of the *recJ* exonuclease gene and/or transformation into RecJ⁻ host strains affects transformation efficiency.

Methods: Wildtype and RecJ⁻ *Synechocystis* sp. PCC 6803 were transformed with a series of circular and linear plasmids that varied in maximum size due to different: (1) non-homologous exogenous DNA insert lengths, (2) recombination target regions, and (3) lengths of flanking homologous sequences. Transformation efficiency was then determined by comparing transformant numbers and confirming successful genomic recombination.

Results: It is expected that shorter and circular DNA molecules will transform *Synechocystis* with higher efficiency. However, as foreign DNA is only maintained after homologous recombination and genomic integration, the length of the exogenous DNA used relative to that of its flanking homologous regions may influence transformation efficiency more than size alone. The RecJ⁻ host strain is also expected to be better transformed than the wildtype; it is unknown whether use of the *recJ* gene as a recombination target affects transformation efficiency.

Conclusions: The results of this study will permit development of size-appropriate high-throughput libraries to functionally identify heterologous genes transformed into *Synechocystis*. With cyanobacteria increasingly considered to be a rich source of bioactive molecules with potential antibiotic, antiviral, and anticancer function, this ability to transform a model cyanobacterium like *Synechocystis* with such heterologous DNA opens new possibilities in the discovery and production of novel drugs.

094

Chu, Cheryl

Medical Student

T35 NHLBI Training Grant

Summer Research Program

Division of Pediatric Critical Care

Departments of Pediatrics, Neurosurgery and Radiology, Washington University in St. Louis School of Medicine

Mentors: Jose Pineda, MD; Jeff Leonard, MD

A clinical prediction tool to guide therapeutic intervention in children with traumatic brain injury

Chu C; Pineda J; Leonard J; Celeste CA

Introduction: Traumatic brain injury (TBI) is a leading cause of death among children. In clinical practice, the severity of TBI is classified based on level of consciousness measured by the Glasgow Coma Scale and presence of anatomical injury on computed tomography (CT) imaging. This information is used to guide initial interventions including the monitoring of intracranial pressure (ICP). However, the ability to accurately identify children who develop increased ICP using only these characteristics is limited, leading to variable clinical practice and treatment delays. The purpose of this study is to create a clinical prediction model that incorporates additional patient and injury characteristics that better identifies children with TBI who are at risk of developing increased ICP.

Methods: Data from 3 pediatric trauma centers (155 patients) were collected. CT scans were reviewed and classified using the Marshall CT and Rotterdam CT scores. An ordered probit model will be used to link informative explanatory variables to the development of increased ICP.

Results: This approach will result in a predictive model that will better inform the initial management of children with severe TBI. Improved ability to identify children who go on to develop increased ICP will facilitate initial treatment and diminish unnecessary risks associated with invasive procedures such as ICP monitoring.

Conclusions: Increased ICP is correlated with worsened outcomes for severe TBI patients. Early and aggressive treatment is associated with improved outcome. Preliminary data shows that only 80% of patients meeting current indications for ICP monitoring actually develop increased ICP. Also, patients with severely increased ICP are not always identified early. Additionally, a subset of children with severe TBI will not develop increased ICP and thus are unnecessarily subjected to invasive ICP monitoring. Our findings should be used when evaluating the risk and benefit of early ICP monitor placement. This project will lead to the development of clearer guidelines that significantly improve early management of children with severe TBI.

100

Dardas, Agnes

Medical Student

T35 NHLBI Training Grant

Summer Research Program

Division of Pediatric Neurosurgery

Department of Neurosurgery, Washington University in St. Louis School of Medicine

Mentor: David Limbrick, MD, PhD

Comparison of spinal deformities in patients with chiari I malformation and/or syringomyelia

Dardas A; Godzik J; Holekamp T; Kelly M; Limbrick D

Introduction: Chiari Type I Malformation (CIM), the herniation of the cerebellar tonsils through the foramen magnum, is a developmental abnormality often associated with syringomyelia, the accumulation of fluid (syrinx) within the spinal cord. Patients with syringomyelia are known to be at an increased risk of scoliosis. Pediatric patients presenting with a moderate tonsillar ectopia of 5-12 mm (CIM) and greater syrinx diameters are at an increased risk of scoliosis, yet the etiology of scoliosis is still unknown. The goal of this study is to determine whether it is CIM alone or the combined effects of CIM and syringomyelia that are associated with progressive spinal deformity in pediatric patients.

Methods: A retrospective review of pediatric patients evaluated for scoliosis with CIM and/or syringomyelia at a single institution from 2000 to 2012 was conducted. Inclusion criteria included children (18 years old or less) with a diagnosis of scoliosis with CIM (tonsillar descent beyond the foramen magnum > 5 mm) and/or syringomyelia (anteroposterior diameter ≥ 2 mm). Exclusion criteria included previous decompression or spinal fusion; missing preoperative MR imaging studies; syringomyelia related to tumor, infection, arachnoiditis, or previous trauma to the spinal cord; history of myelomeningocele, tethered cord, or other dysraphism; and subjects with connective tissue diseases or genetic syndromes. Data will be analyzed using SPSS and results will be confirmed by a licensed biostatistician.

Results: We anticipate that greater degrees of spinal deformity are associated with patients presenting with concurrent CIM and syringomyelia, thereby indicating that scoliosis is associated with a combination of effects brought on by the two developmental abnormalities.

Conclusions: The results of this study add to the scientific knowledge regarding the etiology of scoliosis in this patient population and in doing so, improve future pediatric patient care by allowing for earlier diagnosis and treatment in at-risk populations.

039

Gamble, Paul

Medical Student

T35 NHLBI Training Grant

Summer Research Program

Department of Neurosurgery, Washington University in St. Louis School of Medicine

Mentors: Matthew MacEwan, PhD; Wilson Ray, MD

Observing functional recovery after nerve damage using inductive implanted electrodes

Gamble P; MacEwan M

Introduction: Damage to the peripheral nervous system (PNS) can turn an otherwise insignificant injury into a debilitating trauma. The PNS is capable of substantial amounts of self-repair however its capacity to recover from damage is finite. Studies of PNS auto-repair are themselves often limited by experimental techniques. Maintaining stable long term connections to peripheral nerves in small animal models is notoriously difficult. In this study we aim to demonstrate the efficacy of a small inductively powered implantable electrode for chronic peripheral nerve stimulation by using such an electrode to monitor the recovery of muscle function in rats after sciatic nerve damage over several months.

Methods: The inductive electrodes used in this experiment consist of a 14 mm silicon and copper receiver coil attached to micro-leads. We created 3 cohorts of 6 rats. Each rat had a receiver coil implanted in its lower back with the leads contacting the right sciatic nerve. In the 'crush' cohort, the nerve was crushed several mm distal to the leads. In the 'cut' cohort, the nerve was cut in the same place and repaired with micro sutures. Nerves in the control cohort were not damaged. EMG recordings in response to wireless stimulation of the implanted electrodes were taken weekly from every animal for three months at four sites on the right leg.

Results: The inductive electrodes worked well at providing a long term connection to the sciatic nerve. Rats in all cohorts showed recovery of sciatic nerve function following surgery. Control rats showed nearly full recovery by week 2. Crush rats had a longer regeneration period and more delay but tended to eventually regain full function. Measurements from the Cut cohort are still being taken but these rats appear to take the longest to recover and do not regain full function.

Conclusions: The inductive electrodes used in this study are an important addition to existing experimental methods and could simplify many other PNS research projects. Wireless nerve stimulation also holds promise for patients who now rely on battery powered nerve stimulation for the treatment of a variety of conditions.

011

Groves, Andrew

Medical Student

T35 NHLBI Training Grant

Summer Research Program

Division of Plastic and Reconstructive Surgery

Department of Surgery, Washington University in St. Louis School of Medicine

Mentor: Susan E Mackinnon, MD

Evaluation of inter-rater reliability of the scratch collapse test

*Groves AP; *Bansal A; *Sacks G; Davidge K; Poppler L; Mackinnon S

Introduction: The scratch collapse test is a novel test, which employs a spinal reflex mechanism to evaluate compression neuropathy. The test has previously been validated for ulnar and peroneal compression neuropathies with reported sensitivities of 69% and 77% respectively and specificities of 99%. The objective of this study is to evaluate the inter-rater reliability of the scratch collapse test as a tool for assessing compression neuropathy.

Methods: The scratch collapse test was studied prospectively in 101 sites of potential nerve entrapments among 26 patients. Each patient was separately examined by the senior author and three medical students. All examiners were blinded to the results of the other raters at the time of the examination. The three medical students were blinded to the patient's chief complaint and health history. The results from each examiner were then used to determine the inter-rater reliability of the scratch collapse test.

Results: Among all scratch collapse raters the correlation coefficient (ICC) was 0.59, or "good" reliability. In comparing each medical student rater to the senior author there was 86.1% agreement between rater 1 and the senior author, 96.04% agreement between rater 2 and the senior author, and 90.10% agreement between rater 3 and the senior author.

Conclusions: With the proper teaching methods, the scratch collapse test can be performed with good inter-rater reliability. It is therefore a reliable provocative test for examining compression neuropathy and can be used in conjunction with other clinical findings to make a diagnosis.

* All contributed equally to this work

012

Groves, Andrew

Medical Student

T35 NHLBI Training Grant

Summer Research Program

Division of Plastic and Reconstructive Surgery

Department of Surgery, Washington University in St. Louis School of Medicine

Mentor: Susan E Mackinnon, MD

Evaluation of common peroneal nerve compression in high fall-risk patient populations

*Groves AP; *Bansal A; *Sacks G; Davidge K; Poppler L; Mackinnon S

Introduction: To determine the prevalence of peroneal nerve compression in high risk hospital patients.

Methods: Peroneal nerve compression was evaluated using two “provocative tests”: Tinel’s test and the more recent Scratch Collapse test. Muscle strength (dorsiflexion, plantar flexion, inversion, and eversion) was also tested using Medical Research Council (MRC) grading.

Aim 1: A prospective cross-sectional study was conducted on patients identified as “moderate” to “high” risk for falling.

Aim 2: A prospective cohort study was conducted on patients undergoing elective cardiac surgery.

Results: *Aim 1:* The prevalence of peroneal nerve compression was found to be 42%, as evidenced by the presence of either provocative sign. Peroneal muscle weakness was found to be 35% in this population. Both provocative signs were found to be significantly correlated to muscle weakness, and to falling, tripping, or stumbling. Demographic data including age, heart disease, past joint replacement surgery, and foot numbness were significantly correlated to provocative signs.

Aim 2: In this population, 53% of patients experienced a change in provocative sign testing, and 26% developed peroneal muscle weakness.

Conclusions: This study confirms that peroneal nerve compression is common in patients at high risk for falls, and in patients undergoing elective cardiac surgery.

* All contributed equally to this work

057

Huverserian, Ari

Medical Student

T35 NHLBI Training Grant

Summer Research Program

Department of Anesthesiology, Washington University in St. Louis School of Medicine

Mentor: Michael Avidan, MBCh

Nothing sinister about anaesthetizing lefties

Huverserian A; Rao S; Ben Abdallah A; Willingham M; Avidan MS

Introduction: Several previous studies have linked handedness to anatomical and physiological differences, psychiatric disease and differences in morbidity and mortality. No previous studies have addressed the effect of patient handedness on anesthetic management. The purpose of this study is to compare post-operative mortality, intraoperative awareness with explicit recall, overall health status, and anesthetic requirements between right handed and non-right handed patients.

Methods: This was a multicenter, prospective study in three North American tertiary medical centers conducted from 2008-2010. The population included 5585 surgical patients screening high risk for intraoperative awareness. The main outcome measures included incidence of post-operative mortality, intraoperative awareness with explicit recall, and comparison of anesthetic requirements between right handed and non-right handed patients. Data were collected from patient records and postoperative surveys, and analyzed using mixed effects modeling, Kaplan-Meier analysis, Pearson’s Chi-square, Fisher’s Exact, and Mann-Whitney U tests.

Results: Non-right handedness is not associated with postoperative mortality, anesthetic requirements, intraoperative awareness, or bispectral index values. There were no differences in overall health status based on the American Society of Anesthesiologists Physical Status score.

Conclusions: Previous findings suggesting higher rates of alcoholism, anxiety, and mortality in non-right handed individuals, and differences in episodic memory, sleep architecture, and EEG findings between right and non-right handed individuals are not clinically meaningful in modern anesthetic practice.

044

Jalalizadeh, Rohan A

Medical Student

T35 NHLBI Training Grant

Summer Research Program

Department of Neurosurgery, Washington University in St. Louis School of Medicine

Mentor: Gregory Zipfel, MD

Cerebral vasospasm after the clipping of an unruptured aneurysm

Jalalizadeh R; McCoy K; Zipfel G

Introduction: Cerebral arterial vasospasm is a frequent, life-threatening phenomenon following subarachnoid hemorrhage, and the long-standing hypothesis regarding this is that vasoactive substances in the blood are necessary for the development of vasospasm. However, due to cases of patients with vasospasm in whom subarachnoid hemorrhage was not present, it is likely that another mechanism underlies the development of vasospasm. The purpose of this study is to examine other factors that may predict cerebral vasospasm by analyzing a series of cases of vasospasm after surgical correction of cerebral aneurysm without rupture.

Methods: Patient records are being examined in relation to pre-operative, intra-operative, and post-operative course and potential factors in the development of cerebral arterial vasospasm. Some of the data categories include co-morbidities, initial presentation, lab tests, symptoms of vasospasm, location of aneurysm and surgical complications, residual sequela of vasospasm, and imaging results. Statistical analysis will be used to determine which of these factors and observations are good predictors of vasospasm.

Results: Data on only a small subset of the cases have been obtained, but it is anticipated that one or more of the factors to be examined will show a correlation with increased risk of vasospasm.

Conclusions: The results of this study will likely point to factors that can help predict cerebral vasospasm and will demonstrate the need to search for a new mechanism to explain the development of vasospasm in cases with clipped, unruptured aneurysms. If it is possible to predict which patients are more likely to develop postoperative vasospasm, these patients could be observed more stringently to prevent vasospasm and related complications from cerebral ischemia.

096

Kaufman, Johanna

Medical Student

T35 NHLBI Training Grant

Summer Research Program

Division of Newborn Medicine

Department of Pediatrics, Washington University in St. Louis School of Medicine

Mentor: Amit Mathur, MD

Continuous amplitude-integrated EEG in the preterm infant

Kaufman J; Mathur A

Introduction: Amplitude-integrated EEG (aEEG) has been studied extensively for use as a cerebral function monitor with full term infants. However, the effectiveness of continuous aEEG as a monitoring tool for preterm infants has not been adequately studied. The purpose of this study is to examine the use of continuous aEEG with preterm infants by looking at three areas: gestational age maturity, seizure burden and its correlation with Intraventricular Hemorrhage (IVH), and clinical correlates of abnormal aEEG backgrounds.

Methods: A cohort of 38 preterm infants ranging in gestational age from 24-28 weeks underwent continuous aEEG monitoring (BRM-3) for the first 72 hours of life. Data were analyzed in 1-hour epochs using the scoring system created by Burdjalov *et al.* Data were also analyzed for the presence of seizures and dramatic shifts in background activity. A typical 1-hour epoch was selected for each infant within three time periods: 1-24, 24-48, and 48-72 hours of life. Scores within each time period were correlated with gestational age and linear regressions were performed. Clinical data were examined for the presence of IVH and correlated with seizure burden. Periods of abnormal aEEG background were further assessed for clinical interventions or associations.

Results: Overall, higher gestational ages correlated with higher Burdjalov scores and therefore a more mature aEEG. This correlation was slightly higher in the first 24 hours ($r=.535$) than in the second 24 hours (.402) or last 24 hours of recording (.429). Seizures were present in 34% of our infants. However, only 8 infants had IVH within the time period of interest and only 3/8 also had seizures. No consistent clinical trends were found during time periods of abnormal aEEG backgrounds.

Conclusions: The current data show that aEEG can be of use in monitoring the maturation of cerebral function in the preterm infant. However, larger cohort studies need to be performed in order to describe useful trends.

142

Madubata, Chinwe

Medical Student

T35 NHLBI Training Grant

Summer Research Program

Brown School of Social Work, Washington University in St. Louis

Department of Neurology, Washington University in St. Louis School of Medicine

Mentors: Kimberly Johnson, PhD, MPH; David Gutmann, MD, PhD

Neurofibromatosis type 1 and chronic neurological conditions in the United States

Madubata CM; Johnson, K

Introduction: Neurofibromatosis 1 (NF1) is an autosomal dominant disorder that predisposes affected individuals to nervous system tumors. No large studies to date have assessed the association between NF1 and chronic neurological conditions. The purpose of this study is to compare the estimated prevalence of epilepsy, extrapyramidal disorders, migraine, movement disorders, multiple sclerosis, Parkinson's disease, and sleep disorders in people with and without NF1.

Methods: Administrative claims from 2006-2010 in the MarketScan database were used to estimate the prevalence of chronic neurological conditions, with acute genitourinary infection as a negative control. Control individuals were matched to NF1 patients at a 10:1 ratio by age and enrollment time in months. Unconditional logistic regression was used to calculate the odds ratio (OR) for each comorbid condition, adjusting for age, time enrolled, and number of visits.

Results: 8579 cases and 85790 controls were identified for this study. Subjects identified from administrative claims data as having NF1 have significantly higher odds of developing the neurological conditions studied. There was no difference in risk for acute genitourinary infection. The odds ratios with 95% confidence intervals for each condition are as follows: epilepsy (7.0; 6.3-7.8), paralysis (6.2; 4.8-7.9), Parkinson's disease (3.3; 2.1-4.9), movement disorder (3.3, 2.1-4.9), extrapyramidal disorder (3.0, 2.2-4.0), headache (2.8, 2.6-3.0), multiple sclerosis (1.9, 1.2-2.4), sleep disorder (1.9, 1.2-2.9), and acute genitourinary infection (1.0, 0.9-1.2).

Conclusions: Administrative data analysis suggests that individuals with NF1 are at elevated risk for several neurological conditions. Since some conditions may be undercoded by health providers in health maintenance organizations (HMOs), further analysis will include adjustment for coding differences between HMOs and other health insurance providers. Analysis of another administrative dataset will be needed to verify these results.

023

McGilvray, Martha

Medical Student

T35 NHLBI Training Grant

Summer Research Program

Institute for Public Health

Department of Surgery, Washington University in St. Louis School of Medicine

Mentor: Graham Colditz, MD, DrPH

Adolescent fiber intake and risk of adult breast cancer or benign breast disease

McGilvray M; Stoll C; Liu Y; Fowler S; Colditz G

Introduction: Adolescent exposures may have an important impact on adult breast cancer risk. Migrant studies have shown that environmental exposures are critical in breast cancer etiology, and have identified fiber as a potentially important exposure. Benign breast disease (BBD) is a known risk factor for breast cancer, and provides a helpful outcome measure in assessing breast cancer etiology. Adolescent diet can be retrospectively assessed using a food frequency questionnaire diet-recall method. Because adolescent fiber is potentially modifiable, it could represent a promising intervention strategy for the prevention of breast cancer if there is indeed an association between adolescent fiber intake and risk of adult breast cancer. Our goal was to explore whether there is a correlation between level of fiber intake in adolescence and incidence of adult breast cancer or BBD.

Methods: Because there are few studies that address this possible correlation, we performed a comprehensive literature review and meta-analysis to combine the data of previous studies and provide us with greater statistical power with which to assess this relationship.

Results: We will assess the relationships between fiber intake and risk of breast cancer, BBD, or both, and intakes of individual foods (such as fruits or vegetables) and risk of breast cancer, BBD, or both. We will also assess the different populations used in each of the studies included, and study quality, and investigate potential important differences. Our preliminary data suggest an inverse association between risk of BBD and adolescent fiber intake, and perhaps a more complicated relationship between breast cancer risk and adolescent fiber intake.

Conclusions: Our preliminary data suggest that BBD may be a precursor for only some sub-set of breast cancers, and that there may be an interaction between adolescent fiber and alcohol in determining an individual's risk of adult breast disease. Further research is needed to better tease apart the complicated relationships between adolescent exposure, diet, and adult breast disease in order to better understand breast disease etiology and design future public health interventions.

076

Min, Jaspur M

Medical Student

T35 NHLBI Training Grant

Summer Research Program

Department of Obstetrics and Gynecology, Washington University in St. Louis School of Medicine

Mentor: Tessa Madden, MD

The effectiveness of a checklist to exclude pregnancy at the time of contraceptive initiation

Min JM; Buckel C; Secura GM; Peipert JF; Madden T

Introduction: Effective contraception is essential to reducing the risk of unintended pregnancy. Safe initiation of contraception requires accurately excluding pregnancy. While urine pregnancy tests are easy and reliable, they do not accurately detect early pregnancy. The WHO provides criteria for a pregnancy checklist that can be used to aid the exclusion of pregnancy. Our objective was to measure the sensitivity and specificity of the pregnancy checklist in excluding early pregnancy at the time of contraceptive initiation.

Methods: This is a secondary analysis of the Contraceptive CHOICE Project, a prospective cohort study of 9,256 women in the St. Louis region. We identified participants who met any of the six criteria on the pregnancy checklist. We also identified women who had an undiagnosed luteal phase pregnancy. Women with a known pregnancy at the time of enrollment were excluded from this analysis. We analyzed the effectiveness of the pregnancy checklist at accurately excluding luteal phase pregnancy.

Results: Seventy-three percent of women met any one criterion on the pregnancy checklist. There were 36 luteal phase pregnancies subsequently diagnosed. The sensitivity and specificity of the pregnancy checklist were 0.78 and 0.73, respectively. The negative predictive value of the pregnancy checklist was >0.99. The pregnancy checklist accurately identified 78% of women who had an early pregnancy in CHOICE, while all of them had a negative urine pregnancy test at enrollment.

Conclusions: The pregnancy checklist is an important tool for excluding early pregnancy at the time of contraceptive initiation and may be more effective than urine pregnancy testing.

137

Mohapatra, Anand

Medical Student

T35 NHLBI Training Grant

Summer Research Program

Department of Orthopaedic Surgery, Washington University in St. Louis School of Medicine

Mentor: Michael P Kelly, MD

The influence of topical vancomycin on surgical site infection rates following instrumented spinal surgery

Mohapatra A; Lenke LG; Kelly MP; Warren D; Holekamp T

Introduction: Postoperative spine wound infection rates are as high as 20% in some series. These infections are associated with higher costs of care, higher rates of readmission, and higher acute mortality rates. Topical vancomycin powder is one method employed to reduce postoperative deep wound infections. The purpose of this study was to examine the effects of topical vancomycin on infections and other adverse events. Our hypothesis was that topical vancomycin resulted in fewer infections without causing adverse effects, such as acute renal insufficiency (ARI), pseudoarthrosis, and anaphylaxis.

Methods: The Clinical Investigation Data Exploration Repository (CIDER) at Washington University was used to collect data on the 2320 patients who underwent a posterior thoracolumbar spinal fusion between 1992 and 2012. Complete data were available for 2214 patients. Topical vancomycin usage and wound infections were identified using an automated word-search on each patient's electronic medical records. Patients were divided into groups based upon their exposure to topical vancomycin (NoVanc/YesVanc). Adverse events and comorbidities were identified using ICD-9-CM codes. Chi-squared tests were performed to determine statistical significance, which was set at $p < 0.05$.

Results: The groups were similar with respect to gender, age, BMI, surgical levels, and Charlson comorbidity index. Acute postoperative wound infections were lower in the YesVanc group (8.2% vs. 4.5%, $X^2(df=1, N=2214)=11$, $p < 0.001$). Rates of ARI, pseudoarthrosis, and anaphylaxis were 1.0%, 3.1%, and 0%, respectively, in the patients who got topical vancomycin and 1.4%, 5.1%, and 0% in the patients who did not.

Conclusions: The application of topical vancomycin powder was associated with a 3.7% lower rate of postoperative wound infection. There were no complications associated with the application of vancomycin in this series. Prospective randomized-controlled trials are necessary to determine the extent to which topical vancomycin decreases postoperative wound infection and to determine rates of adverse events.

035

Morris, Marie

Medical Student

T35 NHLBI Training Grant

Summer Research Program

Department of Neurology, Washington University in St. Louis School of Medicine

Mentors: Brad Racette, MD; Allison Willis, MD, MSCI

Appropriateness of dopamine antagonist prescribing in hospitalized patients with dopamine requiring diseases after implementation of an automated prescribing alert system

Morris M; Willis A; Racette B

Introduction: Dopamine antagonists are often prescribed for psychosis and nausea, but are contraindicated for dopa-requiring conditions such as Parkinson disease and Restless Leg Syndrome, as these medications are likely to exacerbate disease symptoms. This retrospective, observational study examined dopamine antagonist prescriptions in hospitalized patients with dopa-requiring diseases, and the physician response to an automated drug contraindication alert system.

Methods: A detailed review of patient medical records was performed for all alert events generated when a physician prescribed a dopamine antagonist concurrently with a dopamine agonist to a hospitalized patient. Two neurologists specializing in movement disorders deemed each prescription appropriate or inappropriate based on patient medical history through consensus. Physician response to alert was compared by disease and physician specialty.

Results: Of 210 alerts triggered, 181 (93.3%) prescriptions for dopamine antagonists were inappropriate and 13 (6.7%) appropriate. Three quarters (75.1%) of the patients who had an inappropriate prescription had Parkinson disease. Prochlorperazine (indication=nausea/vomiting) was the most common inappropriately prescribed drug. The majority of inappropriate orders were generated by the general medicine (58.6%) and surgical (23.2%) services; however 9.9% originated from neurology/neurosurgery. Of the inappropriate prescriptions, 133 (73.5%) were continued in spite of the alert. Response to alert varied somewhat by specialty- 70.8% of surgical, 62.3% of general medicine 44.4% of psychiatric and 73.7% of neurological/neurosurgical patients had inappropriate medications continued after the physician had been alerted.

Conclusions: The study demonstrates that a pharmacy alert system successfully identifies potential disease-drug interactions, but medications are often continued in spite of the alert. This study highlights the need for improved education of health care providers to augment patient safety measures.

008

Patel, Aalok

Medical Student

T35 NHLBI Training Grant

Summer Research Program

Division of Cardiothoracic Surgery

Department of Surgery, Washington University in St. Louis School of Medicine

Mentor: Varun Puri, MD

Comparative effectiveness of chemoradiation alone versus chemoradiation and surgery for locally advanced lung cancer

Patel A; Puri V

Introduction: The treatment of patients with clinical Stage IIIA lung cancer is controversial. We aimed to evaluate the baseline characteristics and long-term outcomes of patients undergoing trimodality therapy (chemoradiation and surgery) versus chemoradiation only in a population based study. We hypothesized that trimodality therapy confers a survival advantage over chemoradiation alone.

Methods: We extracted information on demographic, patient related-, tumor related-variables, and short-, and long-term outcomes in patients with clinical Stage IIIA non-small cell lung cancer (NSCLC) from the participant user file of the National Cancer Database. Patients undergoing trimodality therapy were compared to those who underwent chemoradiation only.

Results: Between 1998 and 2010, 61339 patients underwent definitive treatment for clinical Stage IIIA NSCLC. Of these 51979 (84.7%) received chemoradiation only and 9360 (15.3%) underwent trimodality therapy. Patients in the trimodality group were younger, had higher incomes, were more likely to be Caucasian, presented more so from an urban location, traveled greater distances to obtain treatment, and presented to larger treatment facilities than patients in the chemoradiation group. Trimodality therapy patients also were less likely to be male, had smaller tumor sizes, and less severe comorbidities than chemoradiation patients. The thirty day surgical mortality was 200/8893 (2.2%). In an unmatched comparison, patients in the trimodality group had significantly better long-term survival than the chemoradiation group (median survival 32.36±.6 months v 15.67±.1 respectively, p<.001). Propensity score matching patients on age, gender, race, location, income, comorbidities, tumor size, treatment facility, and year of diagnosis resulted in 5265 matched pairs. Trimodality therapy patients showed increased survival than chemoradiation only patients (median survival 34.33±.8 months v 18.43±.3 months respectively, p<.001).

Conclusions: In selected patients, trimodality therapy including surgical resection provides a clear improvement in long-term survival over chemoradiation therapy in patients with clinical Stage IIIA lung cancer. Short-term outcomes of surgery are acceptable.

043

Qualls, David

Medical Student

T35 NHLBI Training Grant

Summer Research Program

Department of Neurosurgery, Washington University in St. Louis School of Medicine

Mentors: Jeffrey Leonard, MD; Julie Leonard, MD, MPH

Utility of magnetic resonance imaging in diagnosing cervical spine injury in pediatric patients

Qualls DA; Leonard JR; Leonard JC

Introduction: Clearing the pediatric cervical spine of injuries is complicated when the patient is unresponsive due to traumatic brain injury, necessitating cervical imaging. Plain radiography and computed tomography are commonly utilized, but MRI is still considered the gold standard in CSI detection. However, MRI is expensive and delays cervical clearance. Our study aimed to determine the added benefit of MRI to plain radiography and CT in evaluating for clinically significant CSI in children with severe traumatic brain injury.

Methods: We performed a retrospective review of pediatric head trauma patients admitted to the PICU at St. Louis Children's Hospital from 2002 to 2012. Patients who received both CS CT and MRI and demonstrated a Glasgow Coma Scale score (GCS) of 8 or below were included in the study. Radiology reports were analyzed by two pediatric physicians blinded to patient outcome and classified as demonstrating "no injury", "clinically insignificant injury" or "clinically significant injury." Results were compared and discrepancies between CT and MRI findings noted.

Results: Results are still pending completion of blinded physician review. We retrospectively reviewed 1196 head-injured patients reported to the PICU between 01-2002 and 12-2012. 63 patients received CS CT and MRI and met GCS criteria. Chart review yielded 3 patients in which MRI detected an injury which changed the physician's management of the cervical spine. However, blinded physician review of radiology reports has found no patients with clinically significant injury detected only on MRI.

Conclusions: The results of this study suggest that MRI does detect injuries not seen on CT or plain radiography in pediatric patients with traumatic brain imaging. Whether the injuries detected only on MRI are clinically significant remains uncertain. Given the limited patient population for this study, further and more extensive studies investigating the efficacy of MRI in the head-injured pediatric patient are warranted.

011

Sacks, Gina

Medical Student

T35 NHLBI Training Grant

Summer Research Program

Division of Plastic and Reconstructive Surgery

Department of Surgery, Washington University in St. Louis School of Medicine

Mentor: Susan E Mackinnon, MD

Evaluation of inter-rater reliability of the scratch collapse test

*Sacks G; *Groves AP; *Bansal A; Davidge K; Poppler L; Mackinnon S

Introduction: The scratch collapse test is a novel test, which employs a spinal reflex mechanism to evaluate compression neuropathy. The test has previously been validated for ulnar and peroneal compression neuropathies with reported sensitivities of 69% and 77% respectively and specificities of 99%. The objective of this study is to evaluate the inter-rater reliability of the scratch collapse test as a tool for assessing compression neuropathy

Methods: The scratch collapse test was studied prospectively in 101 sites of potential nerve entrapments among 26 patients. Each patient was separately examined by the senior author and three medical students. All examiners were blinded to the results of the other raters at the time of the examination. The three medical students were blinded to the patients' chief complaint and health history. The results from each examiner were then used to determine the inter-rater reliability of the scratch collapse test.

Results: Among all scratch collapse raters the correlation coefficient (ICC) was 0.59, or "good" reliability. In comparing each medical student rater to the senior author there was 86.1% agreement between rater 1 and the senior author, 96.04% agreement between rater 2 and the senior author, and 90.10% agreement between rater 3 and the senior author.

Conclusions: With the proper teaching methods, the scratch collapse test can be performed with good inter-rater reliability. It is therefore a reliable provocative test for examining compression neuropathy and can be used in conjunction with other clinical findings to make a diagnosis.

*All contributed equally to this work

012

Sacks, Gina

Medical Student

T35 NHLBI Training Grant

Summer Research Program

Division of Plastic and Reconstructive Surgery

Department of Surgery, Washington University in St. Louis School of Medicine

Mentor: Susan E. Mackinnon, MD

Evaluation of common peroneal nerve compression in high fall-risk patient populations

*Sacks G; *Groves AP; *Bansal A; Davidge K; Poppler L; Mackinnon S

Objective: To determine the prevalence of peroneal nerve compression in high-risk hospital patients.

Methods: Peroneal nerve compression was evaluated using two “provocative tests”: Tinel’s test and the more recent Scratch Collapse test. Muscle strength (dorsiflexion, plantar flexion, inversion, eversion) was also tested using Medical Research Council (MRC) grading.

Aim 1: A prospective cross-sectional study was conducted on patients identified as “moderate” to “high” risk for falling.

Aim 2: A prospective cohort study was conducted on patients undergoing elective cardiac surgery.

Results: *Aim 1:* The prevalence of peroneal nerve compression was found to be 42%, as evidenced by the presence of either provocative sign. Peroneal muscle weakness was found to be 35% in this population. Both provocative signs were found to be significantly correlated to muscle weakness, and to falling, tripping, or stumbling. Demographic data including age, heart disease, past joint replacement surgery, and foot numbness were significantly correlated to provocative signs.

Aim 2: In this population, 53% of patients experienced a change in provocative sign testing, and 26% developed peroneal muscle weakness.

Conclusions: This study confirms that peroneal nerve compression is common in patients at high risk for falls, and in patients undergoing elective cardiac surgery.

*All contributed equally to this work

027

Scheel III, Paul J

Medical Student

T35 NHLBI Training Grant

Summer Research Program

Division of Cardiothoracic Surgery

Department of Surgery, Washington University in St. Louis School of Medicine

Mentor: Varun Puri, MD

Effect of surgeon experience on short and long term outcomes in stage 1 lung cancer

Scheel PJ; Puri V; Bell J; Frederiksen C

Introduction: The changing healthcare environment has resulted in an increased focus on physician variables affecting patient outcomes. This study aims to determine how surgeon experience impacts short- and long-term outcomes after surgery for lung cancer.

Methods: A retrospective cohort study of patients undergoing lung resection for pathologic stage I lung cancer at Washington University. Baseline variables and treatment-related outcomes were abstracted from a prospectively maintained database and supplemented by chart review. Patients were separated based on the surgeon’s experience at time of operation into 3 groups: <5 years (Low Experience, LE), 5-15 years (Moderate Experience, ME), >15 years (High Experience, HE).

Results: Between 2000 and 2012, 800 patients underwent resection for pathologic stage I lung cancer. Of these, 178, 244, and 398 patients were in the LE, ME, and HE groups, respectively. Patients were similar across groups for major preoperative variables including comorbidities and age. The LE group had a higher proportion of males (LE: 53.4%, ME: 46.4%, HE: 44.9%, P=0.017) and non-white patients (LE: 21.3%, ME: 13.4%, HE: 10.6%, P=0.002). Surgeons in the LE group performed more lobectomies (as opposed to sublobar resection) than the other 2 groups (LE: 88.2%, ME: 78.6%, HE: 76.6%, P=0.005). The ME group performed a smaller proportion of non-thoracoscopic operations (LE: 65.2%, ME: 32.6%, HE: 66.6%, P=0.000). Early post-operative complications (POCs) and perioperative mortality were statistically similar across all groups regardless of operation. Long-term overall survival was worse in the LE group (5-year survival, LE: 67.5%, ME: 76.9%, HE: 71.4%, P=0.001). Dichotomizing patients based on type of operation demonstrated similar significant differences in 5-year survival for lobectomies (LE: 70.5%, ME: 80.7%, HE: 73.6%, P = 0.003), but not sub-lobar resections (LE: 43.8%, ME: 64.0%, HE: 61.5%, P = 0.060).

Conclusions: The experience of the operating surgeon does not seem to impact short-term outcomes after surgery for stage I lung cancer but long-term survival is lower in those undergoing an operation by less experienced surgeons.

040

Sun, Sam Q

Medical Student

T35 NHLBI Training Grant

Summer Research Program

Department of Neurosurgery, Washington University in St. Louis School of Medicine

Mentors: Albert H Kim, MD, PhD; Michael R Chicoine, MD

Recurrence in atypical meningiomas: an analysis of predictive factors and the role of adjuvant radiation

Sun SQ; Kim AH; Murphy RK; Cai C; Dacey RG; Grubb RL; Rich KM; Zipfel GJ; Dowling JL; Leuthardt EC; Leonard JR; Simpson JR; Huang J; Chicoine MR

Introduction: For patients with WHO Grade II atypical meningiomas (AM), it is difficult to predict which tumors will recur following gross total resection (GTR). Clinical features that predict recurrence are useful in identifying tumors that may benefit from closer observation or more aggressive treatment. The efficacy of adjuvant external beam radiation therapy (EBRT) for AMs following GTR also remains to be clarified. This study examines tumor characteristics that prompt adjuvant EBRT, and evaluates the relative benefit of adjuvant EBRT.

Methods: A retrospective review was performed of a database of over 828 meningioma patients to identify patients with primary AMs that underwent GTR between 1998 and 2011. Several risk factors of recurrence were assessed. Univariate analysis was used to assess whether any of these tumor characteristics also increase the likelihood of receiving adjuvant EBRT.

Results: 132 patients with AM underwent GTR (76 female, 56 male) with a median follow-up of 48.2 months (range 1 to 233 months). 11 patients (8.3%) had tumor recurrence at a median time of 43.6 months postoperatively (range 16 to 140 months). Univariate analysis identified mitotic index as a recurrence-predicting factor ($p = 0.03$) and revealed that tumors with larger greatest diameter ($p = 0.002$) and rare variant histology ($p = 0.01$) were more likely to receive adjuvant EBRT. Of 100 patients that had GTR only, nine patients recurred (9.0%) at a median time of 40.5 months postoperatively (range 16 to 130 months). Of 32 patients that had GTR and adjuvant EBRT, two patients recurred (6.3%) at a median time of 133 months postoperatively (range 125 to 140 months).

Conclusions: Overall, AMs exhibit a low recurrence rate after GTR. Although adjuvant EBRT after GTR of AMs delayed the time to recurrence, the potential of complications following EBRT and the lack of difference in overall recurrence between those who received and did not receive adjuvant EBRT suggests a more cautious stance regarding routine use of adjuvant EBRT.

086

Thomas, Ariel

Medical Student

T35 NHLBI Training Grant

Summer Research Program

Department of Obstetrics and Gynecology, Washington University in St. Louis School of Medicine

Mentor: Jenifer Allsworth, PhD

Contraceptive continuation in poverty areas

Thomas A; Allsworth J

Introduction: In this analysis, we intend to examine how residence in a poverty area alters contraceptive continuation among a cohort of women enrolled in the Contraceptive CHOICE Project. CHOICE enrolled 9,256 women living in the St. Louis region who are at risk for unintended pregnancy and provided no-cost contraception for up to 3 years. We hypothesize women in poverty areas are more likely to discontinue use of contraception during their time in CHOICE than women who live in non-impooverished areas.

Methods: This study is a secondary analysis of the Contraceptive CHOICE project. Our sample consisted of 5,034 participants with 24-month continuation data and census data for their tract. Participants were excluded if they were DMPA users. Participants were geocoded using ArcGIS and categorized by poverty measure using census data. Baseline demographics were compared across groups using χ^2 for categorical variables and ANOVA for continuous variables. Nelson-Aalen cumulative hazard curves were used to estimate rates of discontinuation and Cox proportional hazard models were used to generate hazard ratios for poverty categories. Discontinuation rates were compared for each method using a log-rank test of equality. Cox proportional hazard models were used for both 12- and 24-month continuation.

Results: At 24 months, LARC users in all groups discontinued at an estimated rate of 27.0-30.8%, while non-LARC users in all groups discontinued much faster at rates of 81.6-92.5%. Discontinuation rates for LNG-IUS and the pill were found to be associated with the poverty measure of a participant's residential area at both 12 and 24 months, with women living in extreme poverty areas more likely to discontinue either method (LNG-IUS $p=0.04$; OCPs $p=0.004$). There were no significant differences between groups for either all LARC methods or all non-LARC methods combined.

Conclusions: While significant differences in baseline demographics and other sexual history characteristics were noted among groups, contraceptive continuation did not differ significantly overall. This may be the result of the specific aims of the CHOICE project, which targeted women at highest risk.

015 Varman, Rahul
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T35 NHLBI Training Grant
Summer Research Program
Division of Plastic and Reconstructive Surgery
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Mentors: Ida Fox, MD; Susan Mackinnon, MD
Investigating patient access to surgical treatment options for cervical spinal cord injury to improve upper extremity function
Varman R; Hoben G; Fox I
Introduction: Spinal Cord Injury (SCI) can often lead to paralysis of the body. Currently there are various surgical treatment options available that can help improve upper extremity function. We performed this study to explore a hypothesis that patients with cervical spinal cord injury (CSCI) are given little info about and have poor access to surgeries to improve upper extremity function. Evaluations collected from clinical and physical therapy settings regarding initial and continued access to information can help improve continued distribution of knowledge to patients regarding surgical options for upper extremity function.
Methods: Data were collected from patients within the past two years who have recently undergone nerve transplant surgery to improve upper extremity function. Various facets such as gaining information about the surgical procedure or experience during the surgery and post-operative period were evaluated.
Results: Currently, investigation is still in progress and thus incomplete results have not been analyzed yet. Projected completion date for the investigation is early October of 2013 and at this time quantitative and qualitative results pertaining to the entire experimental group will be distributed. On a broad spectrum of current results, it seems as though patients are informed of surgical options, but independent access for further information such as from the Internet or other professionals can be limited or confusing.
Conclusions: Conclusion pending with completion of quantitative data collection in October of 2013.

112 Vryhof, Nicholas
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Summer Research Program
Department of Ophthalmology and Visual Science, Washington University in St. Louis School of Medicine
Mentors: David Beebe, PhD; Ying-bo Shui, MD, PhD; Fang Bai, MD
Examining the antioxidant potential of the eye: the degradation of Vitamin C
Vryhof NW; Beebe D
Introduction: Antioxidants are important in protecting the eye from oxidative stress. A previous study found that patients with a history of vitrectomy surgery or vitrectomy surgery with cataract had higher levels of oxygen and lower levels of ascorbic acid (AsA) in the aqueous humor. However, overall total reactive antioxidant potential (TRAP) values were not significantly different, suggesting some compensatory mechanism by which the eye maintains its antioxidant potential. It is hypothesized that a degradation product of ascorbic acid compensates the loss of TRAP due to ascorbic acid. The goals of this study were two-fold: a) to determine if degradation products of ascorbate also contribute to TRAP and b) to see if the regeneration of TRAP after the degradation of ascorbate seen *in vivo* also occurs *in vitro*, using bovine and human aqueous humor.
Methods: Simultaneous AsA assay (colorimetric assay, in triplicate) and TRAP assays (luminol chemiluminescence method, in triplicate) were performed on bovine aqueous humor under various conditions of temperature, time, and added compounds (e.g., threonate, erythrose, ascorbate oxidase).
Results: Threonate was not found to contribute to TRAP at any concentration, and erythrose only slightly contributed to TRAP. A study of the TRAP and AsA levels over time found that bovine and human aqueous humor lost the majority of its TRAP and all of its ascorbic acid after 48 hours, with no regeneration of TRAP up to 96 hours. It is not known what accounts for the residual TRAP.
Conclusions: Further research is needed to determine by what compensatory mechanism the eyes of vitrectomy patients maintain the total reactive antioxidant potential, despite having lower concentrations of ascorbic acid. Two degradation products of ascorbic acid, threonate and erythrose, were not found to significantly contribute to the TRAP *in vitro*. The expected return of TRAP over time did not occur *in vitro*, suggesting a more complex biological mechanism that requires *in vivo* conditions. Understanding this mechanism may lead to better preventative care for ocular diseases associated with oxidative damage, such as glaucoma and cataract.

003

Wagner, Julia

Medical Student

T35 NHLBI Training Grant

Summer Research Program

Departments of Neurology & Neurosurgery, Washington University in St. Louis School of Medicine

Mentor: Eric C Leuthardt, MD

Phase-power coupling in partial complex neocortical seizures

Wagner J; Leuthardt EC; Maccotta L

Introduction: Epilepsy affects three million Americans annually at a cost of about \$15.5 billion. About two thirds of affected individuals can achieve remission through medication, and while surgery can help a subset of those that cannot, surgical cure rates are 70% at best. Electrocorticography (ECoG) with subdural electrode placement has helped improve seizure focus localization and functional localization of eloquent cortex to assist in surgical procedures. The purpose of this project was to use ECoG data obtained from epileptic patients as a means of improving understanding of the cortical physiology associated with seizures and ultimately improving epilepsy surgery outcomes.

Methods: Phase-power coupling analysis was performed on ECoG data obtained from three patients with neocortical epilepsy during both baseline and seizure states. The analysis was performed with Matlab software using code written by Amy Daitch, a PhD candidate at Washington University in St. Louis, and based on that of Canolty et al., 2006.

Results: Overall, an increase in coupling between the phase of lower-frequency (0-30 Hz) waves and the amplitude of higher-frequency gamma (70-100 Hz) waves was observed during seizures compared to a baseline. When the lower frequency waves were divided into delta (1-3 Hz), theta (3-6Hz), mu (8-12 Hz), and beta (18-23 Hz) bands, phase-power coupling averaged across all patients and all trials was consistently elevated during the seizure ictus relative to baseline ($p < .001$). Furthermore, it was observed that the phase of phase-power coupling for which maximal power of the high-frequency wave occurred was similar for all patients in the baseline case, but highly variable during a seizure.

Conclusions: The results of this study suggest that phase-power coupling increases between various lower-frequency waves and cortical gamma waves during a seizure. We speculate that phase-power coupling is an inhibitory mechanism and, as such, represents the brain's attempt to suppress cortical hyper-activity during a seizure. For instance, phase-power coupling between thalamic delta waves and cortical gamma waves is increased during a seizure, possibly representing thalamic entrainment of the cortex.

090

Xiao, Daphne Y

Medical Student

T35 NHLBI Training Grant

Summer Research Program

Division of Newborn Medicine

Department of Pediatrics, Washington University in St. Louis School of Medicine

Mentors: Daniel Wegner, MA; Jennifer Wambach; F Sessions Cole, MD; Aaron Hamvas, MD

Identification of mutations associated with newborn respiratory distress syndrome.

Xiao DY; Wegner DJ; Wambach JA; Cole FS; Hamvas A

Introduction: Neonatal respiratory distress syndrome (RDS) is characterized by a deficiency in pulmonary surfactant production. Risk for RDS is heritable; however, not much is known about the genetic factors that contribute to this risk. The purpose of this large candidate gene study is to identify new genes that may account for a proportion of the heritability of RDS, using an individual-based approach.

Methods: 1500 lung-expressed genes were selected based on their importance to lung function, lung development, and the fetal-neonatal pulmonary transition. The exons of these 1500 genes were then sequenced in a cohort of 928 infants with and without RDS who were stratified by race. Genes were prioritized by filtering for rare, deleterious variants and by assuming autosomal recessive inheritance.

Results: After performing the variant filtering process and prioritizing by gene function, homozygous or compound heterozygous rare, deleterious variants in five genes were identified in the European-descent cohort in cases but not in controls (*AGER*, *NME8*, *FLNA*, *FER1L6*, and *TXNDC16*) and two genes were identified in the African-descent cohort in cases but not controls (*ABCA8* and *FLNA*).

Conclusions: Genetic factors contribute to risk for neonatal RDS, but little is known about the genes involved in disease pathogenesis. Complex traits, such as neonatal RDS, are likely to be multiple different rare diseases, each with a unique mechanism that warrants analysis at the individual level. By using an individual-based approach, we identified several genes that may contribute to the heritability of RDS. These included genes involved in inflammation (*AGER*), cilia maintenance (*NME8*), lipid transport (*ABCA8*), and vesicle fusion (*FER1L6*), all of which may have a link to the pathogenesis of RDS. While none of these genes were statistically significant after correction for multiple testing, our findings provide the basis for future, smaller candidate gene studies designed to replicate these gene associations.

Zhou, Daisy

Medical Student

T35 NHLBI Training Grant

Summer Research Program

Department of Anesthesiology, Washington University in St. Louis School of Medicine

Mentor: Michael Avidan, MBBCh, FCASA**Reconstitution of consciousness and cognition**

Zhou D; Blain-Moraes S; Alexander A; Tarnal V; Vanini G; Palanca BJ; Avidan MS; Basner M; Kelz MB; Mashour GA

Introduction: It has been previously assumed that emergence from general anesthesia occurs at a discrete point. Recent studies, however, indicate that emergence is a process evolving from basic consciousness to higher executive function. Here, we aim to determine the basic pattern of cognitive reconstruction following general anesthesia. These findings will advance clinical understanding of abnormal transitions from unconsciousness to consciousness, such as postoperative delirium, which are common occurrences that can prolong hospital stays and increase risk for additional complications.

Methods: 60 healthy 20-40 year-old volunteers will be randomly assigned to an anesthetized or an unanesthetized group and will be evaluated for performance in 6 cognitive domains (sensory-motor speed, visual object learning and memory, attention and working memory, sustained or vigilant attention, complex scanning and visual tracking, and abstract reasoning) using the NeuroCATS testing battery.

Results: Preliminary data from one anesthetized participant showed that the only cognitive domain in which the immediate post-anesthesia score was comparable to and not significantly below the baseline score was abstract reasoning. Transfer entropy analysis of EEG data from the same individual revealed that baseline neural networks were restored over time after emergence.

Conclusions: The EEG results support the view that cognitive restoration is a process, though it appears to extend for a longer time period than previously thought. The preliminary cognitive testing results, on the other hand, contradict our original hypothesis that the process of emergence follows a bottom-up pathway beginning with the return of basic responsiveness and ending in higher cognitive functions, such as abstract reasoning. More data are required both from anesthetized volunteers to reproduce these results, and from unanesthetized volunteers to account for the effects of test learning.

T35 NIH NIDDK Short-Term Training Program

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Abraamyan, Torgom

Medical Student

T35 NIDDK Training Grant

Summer Research Program

Department of Orthopaedic Surgery, Washington University in St. Louis School of Medicine

Mentor: Christopher McAndrew, MD

Relationship between pre-operative urinary tract infection (UTI) and surgical site infection (SSI) following traumatic hip fracture repair

Abraamyan T; Gardner MJ; Ricci WM; McAndrew CM

Introduction: Post-operative wound infections are a serious complication that may require re-hospitalization, secondary surgery and can be life-threatening. It has been hypothesized that urinary tract Infections may pose a risk of hematogenous seeding of the surgical site, predisposing the patient to infection. UTIs are common; especially in elderly, immobilized patients. Postponing fracture repair for UTI treatment would expose patients to the known morbidity (pneumonia, decubitus ulcers, GI dysfunction) and mortality associated with operative delays. The purpose of this study is to determine if the presence of pre-operative UTI is associated with an increased incidence of surgical site infection when compared to patients without UTI following operative treatment of hip fractures.

Methods: We examined the records of 723 patients (average age 71.7) who underwent operative hip fracture repair between 2004 and 2010 at BJH Department of Orthopaedic Surgery. We extracted information including SSI outcome, Urinalysis (UA) and Urine Culture (UCX) data, and comorbid conditions. Univariate analysis of independent variables and their relationship to SSI using the fisher exact test was performed.

Results: Overall, 250 (34.6%) out of 723 patients admitted for hip fracture repair tested positive on UA for UTI. Deep SSI, superficial SSI, and no infection rates were 3.73%, 12.2%, and 84.1%, respectively. 3.53% of UCX positive, 4.0% of UA positive, and 3.7% of UTI negative patients developed deep SSI. Patients who developed deep SSI had a higher incidence of comorbid conditions, including diabetes and tobacco. We found no association between positive UA with deep ($P = 1.000$; OR, 1.033; 95% CI 0.432-2.432) or superficial ($P = 0.905$; OR, 1.04; 95% CI, 0.635-1.701) SSI.

Conclusions: The results of this study indicate that pre-operative UTI does not increase the risk of SSI following traumatic hip fracture repair. Thus, pre-operative UTI should not be a reason for operative delay. Additionally, a higher prevalence of comorbid conditions in patients who developed deep infection indicates that overall health plays a major role in the development of SSI.

022

Cheng, Tiffany

Medical Student

T35 NIDDK Training Grant

Summer Research Program

Department of Surgery, Washington University in St. Louis School of Medicine

Mentor: Maria B Majella Doyle, MD

Survival in liver retransplants: a comparison to primary liver transplantation

Cheng T; Vachharajani N; Chapman WC; Doyle M

Introduction: Over 5,000 adult liver transplants are performed annually in this country as treatment for a variety of diseases. If this primary transplant fails, the only treatment option to prevent death is to perform a retransplant, which historically results in a decreased survival rate compared to the primary transplant. This becomes a problem because donor livers are in extreme shortage in this country, and we need to determine what factors are important for patient survival, so that we can best allocate this scarce resource to patients who are more likely to survive. The purpose of this study is to compare primary liver transplant and retransplant patients treated at this institution, and also to look at outcomes from retransplants due to recurrent Hepatitis C Virus.

Methods: This study used a prospectively maintained database at a single center. Out of the 845 adult liver transplants done at this institution between 1/1/2000 – 12/31/2011, 64 patients (7.6%) underwent a liver retransplant. The two cohorts were compared in terms of patient demographics, intraoperative and postoperative care, and survival outcome.

Results: When compared with the primary transplant patients, the re-OLT group was younger, had lower BMI and higher MELD scores, and required greater blood transfusion, longer operative times, and longer ICU/hospital stays. The 1, 3, and 5-year patient survival rate for retransplants was significantly lower than those for primary transplant (77.7%, 70.0%, and 64.2% versus 90.0%, 85.3%, and 79.6%, respectively, $P = 0.0085$). However, further examination indicates that the greatest mortality occurred in patients undergoing re-OLT for HCV recurrence. Remarkably, patients undergoing re-OLT for indications other than HCV recurrence had equivalent survival outcomes to patients undergoing primary transplant ($P = .1224$).

Conclusions: Patients undergoing retransplants do as well as primary transplant recipients, unless they are retransplanted for the recurrence of Hepatitis C Virus. These results suggest that liver retransplantation is a viable treatment option for most patients, and it need not generate as much hesitation and uncertainty as it had in the past.

- 018** **Gluckstein, Jeffrey**
Medical Student
T35 NIDDK Training Grant
Summer Research Program
Department of Surgery, Washington University in St. Louis School of Medicine
Mentor: Corey Deeken, PhD
The effects of mesh design on the mechanical properties of hernia meshes
Gluckstein JG; Deeken CR
Introduction: Tensionless hernia repair procedures using meshes reduce recurrence rates compared to suture repairs, but introduce new complications such as stiffness and infection due to the permanent placement of a foreign body at the repair site. These complications depend in part on the morphology of the meshes, as meshes with small pores or interstitial spaces are more susceptible to infection while meshes with large pores are more prone to the formation of adhesions. This study explored the effects of mesh density, thickness, pore size, and design on the fatigue properties of meshes in order to evaluate data about mesh strength in the context of known mesh complications.
Methods: Five experimental polypropylene meshes representing a range of weave designs, densities, thicknesses, and pore sizes were repetitively loaded for 0, 10, 100, or 1000 cycles to membrane tensions of 37 N/cm using a ball-burst fixture before being tested to failure. The strain and membrane tension during loading and at failure was compared between meshes.
Results: Meshes with small pores produced higher membrane tensions at failure and were significantly stiffer than those with large pores, while thickness and density did not correlate as closely. Nearly all the meshes were stiffer than the abdominal wall. The failure tensions were not slightly reduced by increased duration of repetitive loading, though the failure strengths of all but one mesh were well above the expected loads on the abdomen.
Conclusions: The experimental meshes tested displayed mechanical variability that depended mostly on weave design, with meshes with small pore sizes and higher densities outperforming meshes with lighter, more open designs. Small pore sizes have been linked to higher infection rates, but lower degrees of adhesion. Fortunately, all the meshes tested performed well during a repetitive loading condition representative of a worst-case scenario. The stiffness and anisotropy of meshes should be optimized to match the properties of the abdominal wall. Future studies, including an animal model, will improve on the limitations in loading scenario, loading environment, and mechanical model used in this study.
- 013** **Godbold, Tracey L**
Medical Student
T35 NIDDK Training Grant
Summer Research Program
Division of Public Health Sciences
Department of Surgery, Washington University in St. Louis School of Medicine
Mentor: Melody Goodman, PhD
Correlation between the racial composition of life environment and health literacy among low-income and underinsured patients at the Barnes-Jewish Center for Outpatient Health in St. Louis
Godbold TL; Goodman M
Introduction: This pilot study seeks to examine health literacy, individual health beliefs, health information seeking, health practices, and health outcomes among patients at the Primary Care Clinic at the Barnes-Jewish Center for Outpatient Health (COH); many of these patients are low income, uninsured/underinsured, and/or racial and ethnic minorities.
Methods: In this analysis we examine the association between the self-reported racial makeup of participants' previous (junior high school, high school and neighborhood growing up) and current life environments (place of worship, place of employment, current neighborhood) and their health literacy (assessed using the Newest Vital Sign and the Rapid Assessment of Adult Literacy in Medicine) using chi-squared test. Each participant's answers to these racial composition questions were classified using two dichotomous indicator variables for each environment: "mostly white"/"not mostly white" and "mostly black"/"not mostly black".
Results: Based on data from the pilot study, racial composition (both past and current) appears to correlate with health literacy. Individuals who reported previously or currently living and working in "mostly white" environments consistently scored higher on health literacy assessments than those who reported living and working in "mostly black" environments.
Conclusions: More research is needed to further determine the extent of this association and determine strategies for overcoming disparities in health literacy related to segregation. There is also a need to develop a racial composition/segregation measure that can used with low literacy populations.

052

Kleckner, Vanessa L

Medical Student

T35 NIDDK Training Grant

Summer Research Program

Department of Pathology and Immunology, Washington University in St. Louis School of Medicine

Mentor: Thaddeus Stappenbeck, MD, PhD

Study of the T300A mouse secretory lineage and its contribution to Crohn's Disease pathogenesis

Kleckner VL; Patel KK; Stappenbeck TS

Introduction: The prevalence of Crohn's Disease (CD) has been increasing worldwide. Meta-analysis of genome-wide association studies (GWAS) identified 163 susceptibility alleles for inflammatory bowel disease including ATG16L1 T300A, which is important in CD. Mouse models with Atg16l1 knockout in the intestinal epithelium showed profound defects in the secretion by Paneth cells (antimicrobial proteins) and goblet cells (mucus). To study the function of the T300A polymorphism, mice have been generated that contain this polymorphism. My goal was to examine the effects of the T300A mutation on intestinal secretory lineages in this line of mice. I hypothesized that the T300A allele would lead to abnormalities in secretory cells.

Methods: I compared the T300A knock-in mice to age-matched, wild-type control mice using both histological sections of the intestines and cultured cell lines developed from these mice.

Results: QRT-PCR analysis on the 3D cultured cell lines showed that the T300A knock-in cells had diminished expression of most secretory markers for goblet and Paneth cells. However, knock-in cells expressed higher levels of mRNA encoding the stem cell marker LGR5. Histological analysis of colons showed that T300A knock-in mice uninfected with murine norovirus (MNV) contained fewer goblet cells per crypt than controls. In colons from mice infected MNV, no difference in the number of goblet cells was observed between these two groups. However, the T300A knock-ins had enlarged goblet cells. No difference in goblet cell size was observed in uninfected mice or the cultured colon and small intestine lines.

Conclusions: Our data indicate that the T300A allele is associated with alterations in intestinal secretory cells. The mechanism for these effects is still under investigation. Further study elucidating the mechanism for these differences will help uncover the pathogenesis of this key mutation in CD.

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Lalchandani, Gopal R

Medical Student

T35 NIDDK Training Grant

Summer Research Program

Department of Orthopaedic Surgery, Washington University in St Louis School of Medicine

Mentor: Ryan P Calfee, MD

Impact of obesity on postoperative complication rates in hand surgical patients

Lalchandani GR; London DA; Stepan J; Wildes T; Calfee RP

Introduction: Currently over 36% of US adults are obese; a categorization linked to both general and orthopaedic health problems. In lower extremity surgery, numerous studies have demonstrated heightened complication rates in obese patients. We sought to compare the rates of postoperative complications experienced by obese and non-obese hand surgical patients.

Methods: This was an IRB approved retrospective case-control study. From 2009-2013, 436 patients that received one type of hand surgery (bony, soft tissue, or nerve) with a BMI>35 were identified (cases). Controls were patients (n=436) with a BMI<30 who also had hand surgery over the same period, frequency matched by age, gender, and type of surgery. Post-operative complications were defined as the need for antibiotics post-operatively, infection, poor incision healing, nerve injury, wound dehiscence, hematoma, and reoperations. Medical comorbidities (i.e., hypertension, diabetes, stroke, vascular disease, kidney disease, and liver disease) were recorded. Chi-square analyses were performed to see if there was an association between being obese (BMI>35) and post-operative complications. Similar analyses were performed stratified on surgery type. Logistic regression modeling was performed to identify predictors of post-operative complications accounting for surgery type, BMI, the presence of comorbidities, patient age, and patient sex. This same model was also run separately for case and control patients.

Results: The overall complication rate was 8.7% with similar rates between obese and non-obese patients (8.5% vs 9.0%, p=0.79). An association exists between surgery type and developing post-operative complications in both obese and non-obese patients (p<0.02). Multivariate analysis revealed surgery type as the only significant predictor of complications for non-obese patients (p<0.01). However, for the obese patients, both bony surgery (p=0.02) and increasing BMI (p=0.03) were associated with greater complication rates.

Conclusions: In general, obese patients do not appear to be at any higher risk for post-operative complications after hand surgery. However, there does appear to be a dose-response effect for BMI in obese patients such that greater obesity leads to greater risk of complications.

080

Lindburg, Miranda R

Medical Student

T35 NIDDK Training Grant

Summer Research Program

Division of Emergency Medicine

Department of Internal Medicine, Washington University in St. Louis School of Medicine

Mentor: Lawrence M Lewis, MD

The Rivermead Post-Concussion Questionnaire in the acute and recovery phases of mild traumatic brain injury

Lindburg MR; Lewis LM

Introduction: The Rivermead Post-Concussion Questionnaire (RPQ) is a 16-item measure that attempts to quantify post-concussive symptoms following a traumatic brain injury (TBI). Subjects self-report the presence of symptoms, such as headache, nausea, sensitivity to noise, using a 0-4 Likert scale. Rasch analysis of the RPQ has shown that it is better split into a 3-item scale consisting of items headache, nausea, and dizziness (RPQ-3) and a 13-item scale with the remaining measures. Although the RPQ has been validated in the "recovery phase" (days to months following a TBI), it has not been studied in the acute setting. The purpose of this study was to determine whether the RPQ-3, RPQ-13, and/or RPQ total would be a useful measure in the ED to help rule in concussion.

Methods: The RPQ was administered to 80 subjects in 7 ED centers upon presentation for experiencing a mild TBI. Subjects also took the RPQ at about 38 days post-injury. Comparisons were made with the Wilcoxon Signed-Rank test between initial and final administration on the RPQ-3, RPQ-13, and RPQ total.

Results: Mean scores on both the RPQ-3 and RPQ-13 decreased from initial to final administration. Initial and final scores on the RPQ-3 and RPQ total were significantly different at the $p < .0005$ level, and on the RPQ-13 were significantly different at the $p < .03$ level.

Conclusions: The results of this study suggest that the RPQ normalizes over time as patients recover from concussion, and shows significantly higher scores in the acute setting. This may mean that the RPQ can be used as an instrument to quantify MTBI severity in emergent situations.

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Lohse, Austin

Medical Student

T35 NIDDK Training Grant

Summer Research Program

Department of Ophthalmology and Visual Sciences, Washington University in St. Louis School of Medicine

Mentor: Anjali Borade, MD

IOP surprise study: quantifying the difference in intraocular pressure at home vs. clinic

Lohse AJ; Borade A

Introduction: Elevated intraocular pressure (IOP) is the predominant risk factor for glaucoma. IOP measured at the clinic may not be the most accurate assessment of a patient's true eye pressure. For instance, blood pressure (BP) measured at home or with an ambulatory monitor is a much better predictor of cardiovascular disease, cerebrovascular disease, and end organ damage than BP obtained from a one-time clinical measurement. Few studies have quantified the extent to which IOP values are influenced by the environment. In this study, clinic IOP was compared to home IOP for patients with stable, actively treated glaucoma or ocular hypertension. To assess patient compliance, home measurements were obtained during "surprise" visits.

Methods: Clinic IOPs and BPs were obtained in 120 patients (≥ 18 years) with stable glaucoma or ocular hypertension living within a 50-mile radius of Barnes-Jewish Hospital in St. Louis, Missouri. IOPs were measured once in clinic and once at home using a Tono-Pen AVIA® Applanation Tonometer. BP was measured immediately after IOP with an Omron BP785 10 Series Upper Arm Blood Pressure Monitor. Following BP measurement, patients were asked to complete several questionnaires and rate their anxiety level on a scale of 1-10. Home IOPs were obtained 2-5 weeks after the clinic visit, and patients were not notified until the morning of the home visit.

Results: The data have been collected and verified using patient medical records. Results have yet to be processed by a statistician.

Conclusions: A decrease in IOP at home versus clinic would serve as evidence for the possibility of a "white coat" effect. If "white coat" ocular hypertension is shown to exist, ophthalmologists may be giving their patients unnecessarily high doses of ocular antihypertensives. A reduced effective dose would make ocular antihypertensives more affordable and improve the lives of those with conditions exacerbated by bradycardia, bronchoconstriction, and other common side effects. On the other hand, an increase in IOP at home versus clinic would most likely be the result of reduced adherence to the prescribed treatment. Regardless of the outcome, this study will give the medical community an important first look at how home IOP values compare to those obtained in a clinical setting.

006

Lorbeer, Karly

Medical Student

T35 NIDDK Training Grant

Summer Research Program

Department of Surgery, Washington University in St. Louis School of Medicine

Mentor: L Michael Brunt, MD

Comparison of local institutional and national database outcomes for adrenalectomy: a comprehensive retrospective analysis

Lorbeer KF; Hall BL; Brunt LM

Introduction: Laparoscopic adrenalectomy is the preferred approach for removal of most adrenal lesions. Several studies have used national databases to show the benefits of this approach. Yet, national databases for adrenal surgery may fail to capture important factors that impact patient outcomes and no comparisons of institutional outcomes and national databases have been done. The purpose of this study is to compare the outcomes, complications, indications and trends for selection of open vs. laparoscopic adrenalectomy in a specialized tertiary care center such as Washington University Medical Center to the national community of general surgeons as indicated by the American College of Surgeons National Quality Improvement Program (ACS NSQIP) database.

Methods: Retrospectively collected data for patients over the age of 16 who underwent adrenalectomy as the primary procedure at Barnes Jewish Hospital between 2001 and 2012 were used. Patients in the ACS NSQIP databases from 2005 to 2012 who had primary Current Procedural Terminology for adrenalectomy and a postoperative *International Classification of Diseases, Ninth Revision* (ICD-9) code for adrenal gland pathology were included. Outcomes measures include complication frequency and type, postoperative length of stay, 30-day morbidity and mortality.

Results: It is anticipated that the results of this study will provide new insights into the outcomes, complications, indications and trends for open vs. laparoscopic adrenalectomy for a specialized, tertiary care center compared to those in the general surgery community.

Conclusions: The results may be useful in identifying important variables that should be included in the NSQIP database for adrenalectomy.

089

Martin, Lauren

Medical Student

T35 NIDDK Training Grant

Summer Research Program

Division of Pediatric Emergency Medicine

Department of Pediatrics, Washington University in St. Louis School of Medicine

Mentor: Mark Manary, MD

Comparison of two ready-to-use supplementary foods for the treatment of moderate acute malnutrition in rural Malawian children: a randomized, double-blinded, clinical effectiveness trial

Martin L; Thakwalakwa C; Manary M; Ryan K; Maleta K

Introduction: Worldwide, 10.2% of deaths among children under five years of age have wasting or moderate acute malnutrition (MAM) as an important underlying cause. This study compares a peanut-whey ready-to-use supplementary food (RUSF) to peanut-soy RUSF, which has been proven to be effective in treating MAM. Due to its high mineral content, whey permeate is a cost-effective alternative to some of the added minerals in the micronutrient premix. Growth outcomes are measured to determine efficacy of the RUSF.

Methods: This is a prospective, randomized, double-blinded, clinical effectiveness trial of two RUSF in the treatment of MAM. The study includes 15 rural sites in southern Malawi. The participants are 1800 children 6-59 months old with MAM, defined as mid-upper arm circumference (MUAC) ≥ 11.5 cm and < 12.5 cm without bipedal edema. Children receive approximately 75 kcal/kg/d of one of the two RUSF in two-week rations for outpatient therapy of MAM for up to 12 weeks. The primary outcome measures are recovery from MAM (achieving MUAC ≥ 12.5 cm by 12 weeks) or failure (death, development of severe acute malnutrition, transfer to hospital for inpatient care, failure to recover from MAM by 12 weeks, or loss to follow-up). Secondary outcome measures include rates of weight, height, and MUAC gain, time to graduation, and adverse effects from the RUSF. Fisher's Exact test and Student's t-test will be used to compare the outcomes.

Results: It is anticipated that the two RUSF will have similar efficacies due to the similar nutrient profiles. Therefore, we expect that the proportion of children who recover receiving either soy or whey RUSF will differ by no more than 3%.

Conclusions: In comparing the effectiveness of two supplementary foods for the treatment of MAM, we hope to provide public health agencies with a cost-effective alternative to the standard treatments for MAM.

091

Meyerson, Cherise

Medical Student

T35 NIDDK Training Grant

Summer Research Program

Department of Pediatrics, Washington University in St. Louis School of Medicine

Mentor: Mark Manary, MD

Growth and HIV-free survival of HIV-exposed infants in Malawi: A randomized trial of two complementary feeding interventions in the context of maternal antiretroviral therapy

Meyerson C; Thakwalakwa C; Phiri A; Rollins N; Heikens GT; Barnell EK; Manary M

Introduction: Prevention of mother-to-child transmission of HIV and maintenance of normal growth in HIV-exposed infants has been difficult to achieve in Malawi. Without the use of antiretroviral therapy (ART), HIV transmission rates through breastfeeding are about 0.7%/mo of breastfeeding in the first year, and early cessation of breastfeeding is associated with increased morbidity from diarrheal disease, growth faltering, and death in HIV-exposed infants. This study was designed to test whether infant growth faltering would be better ameliorated using a ready-to-use food (RUF) or milk powder with micronutrient supplement. The main objective was to assess HIV-free survival and compare growth of HIV-exposed children receiving one of two complementary foods following prevention of mother-to-child HIV transmission through maternal lifelong ART.

Methods: HIV-infected pregnant women were identified in rural Malawi and offered ART without consideration of their CD4 counts. All screened mothers were encouraged to exclusively breastfeed after delivery. From this group, 248 children who tested negative for HIV at 6 mo were given a daily micronutrient supplement and randomized to receive either RUF or whole milk powder until the child reached 12 mo. Children were followed until 18 mo.

Results: HIV-free survival at 12 mo was 95% (95%CI 93-97%). Exclusive breastfeeding for the first 6 mo was practiced in 97% of the children. At 12 mo, 89% of the children continued to be breastfed. At 6 mo, infants had a median weight-for-height z score (WHZ) of 0.7 ± 1.1 (mean \pm SD) and length-for-age z score (LAZ) of -1.3 ± 1.2 . Average WHZ was > 0 at 12 and 18 mo in all children.

Conclusions: This study shows that maternal lifelong ART and complementary feeding significantly reduce mother-to-child transmission of HIV and maintain infant growth. Based on these results, there is strong support for hospitals to adopt this standard of care for HIV-infected mothers and their children.

024

Ott, Katherine

Medical Student

T35 NIDDK Training Grant

Summer Research Program

Division of Transplant Surgery

Department of Surgery, Washington University in St. Louis School of Medicine

Mentor: William Chapman, MD

The role of anti-CD47 antibody in phagocytosis of hepatocellular carcinoma in vitro

Ott K; Xiao Z; Upadhyaya GA; Manning P; Frazier P; Chapman W

Introduction: The blockade of CD47 signaling using targeted monoclonal antibodies has been shown to promote macrophage phagocytosis of previously protected tumor cells; however, studies have not investigated the role of CD47 in hepatocellular carcinoma (HCC). The purpose of this study is to examine the expression of CD47 in HCC and to determine if anti-CD47 antibody can induce a therapeutic response in vitro.

Methods: Fixed clinical HCC and normal liver samples were stained and immunofluorescence intensity was measured for each in order to detect the expression of CD47. Macrophages isolated from NOD/SCID/y(NDG) mice and HepG2 cells were grown together in culture in the presence of either IgG control, 2D3 or one of two anti-CD47 antibodies (400 and 440). Phagocytic activity was visualized using confocal microscopy and the phagocytic index was measured for each antibody. For the MTT assay, HepG2 cells were grown in culture, counted and separated into wells in equal number, and 10ug/ml IgG, 2D3, Ab400, and Ab440 were individually added to the wells. MTT was later added and the absorbance of each well was measured.

Results: Normal liver tissue had an average CD47 immunofluorescence intensity of 18.6 (SD 1.41), adjacent tissue had an intensity of 25.7 (SD 2.60) and HCC tissue had an intensity of 87.8 (SD 6.12). The average phagocytic index of the anti-CD 47 antibody 400 was 71 (SD 2.05) and that of antibody 440 was 75 (SD 1.70). The phagocytic index of the IgG was 12 (SD 0.47) and that of 2D3 was 10 (SD 1.25). The MTT assay showed no significant difference in cell toxicity between any of the antibodies. The average absorbance for cells with added IgG was 0.552 (SD 0.02), 2D3 was 0.550 (SD 0.02), mAb400 was 0.547 (SD 0.01) and mAb440 was 0.560 (SD 0.02).

Conclusions: CD47 is expressed at significantly higher levels in hepatocellular carcinoma cells when compared to normal liver cells in patients. While not cytotoxic to tumor cells, anti-CD47 antibodies (400 and 440) induce phagocytosis of HepG2 cells in vitro where IgG and 2D3 antibodies do not. This in vitro study indicates that anti-CD47 antibody could be a useful therapeutic tool for HCC.

070

Slade, Michael J

Medical Student

T35 NIDDK Training Grant

Summer Research Program

Division of Infectious Diseases

Department of Internal Medicine, Washington University in St. Louis School of Medicine

Mentor: Michael Lane, MD, MSc

Process analysis of outpatient parenteral antibiotic therapy in the infectious disease clinic

Slade M; Lane M

Introduction: The practice of treating patients with parenteral antibiotics in an outpatient setting has grown steadily since its introduction in 1974, driven both by decreased cost relative to continued hospitalization and patient preference. Because of the multitude of organizations participating in the provision of OPAT, however, the ongoing management of these patients from the perspective of an infectious disease practice is often complex and difficult. The purpose of this paper is to analyze the challenges of one infectious disease clinic and examine a number of potential solutions using established process improvement methodology.

Methods: Current processes were established through repeated interviews with infectious disease clinic staff and personal observations from time spent following physicians in the clinic. Common process failures were identified in a similar fashion. These areas were then compared to standard practice and analyzed using ideal vs. actual flow state diagrams, Ishikawa diagrams and the "5 Whys" methodology. Results of the analyses were used as a starting point to create solutions.

Results: Failure to monitor patients' labs between hospital discharge and initial office visit was identified as the most common process failure in continuing care of OPAT patients by the infectious disease clinic. Another common process failure was difficulty finding the physician responsible for post-hospital, pre-clinic care. A myriad causes led to failure to monitor labs and the following solutions were considered: identifying a responsible entity for lab reporting, standardizing forms, practice or IT, and the addition of a system to identify missed lab draws.

Conclusions: While some problems can be addressed through training, lack of incentive for multiple organizations to embrace a single standard practice proved the biggest obstacle for any quality improvement intervention. Failure to transfer information effectively across the multiple silos currently inherent to administering OPAT treatment remains the great challenge to improving the quality of care in this area.

084

Swor, Erin

Medical Student

T35 NIDDK Training Grant

Summer Research Program

Contraceptive CHOICE Project

Division of Family Planning

Department of Obstetrics and Gynecology, Washington University in St. Louis School of Medicine

Mentor: Colleen McNicholas, DO

Comparing serum etonogestrel levels in implant users across BMI categories at the end of three years of use

Swor E; McNicholas C; Secura G; Piepert J

Introduction: Almost half of all pregnancies in the United States are unintended. Increasing the use of long acting reversible contraceptive methods has been shown to decrease unintended pregnancy, but research on these methods is limited in overweight and obese women. The contraceptive implant is highly effective at preventing pregnancy via the slow release of etonogestrel (ENG) and has a failure rate of just 0.05%. Previous literature has shown that women with higher BMIs have lower ENG levels following insertion, but not more unintended pregnancies over time. The purpose of this study is to characterize serum ENG levels after three years of implant use and compare the results in overweight and obese women with women of normal weight.

Methods: Women willing to continue using their contraceptive implant beyond the FDA-approved duration (3 years) were enrolled and are being followed prospectively. Participants complete baseline demographic and reproductive health histories as well as undergo periodic venipuncture for analysis of serum ENG levels. Samples from 38 women distributed across BMI categories were analyzed using χ^2 test, Fisher Exact test, and ANOVA.

Results: Of the 115 implant users enrolled, 20.9% were of normal weight (BMI less than 24.9), 27.8% overweight (25-29.9), 28.7% obese (30-39.9) and 22.6% morbidly obese (40 and above). Women with higher BMIs were more likely to be of lower socioeconomic status, higher gravidity, and report a history of unintended pregnancies. Mean three-year ENG levels were not different across BMI categories (normal weight 172.6, overweight 173.3, obese 189.3, morbidly obese 190.0, $p=0.96$). There have been no documented pregnancies.

Conclusions: Overweight and obese women do not appear to have lower serum ENG levels than normal weight women at the end of three years of use. The implant should be considered a highly effective contraceptive method for women of all BMI classes through the entire 3 years of FDA-approved duration.

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Xu, Amy

Medical Student

T35 NIDDK Training Grant

Summer Research Program

Department of Orthopaedic Surgery, Washington University in St. Louis School of Medicine

Mentor: Jacob M Buchowski, MD, MS

Surgical spinal fusion rate following implementation of preoperative serum vitamin D measurement and repletion: a single-center investigation

Xu A; Stoker GE; Buchowski JM

Introduction: Vitamin D has a critical role in maintaining mineral homeostasis and bone health, yet vitamin D deficiency remains common around the world. At this institution, low vitamin D levels are present in a majority of adults undergoing spinal fusion surgery, a condition that can hinder successful bone fusion and prolong recovery time. In 2010, we began measuring the serum vitamin D levels of adult patients scheduled to undergo spinal fusion surgery, supplementing with vitamin D if a deficiency was identified. This study assesses the impact of our implementation of preoperative serum vitamin D measurement and repletion on the rate of successful surgical spinal fusion.

Methods: An investigational cohort was retrospectively assembled of 313 patients who underwent spinal fusion surgery between January 2010 and March 2011, had preoperative serum 25-hydroxyvitamin D (s25D) level measurements, were at least 18 years of age, and had at least 2 years of clinical and radiographic follow-up. Similar inclusion criteria were applied in assembling the 313-patient control cohort, except that control patients underwent spinal fusion before January 2010 and did not have prior serum vitamin D assessment. Chi-squared and Fisher's exact tests will be used to compare rates across the cohorts; variables that differ with a $P \leq 0.2$ will be included as covariates in subsequent multivariate analysis. Binary logistic regression will be performed to determine whether a statistically significant difference in fusion rate exists between cohorts.

Results: Initial cohort assembly was completed in August 2013. Subsequent data analysis will be performed in October 2013, with results expected shortly thereafter.

Conclusions: Given the pivotal role of vitamin D in normal bone homeostasis and long bone fracture healing, we expect that our practice of vitamin D measurement and supplementation will result in higher rates of successful surgical spinal fusion in the investigational cohort as compared to the control cohort.

020

Zhu, Tina

Medical Student

T35 NIDDK Training Grant

Summer Research Program

Division of Public Health Sciences

Department of Surgery, Washington University in St. Louis School of Medicine

Mentor: Kim Kaphingst, PhD

Predictors of health outcome among patients at Barnes Jewish Center for Outpatient Health

Zhu T; Kaphingst K

Introduction: Several factors influence health outcomes, including health literacy, education, social support and socioeconomic status. Patients at the Center for Outpatient Health (COH) were surveyed on how they rated themselves on the aforementioned factors. It is hoped such information can be used to tailor the Center's provision of care and improve outcomes.

Methods: Patients in the COH waiting room were asked to voluntarily complete the survey. Each survey had a written portion and an orally administered health literacy test. Frequencies of each response were tallied per question. The project is ongoing; data here represents the first 332 complete surveys.

Results: 48% of patients were at risk for low health literacy. 84% reported moderate to high confidence filling out medical forms, 68% reported rarely or never needing help reading hospital materials and 45% reported rarely or never having trouble understanding written medical information. Social support satisfaction was average. 82% were on public insurance or no insurance, 50% had incomes below \$10,000, and 20% were employed full or part-time. 83% had at least a high school diploma or GED.

Conclusions: Patients varied in their ranking on predictors of health outcomes. Most finished high school or a GED and were confident filling out medical forms by themselves. Yet 48% were deemed at risk for low health literacy and 55% reported having trouble understanding written medical information at least sometimes. More effort might be necessary to help patients understand and access health information.

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