32nd Annual Research Forum

Wednesday, April 30, 2014
4:00pm – 6:30 p.m.
208 Light Hall

Established and Sponsored by the Vanderbilt University House Staff Advisory Council
Vanderbilt University Medical Center’s Research Forum provides an opportunity for non-faculty VUMC personnel to present research conducted at Vanderbilt. This Forum is open to all Vanderbilt University House Staff and Medical Students.

Research must have been performed at Vanderbilt. Unpublished work is eligible and encouraged. Work already published, or presented at another meeting, is also eligible and encouraged. All submitted abstracts are published in the Vanderbilt University Medical Center Research Forum book.

Abstracts are reviewed and selected for either an oral or a poster presentation by a panel of Vanderbilt School of Medicine faculty members who are actively involved in clinical and basic science research. There are six abstracts selected for oral presentation—three in Basic Science Research and three in Clinical Research. After the oral presentations at the Forum, the best overall project in each category (Basic Science Research and Clinical Research) will be awarded an Elliot V. Newman Award.

The Grant W Liddle Award, which honors a faculty member who demonstrates exemplary leadership in the promotion of scientific research at Vanderbilt University Medical Center, is presented annually at the Forum.
THIRTY-SECOND ANNUAL RESEARCH FORUM

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Resident, General Surgery

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Neurosurgery Department
GRANT W. LIDDLE AWARD

The Grant W. Liddle Award was established in 1983 by the Vanderbilt University Medical Center house staff to recognize faculty members who demonstrate exemplary leadership in the promotion of scientific research at the Vanderbilt University Medical Center.

A native of American Folk, Utah, Dr. Liddle graduated first in his class from the University of Utah in 1943. After obtaining an M.D. degree from the University of California, San Francisco, in 1948, he served as a post-doctoral fellow at the newly formed Metabolic Research Unit at the NIH. In 1956, Dr. Liddle was recruited by Dr. Hugh J. Morgan to become Director of Endocrinology at Vanderbilt University. He was named Chairman of the Department of Medicine in 1968, a position he held until 1983.

Dr. Liddle’s career was marked by commitment to excellence in research, patient care, and the teaching of house staff and medical students. His research accomplishments include developing the dexamethasone suppression test and metyrapone test for assessing pituitary-adrenal gland function; describing a new form of hypertension, pseudohypoaldosteronism (Liddle’s Syndrome); developing spironolactones as useful aldosterone antagonists; and systematically improving methods for treating Cushing’s disease. In 1982, he was elected to the National Academy of Sciences and to the Royal College of Physicians in England.

Past Recipients of the Grant W. Liddle Award are:

2013  Terence S. Dermody, M.D.
2012  Russell Rothman, M.D., MPP
2011  Alfred L. George, Jr., M.D.
2010  Harold L. Moses, M.D.
2009  D. Brent Polk, M.D.
2008  Dennis Hallahan, M.D.
2007  Nancy J. Brown, M.D.
2006  Adrian Jarquin-Valdivia, M.D., R.D.M.S.
2005  Marshall L Summar, M.D.
2004  Denis M. O’Day, M.D.
2003  Herbert S. Schwartz, M.D.
2002  John A. Zic, M.D.
2001  Kathryn M. Edwards, M.D.
2000  R. Michael Rodriguez, M.D.
1999  David H. Van Buren, M.D.
1998  Charles Wright Pinson, M.D., M.B.A.
1997  Steven Leach, M.D.
1996  Jason D. Morrow, M.D.
1995  Robert H. Ossoff, M.D., Ph.D.
1994  William O. Richards, M.D.
1993  Barney S. Graham, M.D.
1992  Gordon Bernard, M.D.
1991  Achilles Demetrious, M.D., Ph.D.
1990  David Robertson, M.D.
1989  Robert Collins, M.D.
1988  Stanley Cohen, Ph.D.
1987  John A. Oates, M.D.
1986  David T. Karzon, M.D.
Elliot Voss Newman was a distinguished cardiologist, scientist, medical scholar and teacher. A graduate of Harvard College and Medical School, Dr. Newman came to Vanderbilt from Johns Hopkins University in 1952 to establish a program of clinical physiology and research. The author of the electrocardiography chapter in Harrison’s Textbook of Medicine and of the renal physiology chapter in Cecil and Loeb’s textbook, Dr. Newman was a pioneer in the development of medical engineering and the use of applied mathematics and computer science for clinical problems. Dr. Newman was the first Joe and Morris Werthan Professor of Experimental Medicine at Vanderbilt and was founder of the Clinical Research Center, which bears his name. He was a friend and mentor to medical students and house officers alike and helped to promote the scientific careers of many.

Recent Elliot V. Newman Award recipients:

2013
Bobak Parang, B.A.— VMS II, *BVES Suppresses Inflammatory Carcinogenesis*
Young Min Lee, B.S.P.H.— VMS III, *Recovery from Sports-Related Concussion: Days to Return To Neurocognitive Baseline in Adolescents vs. Young Adults*

2012
Jonathan Kropski, M.D.— Clinical Fellow, Allergy, Pulmonary & Critical Care Medicine
“*Murine Herpesvirus-68 Infection Exacerbates Endoplasmic-reticulum Stress in Alveolar Epithelial Cells and Acts As a “second-hit” in the Development of Lung Fibrosis*”
Patrick C. Drayna, M.D. – Clinical Fellow, Pediatric Emergency Medicine
“*Ketamine Sedation is not Associated with Clinically Meaningful Elevation of Intraocular Pressure*”

2011
Stephen Tourjee, B.A. - VMS III
*The Impact of Nerve Blocks on Opioid Use and Hospital Length of Stay in Patients with Traumatic Lower-Extremity Injury*”
Young I. Cha, M.D., Ph.D. - Resident, Radiation Oncology
“*Sensitivity of HPV (+) Oropharyngeal Head and Neck Cancers to Poly (ADP-ribose) Polymerase, PARP, Inhibition, Due to Defective DNA Damage Response*”

2010
Daniel J. Moore, M.D., Ph.D. - Clinical Fellow, Pediatrics and Microbiology & Immunology
“*Targeting the Nuclear Import Shuttle Resolves Insulitis and Arrests Type 1 Diabetes*”
Joyce P. Granger, M.D. - Clinical Fellow, Pediatric Emergency Medicine
“*Reliability of End Tidal CO2 Monitoring in Acute Pediatric Asthmatic Attack*”

2009
James M. Dies, M.D. - Clinical Fellow, Emergency Medicine
“*Parental Knowledge and Use of Preventive Asthma Care Measures*”
Shih-Hsin Eddy Yang, M.D., Ph.D. - Resident, Radiation Oncology
“*Inhibition of GSK3β Enhances Repair of Radiation-Induced DNA Double Strand Breaks in Hippocampal Neurons*”
THIRTY-SECOND ANNUAL
VANDERBILT UNIVERSITY RESEARCH FORUM
Wednesday, April 30, 2014 • 4:00pm – 6:30pm • 208 Light Hall

4:00 OPENING REMARKS.............................................................. Jonathan Kropski, M.D.
WELCOME.................................................................................. Donald W. Brady, M.D.
INTRODUCTION OF FORUM MODERATOR............................... Vance L. Albaugh, M.D.
FORUM MODERATOR............................................................... Terence S. Dermody, M.D.

4:15 Roflumilast Abrogates Nontypeable Haemophilus influenzae (NTHi)-induced Inflammation and Remodeling in Polymeric Immunoglobulin Receptor Deficient Mice
Bradley W. Richmond, Ru-Hong Du, Yongqin Zhang, Dong-sheng Cheng, Linda Gleaves, Timothy S. Blackwell, Vasiliy V. Polosukhin

4:30 Cell-free hemoglobin elicits a pro-inflammatory response in lung epithelial cells
Cameron Upchurch, Brandon Grove, Ciara Shaver, David Janz, Lorraine Ware, Julie Bastarache

4:45 B cell responses to HIV antigen are a potent correlate of viremia in HIV-1 infection and improve with PD-1 blockade
Emily Zern, Katherine Nicholas, Louise Barnett, Rita Smith, Shelly Lorey, Courtney Copeland, Shanmugafalshmi Sadagopal, Spyros Kalams

5:00 Heterotopic Ossification After Hemiarthroplasty of the Hip – A Comparison of Three Common Approaches
Chad M. Corrigan, Phillip Mitchell, Arie Francis, Adan Omar, Rachel V. Thakore, Vasanth Sathiyakumar, William T. Obremskey, Manish K. Sethi

5:15 Plasma Kidney Injury Molecule (KIM-1) and Endothelin-1 (ET-1) are associated with worsening renal function in heart failure patients
Eitan Friedman, Daniel Lenihan, John Todd, Joel Estis

5:30 New-onset atrial fibrillation is independently associated with increased mortality in critically ill patients
Ciara M. Shaver, Wei Chen, David R. Janz, Addison K. May, Gordon R. Bernard, Dawood Darbar, Julie A. Bastarache, Lorraine B. Ware

5:45 Excuse Judges for Deliberation............................................ Terence S. Dermody, M.D.

5:50 Poster Presentation Awards...................... Vance Albaugh, MD and Jonathan Kropski, M.D.

6:00 Grant W. Liddle Award................................. Jonathan G. Schoenecker, M.D., PhD.

6:15 Elliot V. Newman Awards.......................... Terence S. Dermody, M.D.
2014 ORAL PRESENTERS

BRADLEY RICHMOND, M.D.
Clinical Fellow, Allergy, Pulmonary and Critical Care Medicine

CAMERON UPCHURCH, B.S.
VMS II

EMILY ZERN, B.A.
VMS III

CHAD CORRIGAN, M.D.
Clinical Fellow, Orthopaedic Trauma

EITAN FRIEDMAN, M.D.
Clinical Fellow, Cardiovascular Disease

CIARA SHAVER, M.D., PH.D.
Clinical Fellow, Pulmonary Disease
ROFLUMILAST ABROGATES NONTYPEABLE HAEMOPHILUS INFLUENZA (NTHI)-INDUCED INFLAMMATION AND REMODELING IN POLYMERIC IMMUNOGLOBULIN RECEPTOR DEFICIENT MICE

Bradley W. Richmond, Rui-Hong Du, Yongqin Zhang, Dong-sheng Cheng, Linda Gleaves, Timothy S. Blackwell, Vasily V. Polosukhin

OBJECTIVES: NTHi is commonly isolated from the sputum of patients with chronic obstructive pulmonary disease (COPD). The small airways of patients with COPD are often deficient in secretory IgA (SIgA) which may increase susceptibility to NTHi-induced inflammation. We hypothesize that NTHi exposure will accelerate small airway inflammation in plgR-/- mice (which are deficient in SIgA), resulting in small airway remodeling and emphysema, and that this effect will be blocked by the phosphodiesterase-4 inhibitor roflumilast.

METHODS: WT or plgR-/- mice (7-9 per group, all C57BL/6) were nebulized with 10 mg of killed NTHi lysates or vehicle (0.9% NaCl) once weekly for 4 months starting at 2 months of age using the InExpose system (Scireq). WT or plgR-/- mice (5 per group, all C57Bl/6) were gavaged once daily with 100 mg of roflumilast (~ 5 mg drug/kg animal weight) while undergoing identical treatment with NTHi. At 6 months of age the animals were euthanized, bronchoalveolar lavage (BAL) performed, and then the lungs perfused, inflated with 10% formalin, fixed overnight, and embedded in paraffin. Small airway wall thickness (as measured by subepithelial connective tissue volume density) and emphysema (as measured by mean alveolar septal perimeter) were quantified by morphometric analysis.

RESULTS: Saline-treated plgR-/- mice had an approximately twofold increase in BAL total cells, macrophages, and neutrophils compared to WT animals (p<0.05). Compared to saline vehicle, NTHi treatment resulted in a 4-5 fold increase in BAL total cells, macrophages, and neutrophils in WT and plgR-/- mice (p<0.05 for all). The magnitude of the increase did not significantly differ between WT and plgR-/- mice. Roflumilast led to significant decreases in BAL total cells, macrophages, and neutrophils in WT and plgR-/- mice (p<0.05 for all), and in plgR-/- mice reduced BAL cell numbers to a similar level as saline treatment. Compared to saline vehicle, NTHi exposure significantly increased both small airway wall thickness and emphysema scores in WT and plgR-/- mice (p<0.05 for both). Roflumilast treatment significantly decreased small airway wall thickness and emphysema scores in WT and plgR-/- mice exposed to NTHi lysates. In plgR-/- mice, roflumilast-treated animals had significantly lower emphysema scores than animals exposed only to NTHi or vehicle.

CONCLUSIONS: SIgA/plgR deficiency results in increased inflammation, small airway remodeling, and emphysema following repetitive NTHi treatment in a murine model, and this effect is blunted by treatment with roflumilast. Roflumilast has been shown to block inflammatory cell trafficking to the lung, an effect which may be particularly important in the setting of altered mucosal immunity due to SIgA deficiency.
CELL-FREE HEMOGLOBIN ELICITS A PRO-INFLAMMATORY RESPONSE IN LUNG EPITHELIAL CELLS

Cameron Upchurch, Brandon Grove, Ciara Shaver, David Janz, Lorraine Ware, Julie Bastarache

RATIONALE:
Cell-free hemoglobin (Hb) is a potent oxidant and vasoconstrictor. Plasma levels of cell-free Hb are associated with mortality in sepsis and levels are high in the airspaces of patients with ALI. We hypothesized that the presence of cell-free Hb in the airspaces of ALI patients is an important mediator of lung injury. To test the effects of Hb on lung inflammation and epithelial permeability we treated lung epithelial cells in culture with cell-free Hb using concentrations within the range detected in pulmonary edema fluid from ALI patients.

METHODS:
Mouse lung epithelial (MLE-12) cells were treated with increasing concentrations (0.001-1 mg/ml Hb) of endotoxin-free, cell-free Hb for 24 hours. KC and TNF-a expression were measured by RT-PCR and ELISA. Cellular oxidative stress was measured using CellROX Green Reagent, a cell-permeable fluorogenic probe. Millicell ERS was used to measure trans-epithelial electrical resistance (TEER) in order to assess the permeability of human bronchial epithelial (16-HBE) cellular monolayers treated for 24 hours with PBS as control, 0.1 mg/ml Hb, and 1 mg/ml Hb. Data were analyzed by ANOVA with post hoc Tukey test.

RESULTS:
Compared to control treated cells, treatment of MLE-12 cells with Hb induced a dose-dependent increase in gene expression and protein concentration of KC (figure, *p<0.05 versus control, 0.001 mg/ml Hb and 0.01 mg/ml treatments) with no change in TNF-a. Cell-free Hb increased cellular oxidative stress compared to control treated and hydrogen peroxide treated MLE-12 cells. Treatment of 16-HBE cellular monolayers with 0.1 mg/ml Hb and 1 mg/ml Hb caused a 39 ± 6% (p<0.05) and 44 ± 5% (p<0.05) reduction, respectively, in mean TEER measurements as compared to PBS treated cells.

CONCLUSIONS:
Cell-free Hb caused a dose-dependent inflammatory response in mouse lung epithelial cells as evidenced by increased production and release of KC, and increased cellular oxidative stress. In addition, exposure to cell-free Hb caused increased permeability in human bronchial epithelial cell monolayers. These findings suggest that cell-free Hb may be contributing to lung epithelial permeability and inflammation, and that cell-free Hb may be a novel mediator of lung epithelial dysfunction in ALI.
B CELL RESPONSES TO HIV ANTIGEN ARE A POTENT CORRELATE OF VIREMIA IN HIV-1 INFECTION AND IMPROVE WITH PD-1 BLOCKADE

Emily Zern, Katherine Nicholas, Louise Barnett, Rita Smith, Shelly Lorey, Courtney Copeland, Shanmugalakshmi Sadagopal, Spyros Kalams

OBJECTIVES:
Infection with HIV-1 induces defects in the humoral immune response, which may partially explain the low frequency of broadly neutralizing antibodies in these individuals. We characterized the ability of B cells to respond to antigen and the role of inhibitory molecule (PD-1) expression on B cell responsiveness in HIV infection.

METHODS:
Peripheral blood mononuclear cells from 21 HIV+ and 7 control subjects were incubated with staphylococcal enterotoxin B (SEB), HIV p24, or inactivated HIV-1 MN virus particles. In isolation experiments, CD19+ B cells were incubated alone or with autologous CD4+ T cells. Anti-PD-1 antibody was used to inhibit the interaction between PD-1 on T cells and ligand PD-L1. After 24h in culture, cells were analyzed by flow cytometry.

RESULTS:
We found that the baseline frequency of CD86-expressing B cells in HIV-infected individuals was higher than in control subjects (p=0.03) and positively correlated with viral load (p=0.003). Increased levels of viremia were associated with decreased ability of B cells to increase expression of CD86 after in vitro stimulation with inactivated HIV-1 (p=0.006). Furthermore, purified CD19+ B cells had a markedly reduced ability to respond to SEB (p=0.02) and HIV p24 (p=0.02), but responses were restored after addition of autologous CD4+ T cells. HIV infected individuals had higher frequency of PD-1 expression on B cells (p=0.04) and CD4+ T cells (p=0.06) compared to HIV negative subjects. We observed that increased CD86 expression on B cells in response to inactivated HIV-1 MN was modestly enhanced by in vitro PD-1 blockade (p=0.003).

CONCLUSIONS:
Our findings demonstrate that during chronic HIV infection, B cells are activated and lose capacity to respond to antigen, but responsiveness is enhanced after providing CD4+ T cell help or by blockade of PD-1 – PD-L1 interactions. The improvement of immune responses with PD-1 blockade suggests a potential prophylactic or therapeutic HIV vaccine strategy.
HETEROTOPIC OSSIFICATION AFTER HEMIARTHROPLASTY OF THE HIP – A COMPARISON OF THREE COMMON APPROACHES

Chad M. Corrigan, Phillip Mitchell, Arie Francis, Adan Omar, Rachel V. Thakore, Vasanth Sathiyakumar, William T. Obremskey, Manish K. Sethi

OBJECTIVE:
Sparse data exists exploring the incidence and causative factors of heterotopic ossification (HO) in patients undergoing hemiarthroplasty (Hemi). The purpose of this study was to investigate a group of patients who had undergone hip Hemi exclusively for geriatric femoral neck fractures in order to explore the incidence of HO and potential influence of operative approach.

METHODS:
From 2000-2009, 169 patients over 60 years with a low energy hip fracture at a single level 1 trauma center who received a hemi specifically for femoral neck fracture were identified. Patients with less than 45 days of radiographic data were excluded leaving 82 Hemis for analysis. Final postoperative AP X-rays at date of last follow up were scrutinized for HO formation, and graded based upon the Brooker Classification Score (BCS). A Kruskal-Wallis test was employed to compare the overall average BCS among 3 operative approaches: anterior (A), anterolateral (AL), and posterior (P). Pairwise non-parametric t-tests (Mann-Whitney U tests) were subsequently used to identify specific differences based on operative approach.

RESULTS:
Of the 82 hemis that met final inclusion criteria, 25 (30.5%) were found to have HO. There was no significant difference in the development of HO based upon surgical approach: 25A (20%, HO, n=5), 29AL (41% HO, n=12), and 28P (29% HO, n=8) (p>.05). However, there was a significant difference in the grade of HO across the three surgical groups based on the Brooker Classification with the posterior approach resulting in a significantly lower grade of HO compared to the other groups: A (BCS=2.60), AL (BCS=2.58), and P (BCS=1.5) (p=.027).

CONCLUSION:
30.5% of patients had HO with a significant risk of developing higher grade HO based on surgical approach (A or AL). Surgeons should consider the risks of higher grade HO when considering A or AL approaches to hemiarthroplasty.
PLASMA KIDNEY INJURY MOLECULE (KIM-1) AND ENDOTHELIN-1 (ET-1) ARE ASSOCIATED WITH WORSENING RENAL FUNCTION IN HEART FAILURE PATIENTS

Eitan Friedman, Daniel Lenihan, John Todd, Joel Estis

OBJECTIVES: Renal dysfunction is a significant comorbidity in patients with heart failure (HF). Traditional blood markers for the diagnosis of renal dysfunction are insensitive, nonspecific, and may only present late in the injury process. Elevations of urinary Kidney Injury Molecule-1 (KIM-1) represent renal tubule epithelial damage; however, there are no reports of its utility in plasma. Endothelin-1 (ET-1) is a plasma biomarker of endothelial function that has been proposed to increase in the setting of renal dysfunction. The aim of this study was to assess the potential for KIM-1 and ET-1 to be novel biomarkers of renal dysfunction in HF.

METHODS: We performed a cross sectional study among 200 HF patients from the Vanderbilt Heart Registry. ET-1 and KIM-1 were measured in plasma using high sensitivity single-molecule counting. Relationships of biomarkers with estimated glomerular filtration rate (eGFR) were determined by multivariable regression analyses.

RESULTS: The high sensitivity assays allowed for ET-1 and KIM-1 determination in all patients. Both plasma KIM-1 and ET-1 values increased with decreasing eGFR (Table). In a linear regression model (adjusted for age, sex, HF stage, BNP, and either KIM-1 or ET-1) for every one unit log-transformed KIM-1 incremental increase, eGFR (β-coefficient) decreased by 11.9 mL/min (P=0.006). For every one unit log-transformed increase in ET-1, eGFR (β-coefficient) decreased by 19.3 mL/min (P=0.013).

CONCLUSIONS: This is the first study to demonstrate that KIM-1 is measurable in plasma. Plasma KIM-1 and ET-1 are independently associated with worsening renal function in HF patients. These findings introduce the potential for using biomarkers to detect renal dysfunction and to further refine HF disease severity.

Table: Relationships between biomarkers and renal status

<table>
<thead>
<tr>
<th>Kidney Function</th>
<th>Biomarker</th>
<th>Quartile 1 (42)</th>
<th>Quartile 2 (70)</th>
<th>Quartile 3 (88)</th>
<th>Quartile 4 (126)</th>
<th>P for trend</th>
<th>β-coefficient (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET-1 (pg/mL)</td>
<td>5.4 (4.5, 7.3)</td>
<td>4.3 (3.8, 5.2)</td>
<td>4.9 (4.3, 6.3)</td>
<td>4.5 (3.3, 5.3)</td>
<td>0.02</td>
<td>-19.3 (-34.4, -4.2)</td>
<td>0.013</td>
<td></td>
</tr>
<tr>
<td>KIM-1 (pg/mL)</td>
<td>337 (182, 745)</td>
<td>273 (168, 78)</td>
<td>227 (137, 74)</td>
<td>180.5 (107, 407)</td>
<td>0.002</td>
<td>-11.9 (-18.6, -5.2)</td>
<td>0.006</td>
<td></td>
</tr>
</tbody>
</table>
NEW-ONSET ATRIAL FIBRILLATION IS INDEPENDENTLY ASSOCIATED WITH INCREASED MORTALITY IN CRITICALLY ILL PATIENTS

Ciara M. Shaver, Wei Chen, David R. Janz, Addison K. May, Gordon R. Bernard, Dawood Darbar, Julie A. Bastarache, Lorraine B. Ware

OBJECTIVE:
Atrial fibrillation (AF) is the most common arrhythmia occurring in the ICU, but its significance is not well understood. Previous studies have retrospectively associated AF occurrence with increased mortality have suggested that AF is primarily a marker of increased disease severity. We designed a prospective study to determine whether AF was an independent predictor of mortality in the critically ill.

METHODS:
Patients admitted to the Medical or Surgical ICUs at Vanderbilt University Medical Center were prospectively enrolled in the Validating Acute Lung Injury markers for Diagnosis (VALID) study within 24 hours of ICU admission. Clinical data including demographics, medical history, medications, and laboratory values were collected at enrollment and daily through ICU day 5. Occurrence of AF, treatments administered for AF, vasopressor use, echocardiographic findings, and evidence of organ failures were also collected. AF was determined by documentation of the arrhythmia in a physician’s progress note, EKG interpretation, or nursing flowsheet. New-onset AF was defined as AF occurring in the ICU with no previous history of AF. Outcome data included length of stay, duration of mechanical ventilation, and hospital mortality.

RESULTS:
AF occurred in 263 of 1770 (13.3%) patients. The incidence of AF was similar in medical and surgical patients (12.6% and 15.2%, respectively). AF was new-onset in 123 (6.9%) patients. Patients with new-onset AF were more likely to be male, Caucasian, and non-smokers and to have a history of hypertension or hyperlipidemia. Severity of illness, assessed by APACHE II, was also associated with new-onset AF. Compared to those without AF, patients with new-onset AF had greater cumulative positive fluid balance over 5 days (8.7 vs. 6.5 L, p=0.029) and increased left atrial size (4.16 vs 3.83 mm, p<0.001). The majority (85.4%) of new-onset AF patients received at least one treatment for arrhythmia control. Patients with new-onset AF had increased hospital mortality compared to patients without AF (31.7% vs. 17.0%, p<0.001). The association of AF with mortality persisted in multi-variable analysis controlling for cardiac risk factors, demographics, presence of sepsis, and disease severity (OR 1.76, p<0.01).

CONCLUSION:
New-onset AF is independently associated with increased mortality in a large prospective cohort of heterogeneous critically ill patients in general medical and surgical ICUs. Whether this finding simply reflects underlying cardiac disease or is a manifestation of the multi-organ dysfunction that is common in sepsis and critical illness is an important area for future study.
BASIC SCIENCE RESEARCH

ABSTRACTS

(alphabetically by presenter’s last name)
2014 Basic Science Research Abstracts

20. James E. Cassat, M.D., PhD., Clinical Fellow, Peds Infectious Disease
21. Elizabeth Riddell, MD, PharmD, Resident, Internal Medicine
22. Allen G. Wu, M.D., Clinical Fellow, Neonatal-Perinatal Medicine
METABOLITE EXCHANGE PROMOTES VIRULENCE OF ANTIBIOTIC-RESISTANT BACTERIAL COMMUNITIES

James Cassat, Neal Hammer, Michael Noto, Lisa Lojek, Eric Skaar

OBJECTIVES:
Antimicrobial-resistant bacterial pathogens are a global source of morbidity and mortality, causing more than 2 million infections and over 20,000 deaths each year in the United States alone. Yet, mutations conferring antibiotic resistance often pose a fitness cost to microorganisms, leading to a reduction in virulence potential. The purpose of this research was to understand how antibiotic-resistant bacteria overcome such fitness reductions to persist within their hosts and cause DISEASE.

METHODS:
To understand how bacterial pathogens might overcome the fitness reductions associated with antibiotic resistance, we created genetically distinct mutations which conferred antibiotic resistance to the bacterial pathogen Staphylococcus aureus. Each antibiotic-resistant S. aureus mutant was subsequently tested for the ability to grow in rich media, secrete virulence factors, destroy host cells, and to cause invasive disease in an experimental model of osteomyelitis. To test the hypothesis that communities of genetically distinct S. aureus mutants might cooperate to overcome the fitness costs associated with antibiotic resistance, we conducted co-culture and co-infection experiments using combinations of staphylococcal mutants.

RESULTS:
We found that mutations conferring antibiotic resistance in S. aureus lead to decreased fitness relative to wildtype whereas co-culture of two independent mutants results in a collective fitness comparable to wildtype both in vitro and in vivo. This phenomenon involves the exchange of critical metabolites between mutants resulting in increased growth yields, virulence factor production, and pathogenicity during osteomyelitis as measured by high-resolution three-dimensional imaging. Moreover, we demonstrate that metabolite exchange also occurs at the interspecies level, as Enterococcus faecalis enhances the growth of antibiotic-resistant S. aureus.

CONCLUSIONS:
Genetic diversity and metabolite exchange within a bacterial community, both at the strain and species level, affords pathogens the ability to tolerate fitness-reducing mutations that promote persistence in their host while maintaining virulence potential.
DOSE AND FREQUENCY OF ADMINISTRATION FOR NEBULIZED INHALED MILRINONE DETERMINED USING A LUNG MODEL

Elizabeth Riddell MD PharmD, Zachary Cox PharmD, Nicholas Haglund MD, Craig Rooks MMHC, RRT

OBJECTIVES:
We sought to establish a dose and frequency for the administration of nebulized inhaled milrinone that would provide a therapeutic plasma level between 100 - 300 ng/ml for use in a clinical trial comparing investigational nebulized inhaled milrinone to standard of care intravenous milrinone.

METHODS:
All studies used a vibrating mesh nebulizer connected to a lung model at Vanderbilt University from July 2013 to August 2013. Lung model parameters were set at a fixed tidal volume of 500 ml and a FiO2 of 50%, using a test lung with a resistance of 20 cm H2O/L/s and compliance of 18 ml/cm H2O. Studies were performed in triplicate at two different respiratory rates, 12 and 20 breaths per minute. A 6 mg milrinone dose (1 mg/ml solution) was placed in a nebulizer reservoir and nebulized until completion. A filter was placed at the end of the nebulizer tubing to collect the nebulized drug product and to calculate the percentage of the dose that reached the lung model versus the amount that was retained in the nebulizer tubing. The percentage of milrinone collected on the filters was determined using liquid chromatography followed by tandem mass spectrometry. Information from our group’s prior studies (fine particle fraction and aerodynamic particle size of nebulized milrinone) was used to develop a pharmacokinetic model using a half-life of 4 hours and a 0.45L/kg volume of distribution to determine the predicted steady state plasma concentrations.

RESULTS:
Mean time to complete one administration of a 6 mg dose (1 mg/ml solution) was eighteen minutes. The mean percentage of the dose that reached the filter with a respiratory rate (RR) of 12 was 39% (2.34 mg) and a RR of 20 was 30% (1.80 mg). Using a bioavailability of 39%, pharmacokinetic modeling demonstrated that 6 mg inhaled every 4 hours produces a steady state plasma milrinone peak of 140 ng/ml and a trough of 55 ng/ml.

CONCLUSIONS:
A 6 mg milrinone dose (1 mg/ml solution) inhaled every 4 hours per nebulizer is predicted to provide therapeutic plasma levels for clinical trial use in advanced heart failure patients.
MECHANISMS OF AGE-DEPENDENT SUSCEPTIBILITY TO REOVIRUS DISEASES

Allen G. Wu, Ardina J Pruijssers, Terence S Dermody

Viral encephalitis is an important cause of morbidity and mortality worldwide. Many neurotropic viruses have a predilection for and display enhanced virulence in younger hosts, but the mechanism for this age preference is not understood. Mammalian reoviruses infect hosts of all ages, but disease manifestations such as encephalitis are restricted to the very young. We hypothesize that the capacity of reovirus to produce encephalitis in mice depends on a combination of age-related cell-intrinsic and cell-extrinsic immune-mediated processes. To pinpoint the timing of the age-restriction to reovirus disease, groups of C57BL/6 mice ranging in age from 2 to 20 days were inoculated intracranially with strain type 3 Dearing (T3D) and monitored for weight gain and illness for 20 days. Mice inoculated at ages between 2 and 10 days gained significantly less weight than those inoculated at greater than 10 days of age. Furthermore, the mortality rate sharply decreased in mice inoculated at greater than 8 days of age compared with mice inoculated at 6 days of age or younger. These data suggest that the susceptibility to reovirus-induced disease decreases between 6 and 10 days of age. Current studies focus on defining the age-dependent cell-intrinsic changes and maturation of immune effectors that contribute to age-dependent susceptibility to reovirus pathology. A better understanding of the mechanisms of age-dependent susceptibility to encephalitis may lead to new therapeutics for vulnerable infant populations.
CLINICAL SCIENCE RESEARCH

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48. Heather M. Kistka, M.D., Resident, Neurosurgery
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EARLY EXPERIENCE WITH 18F-FES PET/CT TO REFLECT PHARMACODYNAMIC AND CLINICAL RESPONSE TO SELECTIVE ESTROGEN RECEPTOR ANTAGONIST, ARN810, IN PATIENTS WITH LOCALLY ADVANCED BREAST CANCER

Karen Ayres, HC Manning, D Delbeke, I Mayer

OBJECTIVE:
Correlate uptake of 18F-FES, a novel molecular imaging probe, with response to a novel estrogen receptor antagonist (ARN810) in patients with estrogen receptor positive (ER+) metastatic breast cancer. Positivity on pretreatment 18F-FES PET scan is predicted to correlate with prolonged time to progression due to presence of active estrogen receptors which serve as a target for therapy.

METHODS:
Patients with locally advanced breast cancer whose initial tumors were ER+ were imaged with 18F-FES, an investigational PET radiopharmaceutical that is a radioactive form of estrogen which allows for imaging of estrogen receptors. PET/CT imaging was acquired at baseline and after one month of therapy with ARN810.

RESULTS:
Two patients have been scanned. Patient 1 had diffusely 18F-FES positive disease on Scan 1 which converted to negative on Scan 2 with therapy. The majority of the lesions in patient 1 were 18F-FES positive. No new lesions developed. Patient 2 had a single 18F-FES positive lesion on Scan 1 that converted to negative on Scan 2 with treatment. Patient 2 had several metastatic lesions known from conventional imaging that were 18F-FES negative on Scan 1. Patient 2 developed a new 18F-FES negative hepatic lesion on the second scan, suggesting progression on study medication.

CONCLUSIONS:
In these two patients, 18F-FES PET/CT imaging correlated with pharmacodynamic response to ARN810. 18F-FES PET was not positive in all lesions, particularly in patient 2. The variable 18F-FES avidity may reflect local dedifferentiation of disease from ER+ to ER-, or could implicate mutation of estrogen receptors to forms not 18F-FES avid. We are currently determining whether pharmacodynamic response to ARN810 as indicated by 18F-FES PET predicts clinical response to therapy and potentially improved outcome.
THE EXPRESSION OF RECEPTOR TYROSINE KINASES IN ENDOMETRIAL CLEAR CELL CARCINOMAS: FREQUENCY AND CLINICOPATHOLOGIC SIGNIFICANCE

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OBJECTIVES:
There are no effective molecularly-targeted therapies approved for use in endometrial cancer, but the recent identification of activating FGFR2 mutations in a subset of endometrioid tumors has renewed investigative efforts into the larger group of receptor tyrosine kinases (RTKs) as potential targets. RTKs are a subclass of transmembrane growth-factor receptors with an intrinsic, ligand-controlled tyrosine-kinase activity. Dysregulation of RTKs is common in epithelial neoplasms, and has been associated with tumor development and progression. Accordingly, anticancer therapies that are directed at RTKs or their associated pathways have shown promising efficacy in a variety of tumors. The aim of this study is to assess the frequency of expression and the clinicopathologic significance of an expansive group of RTKs in endometrial clear cell carcinomas (CCC)

METHODS:
Immunohistochemical analyses for selected class I (HER2/neu, EGFR), class III (PDGFRα, PDGFRβ, c-kit), class IV (FGFR2) and class V (VEGFR) RTKs were performed on 54 CCC, 17 endometrial serous carcinoma (ESC), 49 endometrioid carcinomas (EEC; 18 grade 1, 19 grade 2, 12 grade 3) and 25 non-neoplastic endometrial (NNE) samples in a TMA. HER2/neu scores were assigned according to the current breast ASCO/CAP scoring criteria, while all others were scored on a 0-12+ scale (intensity of staining [1+ to 3+] multiplied by extent of staining [0 to 4+])

RESULTS:
All CCC were negative for HER2/neu and c-kit. Only 1 CCC was PDGFRα+. Scores of 1+ were seen for PDGFRα and EGFR in 61% and 93% of CCC respectively. There were no significant differences between CCC and a) EEC of any grade, b) ESC and c) NNE regarding either the frequency or the semiquantitatively determined level of expression of any RTK. VEGFR and FGFR2 expression at scores 4+ was present in all cases. None of the RTKs showed statistically significant associations with clinicopathologic variables or patient outcomes

CONCLUSION:
The current study documents the expression of RTKs in CCC. HER2/neu, PDGFRα, and ckit are not or are only rarely expressed in CCC, whereas the expression of VEGFR and FGFR2 is apparently ubiquitous. PDGFRα (61%) and EGFR (93%) are expressed in the majority of CCC. There is no association between the assessed RTKs and patient outcomes or clinicopathologic factors. The frequent expression of some RTKs in CCC suggests that investigations are warranted into the potential efficacy of RTK inhibitors (or modulators of their downstream effectors) in this rare histotype of endometrial carcinoma.
THE GUSTILO-ANDERSON CLASSIFICATION SYSTEM AS PREDICTOR OF NON UNION AND INFECTION IN OPEN TIBIA FRACTURES

Michael A. Benvenuti, Rachel V. Thakore, Elvis L. Francois, Michael A. Siuta, Anne K. Smith, Samuel K. Nwosu, Kristen Archer, Jesse M. Ehrenfeld, William T. Obremskey, Manish Sethi

OBJECTIVES: Open tibia fractures are known to have a high risk of complications. Previous large studies, including SPRINT, have focused on closed injuries or excluded higher grade fractures. The purpose of this study was to conduct the largest retrospective study to date of open tibia fractures and evaluate potential predictive risk factors for complications.

METHODS: After IRB approval, patients treated for open tibia fractures by IMN across a 10 year period were identified by a CPT code search at a level I trauma center. Charts were reviewed and potential risk factors including age, gender, American Society of Anesthesiologists (ASA) score, hospital length of stay (LOS), Type (T) of open fracture, distance of fracture from the plafond, and 31 comorbidities. Charts were reviewed for reoperations due to infection, nonunion, and amputation. A multivariate analysis was conducted to determine which risk factors were associated with a greater risk of complications.

RESULTS: 486 patients with open tibia fractures were analyzed (TI: 63, TII: 202, TIIIA: 140, TIIIB: 73, TIIIC: 8). Overall 13% (n=64) of patients had infections, 12% (n=56) had nonunions, and 1% (n=7) had amputations. Infection rates for T1 – 2%, T2- 8%, T3-A14%, T3B-30%, T3C- 62%: Nonunion rates were T1-6%, T2-7%, T3A-11%, T3B-26% and T3C- 25%. Amputation rates were T1 and T2 – 0%, T3A-1%, T3B-7%, T3B-12%. T III fractures had much higher rates of infection, nonunion, and amputation, than T I and T II fractures. After examining all potential risk factors, we found that fracture type was a highly significant risk factor for both nonunion and infection. The risk of nonunion was 4x higher with T IIIb fractures and 5x higher (p=0.001) with T IIIc fractures (p=0.06) compared to T I and T II fractures. In terms of infection, the risk was 2x higher for T IIIa fractures, 6x higher for T IIIb fractures, and 29x higher for T IIIc fractures compared to T I and T II fractures.

CONCLUSIONS: This study determined that the Gustilo Grade of open tibia fractures is by far the greatest predictor of nonunion and infection. Our findings can be used to compare similar fractures at any institution or study and develop a risk calculator for open tibias, which can be used by surgeons to predict care and advise patients with this high-risk injury.
DELIRIUM AND TRANSCATHETER AORTIC VALVE REPLACEMENT

Nyal Borges, Jeniffer Giuseffi, Leanne Boehm, Li Wang, John McPherson, Joseph Fredi, Rashid Ahmad, Chad Wagner, Wes Ely, Pratik Pandharipande

AIMS:
• To determine the incidence of delirium following AVR, both surgical and TAVR
• To assess the association between procedure types and the development of postoperative delirium
• To assess the association between post-operative delirium and 30 days/6 months mortality

METHODS:
Baseline demographic data and daily assessments for delirium using the Confusion Assessment Method for the ICU (CAM-ICU) were prospectively recorded for all patients undergoing either SAVR or TAVR between 7/2011 and 8/2012. We used multivariable logistic regression to assess the relationship between SAVR and TAVR as the independent variable and postoperative delirium on any of the first three postoperative days as the dependent variable, adjusting for age and baseline comorbidity with the Charlson score. A secondary analysis assessed the relationship between postoperative delirium as the independent variable and 6-month survival as the dependent outcome, adjusting for procedure type and age.

RESULTS:
Of 233 patients, 108 underwent TAVR and 125 SAVR. TAVR patients were older (median age 81 vs. 68, p<0.001), had more baseline comorbidities (median Charlson 3 vs. 2, p<0.001), and a higher mortality at 6 months (14.3% vs. 2.5%, p=0.001). The prevalence of post-operative delirium was 19% in TAVR patients vs. 22% in SAVR patients. After adjusting for age and comorbidities, patients undergoing TAVR had lower odds of developing delirium compared to SAVR [Odds ratio, OR 0.4 (0.18-0.92), p=0.03]. Delirium was independently associated with a 3-fold higher risk of death by 6 months [Hazard ratio, HR 3.3 (1.27-8.9) p=0.014], irrespective of procedure type and age.

CONCLUSION:
Despite higher age and comorbidity burden at baseline, patients undergoing TAVR have a lower probability of developing delirium than SAVR patients. Delirium in both groups portended a 3-fold higher risk of death, supporting that monitoring for this complication and form of organ dysfunction should be standard in all AVR patients.
ON-CALL COMMUNICATION: “A PICTURE IS WORTH A THOUSAND WORDS”

Alexandra K Callan MD, Cesar S. Molina MD, Hassan R. Mir MD, MBA

OBJECTIVES:
The exchange of information can vary significantly with the knowledge base of the communicating provider. The interaction can also be affected by the addition of pictorial information. The purpose of this study is to quantify the effects of varying clinical communication styles on the ability of orthopaedic trauma surgeons to understand an injury and formulate an initial management plan.

METHODS:
A REDCap survey was emailed to all OTA members. Respondents quantified (5-Point Likert Scale) how confident they felt understanding an injury and establishing an initial management plan based on the information provided for 5 common orthopaedic trauma scenarios. Three verbal descriptions were created for each scenario and categorized as limited, moderate, or detailed. The questions were repeated with the addition of a radiographic image, and then repeated a third time including a clinical photograph. Statistical evaluation consisted of descriptive statistics and Kruskal-Wallis analyses using STATA (Version 12.0).

RESULTS:
95 orthopaedic trauma surgeons completed the survey. The confidence level of respondents went from 2.28 to 4.22 (p > 0.05).

CONCLUSIONS:
The addition of images in the form of radiographs and/or clinical photos greatly improves the confidence of orthopedic trauma surgeons in understanding injuries and establishing initial management plans with limited verbal information (p<0.001). The inclusion of x-rays and photos raises the confidence for understanding and management with limited verbal information to the level of a detailed verbal description in most scenarios. Mobile technology allows for easy secure transfer of images which can make up for the lack of available information from limited verbal descriptions due to the knowledge base of communicating providers.
ECMO IN SUPPORT OF CARDIOPULMONARY RESUSCITATION AMONG PATIENTS WITH STRUCTURALLY NORMAL HEARTS

Stephanie Conrad, Brian Bridges, Yuvraj Kalra, Andrew Smith

INTRODUCTION:
Extracorporeal cardiopulmonary resuscitation (eCPR) has demonstrated success as a rescue therapy in refractory cardiac arrest among patients with congenital heart disease. Outcome predictors among eCPR-supported patients with structurally normal hearts are less well defined.

METHODS:
Extracorporeal Life Support Organization (ELSO) registry data was retrospectively reviewed from January 1998 through December 2011. Patients with an ICD-9 diagnosis code consistent with structural heart disease were excluded. The remaining subjects were categorized by ICD-9 codes into non-mutually exclusive diagnostic subcategories. Univariate predictors significant for an increase in mortality were included in a multivariate logistic regression model.

RESULTS:
During the study period, 1431 patients met inclusion criteria. Median age was 16 years (2.4, 51 years) and weight was 50 kg (12.5, 71 kg). Subjects were 60% male. Venoarterial support was instituted in 97% of cases, with 86% categorized as a percutaneous approach. Common diagnostic groups included atraumatic acute respiratory failure (15%, n=219), cardiomyopathy (13%, n=189), sepsis (8%, n=119), and myocarditis (8%, n=113). Overall survival to hospital discharge was 32%. Multivariate logistic regression (Goodness-of-Fit p=0.52) demonstrated an independent survival benefit among younger patients (p=0.04) and those with a shorter duration from intubation to cannulation (p=0.02). A diagnosis of sepsis (odds ratio [OR] 3.0, 95% confidence interval [CI] 1.5-5.9) was independently associated with an increase in odds of mortality, while the diagnosis of myocarditis was protective (OR 0.31, CI 0.18-0.54). While supported with ECMO, neurologic complications (OR 6.2, CI 4.2-9.3), pulmonary hemorrhage (OR 2.0, CI 1.1-3.8), serum pH <7.2 (OR 2.3, CI 1.5-3.7), hyperbilirubinemia (OR 2.2, CI 1.1-4.3), and CPR (OR 2.3, CI 1.4-4.0) were all independently associated with an increased odds of mortality.

CONCLUSIONS:
Among patients with structurally normal hearts receiving eCPR, nearly one-third survived to hospital discharge. Defining independent pericannulation predictors of mortality may assist in identifying populations of patients most likely to benefit from this resource-intensive rescue therapy.
COMPARISON OF LIFESTYLE AND DIETARY RISK FACTORS INVOLVED IN SESSILE SERRATED ADENOMA RISK USING A LARGE CASE CONTROL STUDY

James R. Davenport, Yinghao Su, Reid M. Ness, Qiuyin Cai, Walter E. Smalley, Wei Zheng, Martha J. Shrubsole

OBJECTIVES:
Recent evidence has implicated sessile serrated adenomas (SSAs) as important precursor lesions in the development of a sizeable proportion of colorectal cancer. However, these lesions are relatively novel, and characterization of risk factors is minimal. Our objective was to evaluate the risk of SSAs associated with established risk factors in comparison to more recognized polyp types such as traditional adenomas and hyperplastic polyps (HPs).

METHODS:
We analyzed data in a large case-control study (Tennessee Colorectal Polyp Study) in healthy controls (N=4402), cases with HPs (N=265), cases with SSAs (N=139), and cases with traditional adenomas (tubular, tubulovillous, and villous; N=903). Participants underwent a colonoscopy and were invited to take part in a telephone survey regarding lifestyle choices and a mailed food frequency questionnaire detailing dietary choices. We calculated a risk factor score to evaluate the combined association of multiple risk factors. Odds ratios (OR) and 95% confidence intervals (CI) were derived from logistic regression models after adjustment for potential confounders.

RESULTS:
Active cigarette smoking was associated with an increased risk of all polyps with a particularly strong association with SSA risk (OR 5.50; 95% CI 3.33, 9.08; heterogeneity <0.001). Other risk factors associated with SSAs include a higher body mass index and a higher consumption of daily red meat. Factors associated with a decreased risk of SSAs include a diet high in daily fiber and calcium intake and regular use of NSAIDs. Compared with a risk score of 0 to 1, participants with a combined 3 or more risk factors demonstrated an increased risk of SSAs (OR 3.23; 95% CI 1.39, 7.39; p trend <0.001).

CONCLUSIONS:
SSAs share certain risk factors with more traditional adenomas; however, the risk of SSAs appears stronger in certain lifestyle choices such as cigarette smoking. This study helps to clarify potential lifestyle modifications which may be of valuable assistance in the prevention of future sessile polyp formation and subsequent colorectal carcinogenesis.
THE MAJORITY OF METALLIC INTRACRANIAL IMPLANTS AND EXTRACRANIAL HARDWARE ARE COMPATIBLE WITH SERIAL MONITORING OF CEREBROVASCULAR REACTIVITY WITH HYPERCARBIC MRI

Aditi Desai, MD, Carlos Faraco, PhD, Lindsey Dethrage, BA, Lori Jordan, MD, PhD, Manus Donahue, PhD, Megan Strother

OBJECTIVES: Cerebral hemodynamic evaluation can be achieved by serial monitoring of cerebrovascular reactivity (CVR) without exogenous contrast agents by exploiting T2* lengthening secondary to hypercarbia-induced changes in blood oxygenation (i.e. the blood oxygen level-dependent, BOLD, effect). However, for such measurements to be reliable in routine clinical practice, susceptibility-induced influences of endovascular and surgical interventions on the long-TE MRI contrast must be characterized, as BOLD MRI is particularly sensitive to susceptibility variations between different structures. The purpose of this study is to calculate the volume and artifact extent arising from different intracranial and extracranial hardware; results highlight that non-invasive CVR monitoring is feasible in the majority of patients with such hardware, and also report which hardware precludes accurate CVR measurements and should be avoided when possible.

METHODS: BOLD (3.0T; in-plane spatial resolution=3 x 3 mm²; echo time=35 ms; single-shot gradient echo EPI) MRI was performed in patients (n=32) with metallic implants (n=8) and surgical procedures that required placement of extracranial hardware (n=24). Make, model, and composition of hardware, along with the total artifact volume, were recorded.

RESULTS: Intracranial implants included stents or clips composed of titanium or titanium and nickel alloy, as well as platinum embolization coils. The average artifact volume associated with intracranial hardware was 3.7 cm³ +/- 3.4 cm³ (mean +/- standard deviation), with a range of 1.1-9.4 cm³. Extracranial hardware primarily included closure devices composed of titanium alloy, as well as a ventriculoperitoneal shunt with an extracranial programmable valve composed of a combination of 316L stainless steel, unalloyed titanium, tantalum, and neodymium magnets. The average artifact volume associated with extracranial hardware was 33.0 cm³ +/- 25.6 cm³ (range 6.1-139.6 cm³). As a point of reference, the average volume of the human brain is approximately 1380 cm³. CVR data were obtainable in all patients, with the exception of the single patient with the extracranial programmable valve and siphon gauge. In patients with intracranial stenosis, results varied asymmetrically with vascular disease burden as quantified by angiography.

CONCLUSIONS: Reliable CVR maps, including those consistent with lateralizing vascular disease in patients with intracranial stenosis, can be obtained from BOLD MRI performed on patients with a variety of implanted intracranial devices and extracranial hardware, the notable exception being ventriculoperitoneal shunts with a programmable valve and siphon gauge.
ANKLE FRACTURES AND MODALITY OF HOSPITAL TRANSPORT AT A SINGLE LEVEL I TRAUMA CENTER: DOES TRANSPORT VIA HELICOPTER OR AMBULANCE INFLUENCE COMPLICATION RATES?

Dagoberto Estevez-Ordonez, Maximilian F. Lang, Marc A. Prablek, Alexander Chern, Rachel V. Thakore, William T. Obremskey, David Joyce, Manish K. Sethi

OBJECTIVE:
Every year millions of dollars are spent in transporting orthopaedic trauma patients to nearby hospitals for care either by helicopter or ambulance. In this study we sought to evaluate trends and complication rates with regard to transport of patients with isolated ankle fractures to a single level I trauma center.

METHODS:
A retrospective chart review at a level I trauma center identified 439 patients who had isolated ankle fractures from 2000-2010. Patient charts were reviewed for demographics and modality of transport. Only patients that were transported via ambulance or helicopter were included. Each chart was also reviewed for complications including infection, nonunion, or failure of fixation requiring surgical intervention. Statistical analysis between groups was employed with a chi squared analysis. The cost of a helicopter was $10,220 (base) + $108/mile and ambulance charge was $976 (base) + $16/mile.

RESULTS:
303 patients with isolated ankle fractures were included. 87 (28.7%) patients were transported via helicopter and 216 (71.2%) patients were transported via ambulance. There was no significant difference in transport method of patients with open fractures (P= .07). When considering complications requiring reoperation between isolated ankle fractures transported by helicopter (n=11, 12.6%) and ambulance (n=16, 7.41%), there was no significant difference between groups (p=. 19). Only including base charges for transport, the cost for patients in the helicopter group was (n=87, $889,140) compared to (n=216, $210,816) in the ambulance group.

CONCLUSION:
Our study is the first to demonstrate that method of transport does not influence complication rates in isolated ankle fractures. Furthermore, we show that despite transporting almost three times the number of patients with ankle fractures via ambulance, the costs were only 25% of the helicopter group when considering the base prices for transport.
MITOCHONDRIAL GENETIC EFFECTS ON PROLIFERATIVE DIABETIC RETINOPATHY

Christopher B Estopinal, Isaac M Chocron, Megan B Parks, Emily A Wade, L Goodwin Burgess, David C Samuels, Milam A Brantley Jr

OBJECTIVES:
To determine if specific mitochondrial haplogroups associate with non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR).

METHODS:
We obtained de-identified medical records for 54 NPDR patients and 21 PDR patients from BioVU, Vanderbilt University’s de-identified DNA databank. Information regarding diabetes type (1 or 2), duration of diabetes (yrs), and smoking status was recorded. This information was also examined for a replication cohort of 44 NPDR patients and 58 PDR patients recruited from Vanderbilt Eye Institute. HaploGrep software was used to determine mitochondrial haplogroups for patients in both cohorts. We tested for an association between mitochondrial haplogroups and presence of NPDR or PDR.

RESULTS:
Analysis of the BioVU cohort (n=75) showed the common European mitochondrial haplogroup H to be significantly overrepresented in the PDR group when compared to the NPDR group (p=0.038, OR=3.4 [95% CI 1.1-10.7]). Analysis replication in the clinical cohort (n=102) demonstrated an association between haplogroup H and PDR as well (p=0.0024, OR=3.8 [1.6-8.8]). When both cohorts were combined (n=177), a separate common haplogroup, U(k), was found to be significantly protective against PDR (p=0.031, OR = 0.43 [0.20-0.90]).

CONCLUSIONS:
Presence of mitochondrial haplogroup H may predispose patients to develop PDR while mitochondrial haplogroup U(k) may be protective against the development of this severe stage. These results could further current understanding of DR and may help reveal the differences among DR patients that account for variable disease progression or treatment response.
THE RISK FACTORS AND COSTS OF SURGICAL SITE INFECTIONS AT A MAJOR LEVEL I TRAUMA CENTER

Alexandra M. Foxx, Rachel V. Thakore, Hanyuan Shi, Elvis Francois, Marc A. Prablek, Samuel Nwosu, Kristen R. Archer, Jesse M. Ehrenfeld, Hassan R. Mir, William T. Obremskey, Manish K Sethi

OBJECTIVES:
Very little is known about the costs of SSI in orthopaedic trauma. The purpose of this study was to analyze the risk factors and costs of treatment for patients who developed an SSI compared to those who did not.

METHODS:
37 CPT codes representing all ortho trauma surgeries at a level I trauma center were used to find 7,338 patients across a 5-year period. 1,819 had isolated fractures. Charts were reviewed for age, gender, comorbidities, fracture type, surgical duration, overall length of stay (LOS) which included index surgery and readmission, ASA score, smoking status, and infection. Patients were assigned a National Nosocomial Infections Surveillance (NNIS) risk index score and were matched to controls by NNIS score, fracture location, age (all <20 years), and year of surgery if possible. A Wilcoxon test measuring differences in overall, technical, and profession costs was performed and risk factors for infection were analyzed.

RESULTS:
78 (4.3%) patients with isolated fractures had an SSI. The major risk factor for infection was the postoperative LOS, (3.5 days vs 2.5 days) (p=0.012). Infected patients had significantly higher overall mean costs ($123,467) than control patients ($64,241) (p<0.001) and significantly higher costs in all categories of service (p<0.01). The total costs for the infected group over the 5 year period was $9,630,453 compared to $5,010,792 for controls.

CONCLUSIONS:
Our study demonstrates that infections more than double the costs of treatment. In a future global payment model surgeons will be challenged to cover the costs of these complications.
CLINICAL, PATHOLOGIC, AND MOLECULAR FEATURES OF COLORECTAL CARCINOMA WITH MICROPAPILLARY FEATURES

Raul S. Gonzalez, Mary K Washington, Chanjuan Shi

BACKGROUND: Micropapillary (MP) features have recently been described in colorectal carcinoma (CRC), though characterization of this subset is still ongoing. Here, we report our pathologic, clinical, and molecular findings in MP CRC.

DESIGN: Slides from 1,003 CRC resections were reviewed for at least focal MP features. We recorded the percentage of the tumor that was MP and the histologic features present in the remaining tumor. We performed staging and recorded patient follow-up data. In addition, mutational analysis on KRAS, NRAS, BRAF, PIK3CA, AKT, PTEN, and SMAD4 genes was performed using a lab-developed assay.

RESULTS: We identified 35 cases (3%) with MP features, which were defined as small papillary clusters of malignant cells with prominent eosinophilic cytoplasm occupying lacunar spaces and lacking fibrovascular cores. The percentage of MP features ranged from 10% (16 cases) to 100% (1 case). The MP component was frequently associated with dense hypercellular stromal reaction. Twenty-four cases featured a prominent cribriform pattern in the non-MP malignant glands, with dirty necrosis present in the small lumina. Eight displayed mucinous features, including 5 wherein the MP component existed solely in a mucinous background. Average patient age was 60 years, and male:female ratio was 1.5:1. Thirty-one cases showed advanced T-category (T3 or T4), 27 cases had lymph node metastases, and 19 had distant metastases; the nodal metastases often appeared as large cystic spaces lined by malignant epithelium and harboring abundant dirty necrotic material, though nodal metastases in 9 cases showed MP features. Average follow-up length was 45 months. Fifteen patients died of disease, with an average survival length of 25 months (range: 1-71 months); 14 were alive at last follow-up. Gene mutations were seen in 7/12 cases, including 5 cases with KRAS mutation at codon 12 or 13, 1 case with BRAF V600E mutation only, and 1 case with both BRAF V600E and SMAD4 R361H mutations. In 3 cases, mutational analysis was performed on both cribriform and micropapillary areas separately, with no difference in mutational profile observed. Microsatellite instability (MSI) testing was done on 6 cases; all were MSI-stable.

CONCLUSION: MP features in CRC portend an aggressive course, with a high likelihood of advanced local disease, nodal and distant metastases, and a poor prognosis. Cases with focal MP features often show cribriforming glands elsewhere and cystic nodal metastases with prominent necrosis. In addition, they are associated with frequent KRAS and BRAF mutations.
**ADENOMA-LIKE ADENOCARCINOMA: A SUBTYPE OF COLORECTAL CARCINOMA WITH GOOD PROGNOSIS, DECEPTIVE APPEARANCE ON BIOPSY, AND FREQUENT KRAS MUTATION**

**Raul S. Gonzalez, Mary K Washington, Chanjuan Shi**

**OBJECTIVES:**
Biopsy of a colorectal carcinoma (CRC) occasionally yields tissue that can only be diagnosed as an adenoma microscopically. While this could be due to sampling of a precursor lesion, we have identified a subset of CRCs that architecturally and cytologically resemble adenomatous change, making them difficult to diagnose as malignant on biopsy.

**METHODS:**
Slides from 1,003 CRC resections were reviewed for an adenoma-like invasive component. We recorded staging information, patient follow-up, whether residual precursor adenoma was present, and whether prior biopsy had been diagnosed as adenoma or CRC. Mutational analysis on *KRAS*, *NRAS*, *BRAF*, *PIK3CA*, *AKT*, *PTEN*, and *SMAD4* was performed using a lab-developed assay.

**RESULTS:**
Twenty-nine cases (3%) demonstrated adenoma-like features, defined as architectural and cytologic blandness such that observing the tissue on biopsy would not allow for the diagnosis of CRC; the glandular architecture resembled that of adenomas, and the lesions lacked dirty necrosis, high-grade nuclear features, desmoplasia, and tumor budding. These features comprised from 10 to 100% of a lesion. Twenty-two cases (76%) also showed mucinous features at the leading invasive edge. While 21 cases showed advanced T-category (T3 or T4), only 6 cases had nodal metastases, and 4 had distant metastases (2 lung, 1 liver, 1 omentum). Thirteen cases had prior biopsies called adenoma; 16 resection cases showed no adenoma, including 8 cases called adenoma on biopsy. Average follow-up length was 57 months. Two patients died of disease, at 108 and 140 months; 19 were alive at last follow-up. *KRAS* mutation was seen in 8/12 (75%) cases, all but one located at codon 12 or 13. Two of these cases also harbored a *PIK3CA* H1047R mutation. Microsatellite instability (MSI) testing was done on 9 cases, 3 of which were MSI-high with wild-type *BRAF*.

**CONCLUSIONS:**
Adenoma-like adenocarcinoma is a subset of CRC with a low rate of metastasis and a good prognosis. Diagnosis of this lesion as carcinoma may be challenging on biopsy, as the surface component resembles an adenoma despite being invasive. In addition, although this type of CRC has a good prognosis, it frequently harbors *KRAS* mutations.
THE COSTS OF OPERATIVE COMPLICATIONS FOR ANKLE FRACTURES: A CASE CONTROL STUDY


OBJECTIVE:
Given that ankle fractures are one of the most common fractures seen by Orthopaedic surgeons, it is important to understand the costs of complications. The purpose of this study was to perform a case-control cost analysis of complications following ankle fracture.

METHODS:
7 CPT codes were used to find 892 patients, 439 (49.2%) of which had isolated ankle fractures at a level I trauma center across a 10-year period. Charts were reviewed for age, gender, type of fracture, fracture location, and length of stay (LOS) for index surgery and all readmissions, ASA score, complications (nonunion, infection, hardware pain, failure of fixation) and readmissions. Patients with complications were matched to controls based on ASA score (within one score), age (within 10 years), type of surgery (based on CPT code), and type of fracture (open vs. closed). A Wilcoxon test measured differences in costs and LOS between case and control.

RESULTS:
28 out of 439 patients with isolated ankle fractures (6.4%) were found to have complications, including nonunion (n=7, 1.6%), infection (n=8, 1.8%), hardware pain (n=10, 2.3%) hardware failure (n=3, 0.6%), and malunion (n=1, 0.2%). Both groups had 15 closed (53.6%) and 13 (46.4%) open fractures. The mean overall LOS for patients with complications was significantly longer (8.4 days) than the LOS for controls (4.4 days) (p=0.028). Patients with complications required an average of 1.8 reoperations. Each patient with a complication incurred significantly higher overall average costs ($110,369) than each control patient ($58,485) (p=0.001). The total costs for all patients in the group with complications was $3,090,331 compared to $1,637,589 for the control patients - a difference of $1,452,741.

CONCLUSIONS:
This study is the first of its kind to demonstrate the vast financial implications of complications in ankle fracture patients. The financial implications demonstrated in our study could be devastating in a bundled payment system.
FREQUENCY OF DEATH WITHOUT PARENTERAL PROSTAGLANDIN THERAPY IN PULMONARY ARTERIAL HYPERTENSION PATIENTS AT A TERTIARY REFERRAL CENTER

Bryan R. Hay, Meredith E. Pugh, Ivan M. Robbins, Anna R. Hemnes

OBJECTIVES: Parenteral prostaglandin (PP) therapy has been shown to increase exercise tolerance, improve quality of and prolong life in patents with pulmonary arterial hypertension (PAH). Despite this, many patients with PAH die without PP therapy according to recent data from the REVEAL registry. We sought to examine causes of death in PAH patients not on PP therapy with the hypothesis that most of these patients died of non-PAH causes.

METHODS: A single center retrospective cohort analysis of consecutive patients evaluated for pulmonary hypertension at our Center from 1/1/08 to 12/31/12. We considered PP use to be IV epoprostenol/treprostinil or SQ treprostinil. Disease severity, duration, hemodynamics, and cause of death were compared between PAH patients treated with PP (PAH-PP) and those who were not, but were not documented as poor PP candidates (PAH-nonPP).

RESULTS: Of 1786 patients evaluated at our center, 102 were diagnosed with PAH and died. Of these, 61 were PAH-PP, 41 were not treated with PP, 28 were documented by physicians in the medical record to be poor candidates for PP and 13 patients were not documented to be poor candidates, but did not receive PP therapy (PAH-nonPP). Age, sex, medical co-morbidities, PAH sub-type and NYHA functional class were not different in the PAH-PP group versus PAH-nonPP, however time from diagnosis to worst functional class was longer in the PAH-nonPP than the PAH-PP group (median days 301 vs. 833, p<0.05). PAH-nonPP patients had lower right atrial pressure (7.6 ± 2.8 vs. 12.8 ± 6.0 mmHg, p<0.05), but were not different by other hemodynamic measures. PAH-PP patients more frequently experienced their worst functional class within one year of diagnosis (34/61 vs. 2/13, p<0.05) and were less commonly treated with combination oral therapy (p<0.05). Of the 13 PAH-nonPP patients, four refused prostaglandin treatment, three had other life-limiting conditions (dialysis (2), metastatic cancer (1)). Of the remaining patients, cause of death was sudden cardiac death (3), gastrointestinal hemorrhage (2), and pneumonia (1).

CONCLUSIONS: At a large referral center, 13% of PAH patients died without PP therapy but would otherwise be considered candidates for PP. PAH-nonPP had longer duration of disease and more combination therapy with less right heart failure, suggesting greater challenges in identification of patients at risk of death. Our findings are different from those reported in the REVEAL registry and indicate that the majority of patients with advanced PAH who are appropriate candidates receive PP therapy.
COAGULOPATHY IS ASSOCIATED WITH BLOOD TRANSFUSIONS IN PEDiatric TRAUMA PATIENTS

Courtney Horton, Candace McNaughton, Emily Zern

OBJECTIVE:
To determine the prevalence of coagulopathy in pediatric trauma patients at the time of presentation to the pediatric emergency department (PED) and determine the associations between coagulopathy and transfusion among these patients.

Methods: We conducted an observational study of all pediatric trauma patients who met Level I or Level II trauma criteria between Feb 2008 – Feb 2012 for whom coagulation studies were obtained during their PED evaluation. Coagulopathy was defined as an International Normalized Ratio (INR) of prothrombin time (PT) > 1.5. Clinical outcomes of interest included transfusion of any blood products within 24 hours, disposition, and death prior to discharge from the hospital.

RESULTS:
Over 4 years, 941 Level I or II patients underwent coagulation studies and of these, 39 (4.1%) were coagulopathic. Among patients with coagulopathy, the average age was 6.9 years (standard deviation 5.8 years), the average Glasgow Coma Scale (GCS) score on arrival was 6.5 (SD 5.5) and 2 (5%) presented hypotensive and tachycardic; injury mechanisms were: 68% blunt trauma, 10% penetrating trauma, 10% burns, 8% crush, 2% closed head injuries and 2% hangings. Of the 39 patients in this group, 22 (56%) received blood product transfusions within 24 hours of arrival (44% received packed red blood cells, 38% received fresh frozen plasma, and 15% received platelets). At 30 days, 21 (54%) of the coagulopathic patients were discharged home, 2 (5%) remained hospitalized and 16 (41%) were deceased. Coagulopathy was strongly associated with transfusion of blood products within 24 hours of arrival, with an unadjusted odds ratio (OR) of 36.3 (95% confidence interval, CI, 17.6 to 75.2) compared to patients with INR <1.5. After adjustment for age, race, emergency severity index, mode of arrival, and hypotension, this relationship remained significant, with an OR of 13.2 (95% CI 5.6 to 31.2).

CONCLUSION:
Coagulopathy in pediatric trauma patients is strongly associated with blood product transfusion in the first 24 hours of arrival to the Emergency Department. Studies are needed to determine whether abnormal coagulation studies upon PED arrival among pediatric patients is an effective marker for increased risk of morbidity and mortality and to determine whether interventions addressing coagulopathy may improve patient outcomes.
LONG TERM FOLLOW-UP CONFIRMS THE SAFETY AND EFFICACY OF PAROTID SENTINEL NODE BIOPSY AS A STAGING PROCEDURE FOR HEAD AND NECK MELANOMA

Chelsea Isom, Mark Kelley, M.D., RB Yates, V Viar, JA Sosman

Sentinel lymph node biopsy (SLNB) is an effective staging procedure for melanoma of the trunk and extremities. The accuracy and safety of SLNB for melanomas with lymphatic drainage to the parotid nodes has been questioned. We evaluated the long term outcome of patients undergoing parotid SLNB to determine the safety and efficacy of this procedure. Sixty one patients underwent wide excision and parotid SLNB for clinical stage I and II head and neck melanoma between 07/01/1997 and 06/30/2008. Tc-99m sulfur colloid, blue dye, lymphoscintigraphy, and a gamma probe were used. Clinical and pathological data were collected through a prospective, IRB-approved data repository. Most patients were older (mean age 62), males (88%) with melanomas of the ear (32.7%), cheek (19.7%), forehead (19.7%), neck (11.5%), scalp (9.8%), or eyelid/brow (6.6%). Mean tumor thickness was 2.0 +/- 1.9 mm; 23% were ulcerated, 54% had a mitotic rate >1/mm2. SLN were identified in 59/61 (97%) patients. 119 basins were mapped (60 parotid, 54 cervical, 5 other), with 3.4 +/- 1.6 SN per basin. Twelve of 61 (19.7%) had tumor-positive parotid SLN. One false negative (FN) result (Accuracy 99%, FN rate 7%) was confirmed after 5 years actuarial follow-up. Seven (11.5%) patients experienced complications, (2 temporary facial nerve paresis). Long-term follow-up was available for 50 patients; 34 (56%) were alive with median overall survival of 83 months. 15 of 50 (30%) developed recurrence with median disease-free survival of 32 months. With careful attention to technical details, parotid sentinel node biopsy can be performed with a low rate of serious complications. The procedure is associated with a low long-term false negative rate and is the procedure of choice for staging the parotid nodes in head and neck melanoma.
OPEN ANKLE FRACTURES AND EARLY FIXATION: ARE THEY SAFE TO FIX? A TEN YEAR REVIEW OF ISOLATED OPEN ANKLE INJURIES

David Joyce, Rachel V. Thakore, Vasanth Sathiyakumar, William T. Obremskey, Manish K. Sethi

OBJECTIVE:
Little data exists to support immediate fixation of isolated open ankle fractures. Given limited evidence, surgeons often base their decision to acutely fix open ankle fractures on data surrounding closed injuries. This study sought to explore the complication rate of early fixation of open ankle injuries at a single level 1 center.

METHODS:
A search using CPT codes related to ankle fractures identified 1469 patients between 2001 and 2011. We identified 72 isolated open ankles in skeletally mature patients by confirming through x-rays and operative notes. We performed a retrospective review of our open ankle fractures to determine rates of complications which included deep infection, hardware removal for pain, nonunion, and arthrodesis. Information was also gathered regarding numbers of surgeries and timing of definitive fixation. Chi Squared analysis between open fracture types was performed.

RESULTS:
A total of 72 isolated open ankle fractures (Gustilo type I n=11 (15.27%), type II n=34 (47.22%), type III n=27 (37.7%)) were treated with operative fixation during their initial hospital admission. The overall complication rate was found to be 29.16% (n=21). The most common complication was deep infection at 20.83% (n=15). Other complications included hardware removal for pain (n=3), nonunion (n=3), fusion (n=4) and 2 amputations. There was no significant difference in complication rates between fracture grades (p>.05). A sub-analysis of fractures fixed within 24 hours (n=54) showed a deep infection rate of 18.5% (n=10).

CONCLUSIONS:
Our data demonstrates an overall 29.16% complication rate in the acute management of open ankle fractures that is driven mostly by infections and wound complications. In fact, our data demonstrates striking similarity to the complication rates in acute fixation of pilon fractures. This study suggests that debridement and external fixation or splinting are warranted in the early management of open ankle fractures.
GEOGRAPHIC VARIATIONS IN ORTHOPEDIC TRAUMA BILLING AND REIMBURSEMENTS FOR PELVIS, ACETABULAR AND HIP FRACTURES IN THE MEDICARE POPULATION

David Joyce, Catherine M. Bulka, Rachel V. Thakore, Melinda Buntin, William T. Obremskey, Jesse M. Ehrenfeld, Manish K. Sethi

OBJECTIVES:
Recently, there has been much discussion about geographic variations in billing and Medicare reimbursement. Hip fractures are among the top 100 Disease-Related Groups (DRGs) billed to Medicare. We investigated the variations in hospital charges or payment data surrounding hip fractures.

METHODS:
We obtained hospital charge and Medicare reimbursement data for DRG 536 (acetabular, hip and pelvis fracture) from 1,142 hospitals accounting for 22,728 patients in the U.S. for 2011. Hospitals were aggregated into Core Based Statistical (CBS) areas, which are used by Medicare to assign a hospital wage index to all hospitals in the same area. We calculated the coefficient of variation (CV) for each sector with regard to both hospital charges and reimbursements.

RESULTS:
875 hospitals, accounting for 22,634 patients with DRG 536, were assigned into 170 CBS areas. The average hospital charge and SD was $17,516 ± 8,773 with a wide range of charges ($3,986 - $64,016). The average Medicare reimbursement and SD was $4,790 ± $1,070.31 with a range of reimbursements ($3,217 - $11,923). There was a very wide variation in hospital billing for DRG 536 within each area as evidenced by more areas with higher CVs; we identified 4 areas with very high CV-Charges between 60-80% and 14 with high CVs CV-Charges between 40-60% . Medicare reimbursements also demonstrated variability within each area, but much less than hospital charges. Although the majority of areas (138) demonstrated a low CV (0-20%, Fig 1 b, blue), 30 areas maintained a higher CV (20-40%).

CONCLUSIONS:
Hospital charges demonstrated a high degree of variability even when using areas to control for differences in hospital wages. We also found high variation in reimbursements in some areas that remain unexplained by Medicare’s current methodology.
OUTCOMES AFTER EMPIRIC OUTPATIENT TREATMENT FOR POSSIBLE TICK-BORNE INFECTIONS IN THE PEDIATRIC EMERGENCY DEPARTMENT

Ian Kane

OBJECTIVE:
To evaluate for adverse outcomes including missed cases of bacterial meningitis among pediatric patients who were seen in the PED and discharged with possible tick-borne illness.

METHODS:
The study included years 2004-2013 and was a retrospective review of all children who presented to the PED from May to August and were discharged with a diagnosis of tick-borne illness, ehrlichia/ehrlichiosis, RMSF, meningitis, or fever and headache. Clinical and laboratory characteristics of all patients who returned to the PED within two weeks were collected from the electronic medical record.

RESULTS:
676 patients were discharged from the PED over our study period and 43 (6.4%) returned to the PED within 2 weeks and were included for analysis. There were no deaths and no cases of bacterial meningitis among patients who returned to the PED. 27 children (63%) were discharged with a prescription for doxycycline. 10 children (23%) underwent lumbar puncture (LP) at their initial visit; only 3 patients (6.9%), all of whom had neck pain, had an LP at their return visit. These 3 patients were diagnosed with viral meningitis. 16 patients (37%) were admitted after their second visit, with an average length of stay of 2.7 days. One patient was admitted for 16 days and subsequently diagnosed with anaplastic large cell carcinoma.

CONCLUSION:
Empiric treatment of suspected tick-borne illness in our PED did not result in any missed cases of bacterial meningitis. Further prospective studies may identify low risk children who may be discharged from the PED without extensive laboratory testing.
CHANGE OF FRACTIONAL EXHALED NITRIC OXIDE IN PEDIATRIC PATIENTS AFTER ASTHMA EXACERBATION NECESSITATING EMERGENCY DEPARTMENT CARE

Eric Karlin, Tebeb Gebretsadik, R. Stokes Peebles, Jr., Tina V. Hartert, Emily W. Langley, Donald H. Arnold

OBJECTIVES:
Fractional exhaled nitric oxide (FeNO) is elevated in pediatric patients during acute asthma exacerbations. We sought to determine whether patients with high FeNO values during acute exacerbations have meaningful decreases during improved symptom control. We hypothesized those pediatric subjects with high FeNO levels during exacerbation would have at least a 20% decrease at time of improved asthma control.

METHODS:
Participants were selected from a cohort of children aged 5 – 17 years who had FeNO measurement previously performed in our pediatric emergency department (ED) during acute asthma exacerbations. We recruited participants who had FeNO values above the median value for this cohort. Exclusion criteria included a febrile illness, systemic corticosteroid treatment, or an acute exacerbation necessitating ED care within the preceding 4 weeks. FeNO was measured and each participant completed a questionnaire to ascertain asthma severity and current asthma medications. We performed a multivariable linear regression model accounting for the repeated measures to calculate the adjusted mean difference of FeNO at follow-up compared to the value during the acute exacerbation.

RESULTS:
Between April 11 and January 11, 2014, we enrolled 80 participants with median [IQR] age 13 [11, 16], male gender 50 (62%), and African-American race 40 (50%). Median FeNO at the time of prior exacerbation was 60 ppb [49, 76] and at the follow-up visit was 53 ppb [30, 81]. Using multivariable regression analysis and adjusting for age and sex, there was a 23% (95% CI: 9%, 35%; p=0.003) decrease in FeNO level at follow-up compared to values obtained during exacerbation.

CONCLUSIONS:
Pediatric patients with elevated FeNO during acute asthma exacerbation have lower values of FeNO at a time of improved symptom control.
TRENDS IN FOLLOW-UP OF PATIENTS SURGICALLY TREATED FOR NONFUNCTIONING PITUITARY ADENOMAS

Heather M. Kistka, Arash Nayeri B.S., Rebecca A. Kasl B.S., Andrea L. Utz M.D., Ph.D., Kyle D. Weaver M.D., Lola B. Chambless M.D.

INTRODUCTION:
Nonfunctioning pituitary adenomas (NFPA) are surgically treatable entities which frequently recur even after gross total resection. Their nonfunctional nature makes them difficult to monitor postoperatively and annual magnetic resonance imaging (MRI) is recommended. Failure to comply with these recommendations can lead to devastating visual compromise. However, many patients are lost to follow up. We sought to determine whether demographic or socioeconomic factors influenced patient compliance with follow-up recommendations.

METHODS: After obtaining IRB approval, we retrospectively reviewed the records of 121 patients who underwent primary transsphenoidal resection of NFPA between 2003 and 2011. Clinical history and demographics were reviewed. Length of follow-up and interval between scans were analyzed according to patient age, gender, marital status, education, insurance coverage, employment, distance of travel to Vanderbilt University, and mode of presentation via student’s t-test.

RESULTS: Patients received between one and eleven surveillance MRI scans following their routine post-operative imaging. The median and mean intervals between scans were 356 and 388 days, respectively. The median follow-up period was 47 months (mean = 54 mos). Patients who were married or presented with a decline in their vision had a significantly shorter mean interval between their surveillance scans (348 vs. 395 days, p=0.01 and 309 vs. 383 days, p=0.004) whereas patients who were employed at the time of surgery had a significantly longer mean scan interval (389 vs 335 days, p=0.02). No variable was associated with longer follow-up duration. Tumor recurrence was detected in 37 (31%) of patients.

CONCLUSIONS: Patients who originally experienced a deficit related to their NFPA or are married are more likely to obtain timely scans. This implies a heightened vigilance among these patients, however overall follow-up duration is poor. Furthermore, less stringent follow up in employed patients suggests that taking time from work for imaging may present a barrier to care. Efforts to improve compliance with surveillance should focus on patient education regarding the high risk of remote recurrence and importance of regular follow-up as well as identify and combat socioeconomic barriers to care.
IMAGING OF NONFUNCTIONING PITUITARY ADENOMAS: THE COST OF SURVEILLANCE

Heather Kistka MD, Rebecca Kasl, Arash Nayeri, Andrea Utz MD PhD, Kyle Weaver MD, Lola Chambless MD

OBJECTIVES: Nonfunctioning pituitary adenomas (NFPA) are treatable but notoriously recurring entities that are frequently asymptomatic until late in their course. Most lesions can be effectively treated surgically, but recurrent disease is common. As the potential visual compromise from these lesions can be devastating, they present a costly surveillance challenge, and annual MRI scans are recommended. We sought to define the cost of this practice and determine whether it was effective at reducing the long-term risk of vision loss.

METHODS: After obtaining IRB approval, we retrospectively reviewed the records of 143 patients who underwent resection of NFPA between 2003 and 2011. Clinical history, visual field testing, and magnetic resonance imaging (MRI) were reviewed. MRI costs were estimated at $571.93 per scan based on the Centers for Medicare and Medicaid national average. Differences between groups were compared via student’s t-test, chi-squared and Fisher’s exact test.

RESULTS: One hundred twenty patients received between 1 and 11 (median =2, mean =3.20) surveillance MRIs for a total of 382 scans. The median interval between scans was 357 days and the median follow-up period was 47 months. Initial tumor recurrence was detected in 37 (31%) of patients, further growth was noted in 13 scans, and 332 (87%) were stable. Estimated cost of all imaging was $218,477.30. The cost per scan which revealed growth was $4,369.55. Recurrence was significant enough to warrant retreatment with a surgery in 15 patients and radiation in four. The cost to identify these 19 (16%) patients with clinically significant growth was $11,498.80/patient. Overall, 5/19 patients (26%) with clinically significant growth experienced new visual field deficits prior to intervention. These patients had significantly longer mean intervals between scans than those who did not have visual deterioration (380 vs 1576 days, p=0.00036).

CONCLUSIONS: Recurrence occurred in one-third of patients with nonfunctioning pituitary adenomas. Annual imaging was associated with preservation of vision in patients with clinically significant growth during the observation period. Given the association between regular follow up and preservation of visual function, we feel the avoidance of possible visual impairment justifies this cost.
MEDICAL STUDENTS AS HEALTH EDUCATORS AT A STUDENT-RUN FREE CLINIC: IMPROVING THE CLINICAL OUTCOMES OF DIABETIC PATIENTS

Travis R. Ladner, Phillip Gorrindo, Alon Peltz, India Reddy, Bonnie M. Miller, Robert F. Miller, Michael J. Fowler

OBJECTIVES:
Student-run clinics provide service-learning experiences to medical students and care to underserved patients. Although it is assumed that student-run clinics provide high quality medical care, there are few published studies that support this assumption. This study examined the quality of care for diabetic patients enrolled in a diabetes educator program at Shade Tree Clinic, a student-run medical clinic in Nashville, Tennessee.

METHODS:
This study retrospectively reviewed medical records of patients with diabetes who established care at Shade Tree Clinic between 2008 and 2011. Clinical measures (based on American Diabetes Association guidelines) and the number of patient-student encounters were abstracted, at time points reflecting patients’ initial visits and 12 months later.

RESULTS:
There were 45 patients with diabetes included in this study. Mean hemoglobin A1c values improved significantly from 9.6 to 7.9, after a mean of 12.5 ± 1.5 months (P < .0001). A trend was found between increased patient-student contact and increased A1c improvement (r²=0.06, p=0.10). Clinical process measures were moderate to high, whereas clinical outcome measures for A1c, LDL and blood pressure were low to moderate.

CONCLUSIONS:
After 12 months of participation, patients with diabetes in a service-learning program at a student-run free medical clinic demonstrated improved A1c values. Medical students as patient health educators may have contributed to higher quality of care, suggested by high patient-appropriate clinical process measures. However, a minority of patients met national care goals for clinical outcome measures, perhaps reflecting additional difficulties in caring for this patient population.
SYRINX AND HEADACHE RESOLUTION CORRELATES WITH THE PB-C2 LINE IN PEDIATRIC CHIARI I MALFORMATION


OBJECTIVES:
The clinical significance of radiographic measurements of the craniocervical junction (CCJ) in Chiari I malformation (CM-I) is not well understood. The authors examine an institutional experience with the pB-C2 line, a measure of ventral canal encroachment, and its relationship with symptomatology and syringomyelia in pediatric CM-I.

METHODS:
A neuroradiologist retrospectively evaluated pre and post-operative MRI examinations on 80 pediatric CM-I patients undergoing posterior fossa decompression, obtaining pB-C2 line length and documenting syringomyelia. pB-C2 length was divided into Grade 0 (< 3 mm) and Grade I (≥ 3 mm). Demographic and clinical data were additionally collected. Statistical analysis was performed using t-test for continuous variables and univariate chi-square analysis for categorical variables.

RESULTS:
The median pB-C2 length was 3 mm, ranging from 0 to 10 mm. 65% of patients had a Grade I pB-C2. Patients with a Grade I pB-C2 were much more likely to have a syrinx preoperatively (RR 1.57 95% CI: 1.05-2.34, p=0.020) and, when present, greater resolution of syrinx postoperatively (mean difference: 3.56 vs. 0.17 mm, p<0.0001). Grade I patients were also more likely to have improvement in headache postoperatively (RR 1.69 95% CI: 1.031-2.750, p=0.009).

CONCLUSIONS:
Ventral canal encroachment may explain the symptomatology of select CM-I patients. The clinical findings presented suggest that Grade 0 patients are less likely to benefit from decompressive surgery with duraplasty than Grade I patients when syrinx and/or headache are present. These measurements may be useful in counseling patients and should help direct further prospective studies of preoperative radiographic measurements in Chiari I malformation.
ODONTOID RETROFLEXION CORRELATES WITH DEGREE OF TONSILLAR ECTOPIA IN CHILDREN WITH CHIARI I MALFORMATION


OBJECTIVES:
While it is known that patients with Chiari I malformation (CM-I) have greater angulation of the odontoid process than the general population, the effect of odontoid retroflexion on the degree of tonsillar ectopia remains an open question. The authors review an institutional experience with odontoid angulation and tonsillar ectopia in pediatric CM-I.

METHODS:
A neuroradiologist retrospectively evaluated pre-operative MRI examinations on 79 pediatric CM-I patients undergoing posterior fossa decompression, obtaining measurements of odontoid retroflexion and tonsillar ectopia, as well as presence of syringomyelia. Retroflexion was classified according to the following: Grade 0 >90, Grade I 85-89, Grade II 80-84, and Grade III <80 degrees.

RESULTS:
The median angle of odontoid retroflexion was 81 degrees, ranging from 57 to 113 degrees. The percentages of patients with Grades 0-III angulation were 16.5%, 20.3%, 17.7%, and 45.5%, respectively. The median length of tonsillar ectopia was 14 mm, ranging from 1 to 33 mm. The mean lengths of tonsillar ectopia for Grades 0-III were 10.4, 13.4, 17.9, and 15.5 mm, respectively. On multivariate analysis controlling for age and sex, odontoid angulation was found to be an independent predictor of length of tonsillar ectopia (p=0.002). Every 10 degrees of retroflexion was associated with 1.9 mm of additional tonsillar ectopia.

CONCLUSIONS:
These findings suggest a role for odontoid retroflexion in the pathogenesis of the cerebellar tonsil herniation observed in CM-I. Increasing angulation corresponded with increasing severity of tonsillar herniation. However, we did not observe a relationship between angulation and syringomyelia, the pathogenesis of which is likely multifactorial.
INFANTS WITH FRACTURES IN A PEDIATRIC EMERGENCY SETTING: ARE WE CONSIDERING CHILD PHYSICAL ABUSE?

Lindsay Roofe Lavin, MD, Cody Penrod, MD, Donald Arnold, MD, MPH, Cristina Estrada, MD, Benjamin Saville, PhD, MPH, Meng Xu, MS, Deborah Lowen, MD

OBJECTIVES:
Recognition of child physical abuse (PA) is critically important to avoid further morbidity and mortality. There is limited knowledge regarding how frequently pediatric emergency department (PED) clinicians consider child abuse in infants with fractures. Our two objectives were to estimate the percentage of infants with radiograph-confirmed fractures for whom PA was considered, and to examine patient and clinician characteristics that are associated with consideration of PA.

METHODS:
We reviewed the electronic medical record (EMR) of all patients less than 1 year of age with radiograph-confirmed fractures in a tertiary PED evaluated between 2008 and 2013. We used a multivariable logistic regression model to examine associations of patient and attending physician characteristics with our primary outcome variable, consideration of PA, defined as clearly-documented consideration of PA in attending or trainee note OR skeletal survey ordered OR child-abuse team consult ordered. Covariates included age, gender of attending physician, fracture location, previous injuries, encounter time, skin injury, social work consult performed, injury mechanism, medical complexity, and PEM-fellowship trained.

RESULTS:
There were 529 cases identified. For the entire cohort, consideration of PA occurred in 346 cases (65%), whereas consideration in infants < 6 months of age occurred in 194 cases (78%). EMR clearly-documented consideration of PA occurred in 288 (54%) of cases. Characteristics associated with greater odds for consideration of PA after covariate adjustment (OR and 95% CI) included younger patient age (increase across IQR of 12.1 to 38.7 weeks: 0.53 [0.33,0.84]), social work consult performed (7.93 [4.79, 13.13]), no history provided for injury (9.41 [3.88, 22.82]), soft-tissue injury (4.95, [1.57,15.54]), and male attending (1.84, [1.12, 3.01]).

CONCLUSIONS:
PED attending and trainees frequently do not consider PA in infants with fractures. Characteristics associated with consideration for PA include patient age, no history provided to explain the injury, soft-tissue injury, and male attending gender.
IMPACTING THE GLOBAL HEALTH BURDEN – TRAINING LAYPERSONS IN MOZAMBIQUE

Amina Merchant, Kelly McQueen

OBJECTIVE:
The hypothesis is that basic prehospital and primary hospital interventions made by layperson first responders and healthcare personnel will decrease trauma mortality and increase the number of capable first responders. In order to test this hypothesis, communities with hospitals that advertise surgical capacity in Mozambique were assessed.

METHODS:
Six hospitals and communities served as the intervention group that receives training on four basic resuscitative and stabilizing efforts in their native language in the Zambezia province of Mozambique. Community members received a one-hour seminar that taught four basic resuscitative and stabilizing interventions prior to transport by ambulance or taxi/bus. These techniques include a modified ABCD (airway, breathing, circulation, disability) noted in developed nations. A is for airway opening that allows victims to receive oxygen by simply opening their mouths and removing any foreign objects if present. B is for bleeding and laypersons were taught how to apply compression or a tourniquet to control bleeding. C represents cervical spine immobilization with simple tools such as rice bags and newspapers. D is for disability which is reduced by transporting victims with a flat, immobile, safe method. Hospital personnel received the same ABCD training as the community with two additions – assessment that involves vital sign monitoring and IV fluid resuscitation as they are markers of shock and injury.

RESULTS:
Pre- and post- tests were administered to participants in their native language. Results of the study suggest community members can be trained in basic resuscitative techniques.

CONCLUSIONS:
While laypersons and hospital personnel may receive and feel comfortable administering basic resuscitation techniques, further data must be collected to see if this intervention improves mortality.
INCREASED CEREBROVASCULAR REACTIVITY IN THE DAYS FOLLOWING SPORTS-RELATED CONCUSSION IN COLLEGE ATHLETES

Adam R. Militana, Manus J. Donahue, Ph.D., Megan K. Strother, MD, Allen K Sills Jr, MD, Gary S. Solomon, Ph.D., Victoria L. Morgan, Ph.D.

OBJECTIVES:
Cerebral blood flow (CBF) increase as a physiologic response to hypercapnea through cerebral arteriolar dilatation and cerebrovascular reactivity (CVR) is a measure of this response. No study has been published using fMRI to assess CVR following sports-related concussion and what little has been published using other modalities has been inconclusive. The purpose of this study is to evaluate CVR using fMRI in college athletes in the days following a sports-related concussion.

METHODS:
We have enrolled six college athletes (3M/3F, 18-21 yrs) 2-6 days after suffering a sports-related concussion diagnosed by an athletic trainer and seven healthy (3M/3F, 18-21 yrs) college students who have never suffered a concussion. CVR was measured by resting functional echo-planar imaging by calculating the average percent signal change in BOLD signal. Subjects alternated breathing room air and room air with 5% CO2 via mask at intervals of two minutes. Baseline CBF was quantified using arterial spin labeling techniques. A total of 18 regions of interest(ROIs) were evaluated across the brain.

RESULTS/CONCLUSIONS:
Our data indicate that CVR is increased approximately 42% (average across all ROIs) in patients compared to controls (p = 0.04). This is compared to baseline CBF values which differ less than 1%. While the exact pathophysiology is unclear, we suspect that this hypereactive vasodilatory response is potentiated by the local metabolic environment surrounding cerebral arterioles following concussion. Furthermore, we believe our results suggest hypercapnea and the exaggerated vasodilatory response that ensues may represent a potential etiology for return to play symptoms. This is the first set of data presented using fMRI to evaluate CVR in concussion patients. Additionally, our finding of increased CVR in the days following sports-related concussion has not previously been suggested in any published study regardless of modality.
13-YEAR EXPERIENCE IN EXTERNAL FIXATION OF THE PELVIS: COMPLICATIONS, REDUCTION AND REMOVAL

Phillip M. Mitchell, Chad M. Corrigan, Neelam A. Patel, Arnold J. Silverberg, Rachel V. Thakore, William T. Obremskey, Jason M. Evans, Jesse M. Ehrenfeld, Manish K. Sethi

OBJECTIVE:
Previous studies of external fixation for pelvic ring injuries have reported a high incidence of complications. We reviewed the history of pelvic EF at our institution, including the utility of pelvic EF in maintaining reduction of the anterior ring, the risks of complications, and the location of removal of these devices.

METHODS:
We found 195 who underwent anterior external fixation of the pelvis and SI screw placement for their pelvic ring injuries over a 13-year period at a level 1. After excluding ineligible patients, 130 charts were reviewed for age, sex, race, BMI, duration of EF, location of EF removal, associated injuries and postoperative complications. The symphysis diastasis and the vertical and posterior displacement of each hemi-pelvis relative to the contralateral side was measured. 76 patients with radiographic follow-up > 2 months were identified and radiographs prior post EF removal were compared to evaluate for a loss of reduction.

RESULTS:
Mean duration of external fixation was 61 days. 14 (10.8%) patients presented to an ER with issues related to the EF device, 7 (5.4%) of which required readmission for deep infection. Of those requiring readmission, all were admitted for IV antibiotics and 6 (4.6%) required operative debridement. 13 (10.0%) had superficial pin site infections requiring oral antibiotics. Reduction was maintained in all patients (n=76) following removal of their EF with an average change in the symphysis diastasis, anterior and posterior displacement of 1.2 mm, 3.9 mm, and 4.0 mm. 38 patients (30.2%) had their EF removed in clinic while the remaining 88 (69.8%) were removed in the operating room.

CONCLUSIONS:
We found low complication rates while maintaining reduction of the pelvic ring and that these devices could be reliably removed in a clinic setting, saving the additional time and expense associated with removing an external fixator in the operating room.
A RETROSPECTIVE ANALYSIS OF HYDROCEPHALUS FOLLOWING THE BI-DIRECTIONAL GLENN PROCEDURE FOR SINGLE-VENTRICLE CONGENITAL HEART DISEASE

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**OBJECTIVE:**

The Bi-Directional Glenn (BDG) procedure involves the anastomosis of the superior vena cava (SVC) to the pulmonary artery, resulting in an abruptly increased central venous pressure (CVP). We hypothesize that this increase in CVP triggers an acute neurologic insult, promoting the development of hydrocephalus in the developing infant.

**METHODS:**

We identified 176 patients that underwent the BDG procedure between August 2006 and July 2013. Within our initial cohort, 25 patients had head imaging (CT, MRI, or ultrasound) performed both before and after the BDG. From these images, we retrospectively measured the Frontal-Occipital horn Ratio (FOR), a well-validated indicator used to assess cerebral ventricular volume. Using central venous access catheter data we were able to assess pre and post-operative pressure transducer data at discrete time-points. Paired t-tests and linear regression were used to evaluate our cohort. As this was a pilot study, statistical significance was set at p=0.10.

**RESULTS:**

The median age of our cohort was 3.5 months. Mean FOR was 0.393 before and 0.429 after the procedure. BDG procedures were found to be associated with increased post-operative FOR (p<0.0001). Furthermore, a simple linear regression demonstrated a statistically significant association between increasing change in FOR following the BDG and CVP at 12 hours post Glenn procedure (p=0.003).

**CONCLUSION:**

With the development of surgical palliation for single-ventricle congenital cardiac lesions, more children are surviving into adulthood. Our study is the first to demonstrate mild hydrocephalus (FOR>0.42) developing in a cohort after the BDG. Further, we present a potential physiologic correlate with CVP after the Glenn procedure increasing with increased cerebral ventricle volume. This study has informed a prospective study currently in development, to evaluate the link between the BDG procedure and neurological outcomes.
DEEP SEQUENCING OF THE HIV GAG-SPECIFIC T CELL RECEPTOR REPERTOIRE REVEALS EXTENSIVE T CELL RECEPTOR SHARING BETWEEN HIV-SPECIFIC CD4+ AND CD8+ T CELL SUBSETS

Mark Pilkinton, Louise Barnett, Spyros Kalams

HIV evades control by the adaptive immune system, however a minority of individuals can maintain control of viral replication in the absence of anti-retroviral therapy. The HIV specific T cell receptor (TCR) repertoire is critical for this control and studies suggest a diverse repertoire of virus-specific T cell receptors favors control of viremia. However, these studies have been restricted to a few epitopes and the contribution of the HIV specific CD4+ T cell receptor repertoire is unknown. In this study, we used deep sequencing to analyze the polyclonal TCR repertoire of HIV Gag-specific CD4+ and CD8+ T cells. Peripheral blood mononuclear cells (PBMC) from two HIV controllers were stimulated with Gag peptides for 24 hours and stained with markers of acute immune activation. Virus-specific CD4+ and CD8+ T cells were sorted and the TCR CDR3 region underwent deep sequencing. We identified substantial sharing of identical TCRbeta CDR3 hypervariable region in Gag specific CD4+ and CD8+ T cells. CD4+ and CD8+ Gag-specific T cell sequences from subject 10067 had 17 sequences in common and in subject 10066 there were 29 sequences in common. We went on to identify these sequences in the central and effector memory of resting CD4+ and CD8+ T cells; in the naïve subset they were found rarely or not at all. We hypothesize this overlap in TCR use may be due to the existence of known HLA class 1-restricted epitopes nested within HLA class 2-restricted epitopes. These findings have implications for evaluation of the TCR repertoires of CD4+ and CD8+ T cells induced by HIV vaccines designed to elicit cell-mediated immune responses.
HISTOPATHOLOGIC REVIEW OF 310 RADICAL CYSTECTOMIES AND LYMPH NODE DISSECTIONS WITH EMPHASIS ON HISTOLOGIC VARIANTS OF UROTHELIAL CARCINOMA

Katrina Salazar, Michael Cookson, Giovanna Giannico, Omar Hameed, Lan Gellert

Urothelial carcinoma has a marked propensity for divergent differentiation. Histologic variants of urothelial carcinoma are clinically significant for prognosis and therapy. Few studies have described the prevalence and extent of such variants in the bladder and associated metastases.

OBJECTIVE: We systematically characterized the histologic variants in a large series of primary bladder urothelial carcinoma as well as their lymph node (LN) metastases.

METHODS: Three hundred ten radical cystectomy cases and their associated LN dissections performed at a single institution over a 4-year period were reviewed by GU pathologist(s). Strict diagnostic criteria are used for each histologic variant, such as “unequivocal keratin formation and/or intercellular bridges” for squamous differentiation and “multiple small nests in the same lacunar space” for micropapillary features. Clinical data were collected from patient charts.

RESULTS: Of the 310 cases, 33% (101/310) exhibit variant morphology at least focally in the tumor, including 11% squamous, 6% micropapillary (MP), 4% glandular, 4% sarcomatoid, 2% diffuse/plasmacytoid, 2% neuroendocrine/small cell, and 2% others while 4% of the cases displayed more than one variant morphology. LN metastases were present in 36% (36/101) of the cases with variant morphology vs. 15% (31/210) of the remainder. Concordant variant morphology is present in LN metastases. Twelve of the 34 tumors with squamous features had LN metastases, and 9 of them exhibited squamous features in the LN. No correlation between the presence of squamous features in the LN and the extent of such features in the primary tumor was identified. Thirteen of the 20 tumors with MP features had LN metastases, and 9 of them exhibited MP features in the LN. Of the 4 cases without variant morphology in the LN, 3 cases had MP features in <5% of the primary tumor.

CONCLUSIONS: A significant proportion of bladder urothelial carcinoma (33%) show at least focal divergent differentiation, which is often replicated in their LN metastases when present. The presence of the variant morphology in LN metastases is associated with the extent of such morphology in the primary tumor for MP, but not squamous differentiation. Further clinical follow up are ongoing to thoroughly characterize the correlation between histologic variants and LN metastases as well as their clinical significance.
DOES PHYSICIAN REIMBURSEMENT CORRELATE TO RISK IN ORTHOPAEDIC TRAUMA?

Vasanth Sathiyakumar, Rachel V. Thakore, Cesar S. Molina, William T. Obremskey, Manish K. Sethi

OBJECTIVE:
With the recent changes in the American Healthcare landscape, reimbursement models are likely to also shift. But in developing new policy, how will the risk of complications for a given injury be considered? Utilizing the ACS-NSQIP database, we sought to evaluate the relationship between reimbursement and risk in order to determine if procedures with higher risk of complications received increased physician compensation.

METHODS:
91 CPT codes representing orthopaedic trauma surgeries, which included hip/pelvis (HP), upper extremity (UE) and lower extremity (LE) fractures (fx), were identified in the 2005-2011 ACS-NSQIP database. Peri-operative complications were recorded. Physician Payment (Medicare Part B) amounts for each CPT code were recorded. A linear regression was performed to determine the correlation between complication rates and payment amounts.

RESULTS:
41 orthopaedic trauma CPT codes representing 18,854 patients (HP = 5029, UE = 4091, LE = 8582) were included in the analysis. Only a moderate correlation between payment amount and complication rates was found (r=0.55, p=0.001). Overall, a 1.8% increase in complication rate was associated with a payment increase of only $100 dollars. There was a minimal relationship between Medicare reimbursement and complication rate, for example above knee amputations demonstrate a complication rate of 25.1% and reimbursement of $832.00 and ORIF of the distal femur demonstrates a similar payment ($989) and high complication rate (24.2%). However, other injuries had much higher reimbursement but lower complication rates: pilon ($1294, 7.2%) and proximal humerus fractures ($1249, 5.7%).

CONCLUSIONS:
Our data demonstrates the current Medicare payment structure does not heavily weigh the risk of adverse events in providing compensation to physicians. In a future bundled payment plan, fractures with lower compensation but higher risks of complications will challenge the financial viability of caring for patients.
THE EFFECT OF FLAP COVERAGE ON THE LENGTH OF STAY AND COSTS FOR PATIENTS WITH OPEN FRACTURES OF THE TIBIA

Vasanth Sathiyakumar, Rachel V. Thakore, Jake McClure, Kent K. Higdon, William T. Obremskey, Manish K. Sethi

OBJECTIVE:
An effective method of reducing costs for orthopaedic trauma patients is by reducing the length of stay (LOS). The effect of a reconstructive procedure for flap coverage on LOS and cost has not yet been quantified. In this study, we compared the LOS and costs for the treatment of patients with open tibia fractures requiring flap coverage to those open tibia fractures that had primary closure of their wounds.

METHODS:
We searched medical records at a level I trauma center for patients with isolated open tibia fractures treated with an intramedullary nail across a four year period. Eight CPT codes were used to find patients with isolated open tibia fractures with muscle, pedicle, or free flap coverage. Patients with multiple injuries, or incomplete charts were excluded. Age, gender, race, and ASA score were collected. LOS was calculated by subtracting the admission date from the discharge date at a cost of $4503 per night. A Mann-Whitney U-test and linear stepwise regression was performed adjusting for age, gender, race, and ASA classification.

RESULTS:
The mean LOS for patients with tibia fractures who received primary closure of an isolated open tibia fracture was 4.5 days. The average hospitalization cost was $20,341.14. Patients that required flap coverage had a mean LOS of 11.0 days and $49,428.28 in costs. There was a significant difference in mean LOS and costs between patients who required flap coverage and those who received primary closure of their wounds (p<0.001). The mean number of days between IMN and flap coverage was 2.9 days. Patients remained in the hospital for an average of 6.5 days following reconstructive surgery.

CONCLUSIONS:
Our results show that the need for flap coverage significantly increases the LOS and hospitalization costs for patients with open tibia fractures. Improved communication between plastic and orthopaedic teams and early involvement by plastic surgeons can improve interdepartmental coordination of care.
ANATOMIC REGION AND THE RISK OF ADVERSE EVENTS IN ORTHOPAEDIC TRAUMA: AN ANALYSIS OF 19,000 PATIENTS

Vasanth Sathiyakumar, Cesar S. Molina, Rachel V. Thakore, Eduardo J. Burgos, William T. Obremskey, Manish K. Sethi

OBJECTIVE:
Little data exists exploring adverse events in Orthopaedic trauma surgery. Through the ACS-NSQIP database, we compared adverse events in orthopaedic trauma procedures by anatomic region (upper extremity (UE), hip & pelvis (HP), and lower extremity (LE)).

METHODS:
ACS-NSQIP was used to identify a total of 91 CPT codes representing 19,028 orthopaedic trauma patients from 2005-2011. These patients were then divided into three anatomic regions: UE (n=4925), HP (n=5273) and LE (n=8830). Perioperative minor and major complications were recorded. We used a multivariate analysis that controls for age, medical comorbidities, ASA status, operative time, baseline functional status and anatomic region to evaluate risk factors for complications.

RESULTS:
A total of 19,028 orthopaedic trauma cases were divided into three anatomic regions: 25.9% (n=4925) UE, 27.7% (n=5273) HP, and 46.4% (n=8830) LE. Statistically significant differences were identified when comparing demographics between HP and UE patients; these include the number of patients in each group over 65 years of age (85% vs. 32.2%) ASA>2 (78.9% vs. 32.4%) and diabetes (17.9% vs. 11.1%) p=0.01. No other variables were significantly different among the groups. After controlling for several important individual patient factors, hip and pelvis patients are nearly four times more likely to develop any perioperative complication than upper extremity patients (OR:3.79,95%CI:3.01-4.79,p=0.01). Also, patients in the LE group are three times more likely to develop any complication vs. UE patients (OR: 2.82, 95%CI:2.30 –3.46,p=0.01).

CONCLUSIONS:
Even after controlling for several variables, patients with LE fractures are almost three times more likely and those with HP fractures are almost four times more likely to develop a complication than patients in the UE group.
OPEN DISTAL TIBIAL SHAFT FRACTURES: A RETROSPECTIVE COMPARISON OF MEDIAL PLATE VERSUS NAIL FIXATION

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OBJECTIVE:
The treatment of open distal tibial shaft fractures by either open reduction internal fixation (ORIF) or intramedullary nailing (IMN) remains controversial. The purpose of this present study was to conduct the largest retrospective study to date comparing complication rates for IMN and ORIF of open distal tibia shaft fractures.

METHODS:
Patients who were treated for open tibia fractures by ORIF or IMN across a ten year period were identified through a CPT code search at a level I trauma center. Patient charts were reviewed for age, gender, ASA score, hospital length of stay (LOS), and Gustilo Grade of open fracture. Distal tibia fractures were identified as 4 to 11 cm from the plafond. Patient charts were reviewed to determine reoperations due to hardware pain/prominence, wound healing issues, infection, nonunion, and other bone issues occurred. A multivariate analysis comparing complication rates while controlling for age, gender, ASA score, hospital length of stay (LOS), and fracture grade was performed.

RESULTS:
Of the 219 patients with open distal tibia shaft fractures included in analysis, 83.1% (n=182, G1 22, G2 78, G3 80) were treated with IMN. 16.9% (n=37, G1 10, G2 16, G3 10) were treated with medial plating. After controlling for fracture grade, age, gender, ASA score, and LOS, no significant difference in overall complication rate between IMN (31.3%, n=57) and ORIF (44.4%, n=26) was found. When further breaking down the complications into the five categories mentioned above, the ORIF group was found to have a significantly higher rate of nonunion (22.2%, n=8) when compared to IMN (8.8%, n=16). No significant difference in the rate of infection, hardware pain, delayed wound healing, or other bone issues was found.

CONCLUSION:
This study demonstrates a significantly higher rate of nonunion in the ORIF group. Our findings differ from the current literature demonstrating similar union rates regardless of the implant used.
PROSPECTIVE RANDOMIZED CONTROLLED TRIAL USING TELEMEDICINE FOR FOLLOW-UP VISITS IN AN ORTHOPAEDIC TRAUMA POPULATION: A PILOT STUDY

Vasanth Sathiyakumar, Jordan C. Apfeld, William T. Obremskey, Rachel V. Thakore, Manish K. Sethi

OBJECTIVE:
Proper follow-up is critical for patients sustaining orthopaedic trauma injuries. However, several barriers to follow-up exist. The purpose of this prospective, randomized controlled pilot trial is to investigate the feasibility of telemedicine (TM) for follow-up.

METHODS:
24 total patients were recruited based on power analysis at the two-week follow-up visit. Inclusion criteria was age >18 years, closed fracture evaluated at the university, and access to TM video calls. Patients were assigned into the control (C) (n=12) or TM (n=12) group and all had 2-week, 6-week, 3-month, and 6-month follow-up visits. C patients had all visits in-person at the university’s clinic, while TM patients had 6-week and 6-month follow-ups occur through video calls. TM patients obtained x-rays of their fractures at local facilities. Patients answered surveys detailing their experiences at the conclusion of the study and statistical analyses compared patient satisfaction.

RESULTS:
9 control patients (3 lost to follow-up) and 8 telemedicine patients (3 lost to follow-up, 1 sustaining an open fracture) completed the study. There were no significant differences between the C and TM group with satisfaction and complications. Significantly fewer patients in the TM group (n=0, 0%) took time off from work for appointments compared to the C group (n=5, 56%) (p=.03). In the TM group, patients traveled significantly fewer miles for an x-ray at a local facility (avg. 14.1 mi) compared to traveling to the University (avg. 53.8 mi) (p<.001). The TM group spent significantly less time per visit for video calls including travel time for x-rays, (79.4 min) (156.9 min) (p=.007).

CONCLUSION:
This study was the first to illustrate telemedicine as an alternative to in-person clinic visits based on reduced time away from work, and reduced travel distance and time for visits. TM may be used to decrease barriers to follow-up. Further study with a larger patient population is warranted.
ADVERSE EVENTS IN ORTHOPAEDIC SURGERY: IS TRAUMA MORE RISKY?
AN ANALYSIS OF THE NSQIP DATA

Vasanth Sathiyakumar, Cesar S. Molina, Rachel V. Thakore, Eduardo J. Burgos, William T. Obremskey, Manish K. Sethi

OBJECTIVE:
As we move towards a value based system of healthcare, surgeons will increasingly be measured on peri-operative complication rates and outcomes. In this study utilizing the NSQIP data we wanted to better understand the perioperative complication rates and risk factors in Orthopaedic trauma and compare them to general orthopaedics.

METHODS:
Utilizing the NSQIP database, a total of 1,066 ortho procedures with 146,773 patients were identified. Of these procedures, 91 were ortho trauma (upper/lower extremity and hip/pelvis fractures) involving 22,361 patients. The remaining 975 codes represented all other ortho surgeries involving 124,412 patients. Peri-operative complications were recorded and categorized as minor or major. Using a multivariate analysis controlling for age, medical comorbidities, ASA status, operative time and baseline functional status, perioperative complications were compared between the two groups.

RESULTS:
The overall complication rate in the ortho trauma group was 11.4% (2,554/22,361) vs. 4.1% (5,137/124,412) in the general ortho group, p=0.001. Similar variables were identified as risk factors for complications in both the ortho trauma group and the general ortho group (Age >65, history of CHF, ASA >2, and longer operative time). When controlling for all variables, trauma was identified as a risk factor for developing any type of complication, OR: 1.69, 95% CI: 1.57 – 1.81.

CONCLUSIONS:
Utilizing the NSQIP data we demonstrate that Orthopaedic trauma patients are almost 2 times more likely than those in the general orthopaedic population to sustain complications, despite showing similar risk factors and controlling for individual patient factors. Furthermore we demonstrate a significant difference between complication rates between the two groups (11.4%vs 4.1%). Our data suggests that Orthopaedic trauma should not be grouped with general Orthopaedic surgery when benchmarking for complication rates and adverse events.
DOES ANESTHESIA TYPE INFLUENCE RISK OF PERIOPERATIVE COMPLICATIONS IN HIP FRACTURE SURGERY?

Vasanth Sathiyakumar, Rachel V. Thakore, Cesar S. Molina, Paul S. Whiting, William T. Obremskey, Manish K. Sethi

OBJECTIVES:
Several recent studies have advocated the use of regional anesthesia over general anesthesia as a means of reducing the risk of perioperative complications for hip fracture surgery. However, conclusive evidence demonstrating clinically significant differences in complication rates does not exist. We explored impact of anesthesia type on perioperative complications in hip fracture surgery using the recently expanded ACS-NSQIP database - a large, multicenter, prospective cohort of hip fracture patients.

METHODS:
Four CPT codes were used to identify a prospective cohort of 7,808 hip fracture patients from 2005-2011 in the NSQIP database. Only patients who were administered general anesthesia or regional anesthesia (spinal or nerve blocks) were included in the analysis (n=7,764). Peri-operative complications were recorded and categorized as minor or major. Using a multivariate logistic regression analysis controlling for age, medical comorbidities, ASA status, operative time and baseline functional status, perioperative complications were compared.

RESULTS:
7,764 patients with hip fractures were included in the final analysis. Rates of minor, major, and total complications by anesthesia type are displayed in Table 1. Patients undergoing surgical treatment for hip fractures who received regional anesthesia had a significantly higher risk of total complications (OR: 1.05, p=0.025) and minor complications (OR: 1.09, p=0.001) compared with patients who were administered general anesthesia. There was no significant difference in risk of major complications between the two groups (OR: 0.99, p=0.720) (Table).

CONCLUSION:
Regional anesthesia was associated with a small (OR=1.05) but statistically significant increase in the risk of perioperative complications. Our results do not support the conclusions of several recent studies, which suggest decreased rates of perioperative complications with regional as compared to general anesthesia.
HIP FRACTURES ARE RISKY BUSINESS: AN ANALYSIS OF THE NSQIP DATA

Vasanth Sathiyakumar, Rachel V. Thakore, Cesar S. Molina, Eduardo J. Burgos, William T. Obremskey, Manish K Sethi

OBJECTIVE:
The recent expansion of the American College of Surgeons National Quality Improvement Program (ACS-NSQIP) database provides an unparalleled opportunity to analyze the highest-risk orthopaedic surgeries. In this study, we begin by utilizing ACS-NSQIP data to compare the rate of 13 adverse events among the 30 most common orthopaedic procedures. We then use our findings to investigate risk factors and complication rates among the top five surgeries found to have the greatest rate of adverse events in orthopaedic surgery.

METHODS:
Using the ACS-NSQIP database, a prospective cohort of 101,862 orthopaedic patients from 2005-2011 were categorized by Current Procedural Terminology Codes (CPT). Demographics including age, sex, race, and comorbidities were recorded. The incidence of 13 adverse events was calculated. For the five procedures with the greatest rate of adverse events, the most common postoperative complications and risk factors for adverse events were identified. Statistical significant was set at p<0.05.

RESULTS:
The top five orthopaedic procedures with the highest rate of adverse events were all hip fracture surgeries (n=9,460). Adverse events occurred in 15.9% to 27.4% of cases among these five procedures. These surgeries also accounted for 36.1% (2,433/9,460) of all adverse events in orthopaedics. Among the top five procedures, the most common adverse events were death (6.90%), myocardial infarction (1.69%), and UTI (5.92%). Five significant risk factors were identified for adverse events following hip fracture repair, including age, history of CHR, esophageal varices, ASA class, and functional status.

CONCLUSION:
This study, which is the first to use the expanded orthopaedic ACS-NSQIP database, demonstrates that over one-third of all adverse events in orthopaedics are due to hip fractures. Quality improvement programs targeted towards hip fracture patients, especially those with the risk factors identified above, can dramatically reduce adverse events in orthopaedic trauma.
RISK FACTORS FOR DISCHARGE TO REHAB AMONG HIP FRACTURE PATIENTS

Vasanth Sathiyakumar, Rachel V. Thakore, Cesar S. Molina, William T. Obremskey, Manish K. Sethi

OBJECTIVES:
Length of stay (LOS) is a powerful driver of cost in hip fracture surgery. One frequent cause of prolonged LOS is delayed transfer to rehabilitation centers following surgery. Using the recently expanded ACS-NSQIP database, this is the first national multicenter study to identify risk factors for discharge to rehab for hip fracture patients.

METHODS:
A prospective cohort of 7,808 hip fracture patients from 2005-2011 were identified in NSQIP using 4 CPT codes. 5,615 patients were included in analysis. Rehab destinations included skilled care (SNF), unskilled facility (USF), separate acute care (SAC), and rehabilitation facility (RF). All other patients were discharged home. Using a multivariate logistic regression analysis, we analyzed 19 potential risk factors including type of procedure, age, medical comorbidities, ASA status, operative time, and baseline functional status.

RESULTS:
Of the 5,615 hip fracture patients in this analysis, 71.0% were discharged to a rehab facility (SNF 44.3% n= 2489) (USF 0.6%, n=34) (SAC 2.0%, n=112) (RF n=24.0%, 1349), and 29.0% were discharged home. Type of hip fracture procedure was not found to significantly increase the risk of going to rehab (p=0.66). Patients over the age of 65 were 4.25 times more likely, females were 1.53 more likely, patients who received general anesthesia were 1.68 times more likely, and patients with an ASA score greater than 2 were 3.09 times more likely to be discharged to rehab (p=<0.001). Patients who had hypertension were 1.61 times more likely to go to rehab, while patients who needed dialysis were 8.74 more likely. Patients with poorer pre-injury functional status were 1.92 times more likely to go to rehab (p=<0.001). (Table).

CONCLUSION:
In a large prospective series of patients with hip fractures, we demonstrate clear risk factors that predict potential postoperative transfer to rehab centers. Orthopaedic surgeons must utilize such predictors in planning for eventual discharge to rehab.
EVALUATION OF PREOPERATIVE RISK FACTORS AND COMPLICATION RATES IN RHYTIDECTOMY

Hanyuan Shi, Varun Gupta, Julian Winocour, R Bruce Shack, Kent Higdon, James Grotting

OBJECTIVES:
Rhytidectomy remains a prominent technique for facial rejuvenation. According to the ASAPS Cosmetic National Database, 119,006 rhytidectomies were performed in 2012. Although the overall incidence of complications is low, any complication can leave a potentially devastating cosmetic outcome and pose a significant financial burden on the patient and the surgeon. This study analyzed the risk factors and significant complications after rhytidectomy.

METHODS:
A retrospective cohort of patients who underwent rhytidectomy (either alone or as a combination with other procedures) between May 2008 and May 2013 was identified from the CosmetAssure database (total of 183,914 procedures). Univariate and multivariate analysis was performed looking at risk factors.

RESULTS:
Of the 11,300 rhytidectomies, 4,809 (42.6%) were performed as a solitary procedure and 6,491 (57.4%) with additional procedures. A total of 205 major complications were recorded (1.8%); 127 (62.0%) hematomas, 31 (15.1%) infections, 16 (7.8%) pulmonary dysfunction, 7 (3.4%) cardiac complications and 4 (2%) nerve injury. Male gender (p=0.000), combined procedures (p=0.016) and type of facility (p=0.002) were independent predictors of complications on multivariate analyses. Age, diabetes and smoking were not significant. BMI was significant only in univariate analysis (p=0.041).

CONCLUSIONS:
Rhytidectomy remains an extremely safe procedure with a low complication rate. This study details specific risk factors associated with these complications. This is important to appropriately select patients that might be better suited for staged rather than combined procedures.
CONSERVATIVE FLUID MANAGEMENT DECREASES MORTALITY IN ACUTE RESPIRATORY DISTRESS SYNDROME PATIENTS WITH LOW CENTRAL VENOUS PRESSURE

Matthew W. Semler, Arthur P. Wheeler, Gordon R. Bernard, B. Taylor Thompson, Todd W. Rice

OBJECTIVES:
In the Fluid and Catheter Treatment Trial (FACTT), a conservative fluid strategy targeting lower intravascular pressures using fluid restriction and diuretics increased ventilator-free days (VFDs) in patients with Acute Respiratory Distress Syndrome (ARDS) but did not reduce mortality. Participants had a wide spectrum of initial intravascular pressures and the efficacy of the conservative fluid strategy might differ between subgroups with “high” and “low” initial pressures.

METHODS:
We conducted a retrospective analysis of the subgroups of FACTT participants enrolled with “high” vs. “low” central venous pressure (CVP). We hypothesized that participants with “high” CVP at enrollment would experience a greater difference in clinical outcomes between conservative and liberal fluid management than those with “low” CVP at enrollment. Primary outcome was 60 day mortality.

RESULTS:
In 966 patients with a baseline CVP, values ranged from 0-30 mmHg with a mean of 12±0.3mmHg. Compared to the 234 patients in the highest quartile (CVP 15-30mmHg), the 234 patients in the lowest quartile (CVP 0-8mmHg) were more likely male (p=0.013) and HIV positive (p<0.001). Despite receiving less pre-randomization fluid (p<0.001), those in the lowest quartile were less frequently on vasopressors (p=0.039), had similar cardiac index (p=0.445), and had lower creatinine (p=0.012) at baseline. They had lower plateau pressure (p<0.001) and PEEP (p<0.001) with higher PaO2:FIO2 ratio (p=0.003). Within each CVP quartile, patients randomized to each intervention arm had similar baseline characteristics. In the conservative arm 60 day mortality was similar in each CVP quartile (p=0.687) while in the liberal arm 60 day mortality increased with lower filling pressures (highest to lowest: 19.2%, 30.6%, 27.6%, 39.3%; p=0.010) resulting in a mortality difference of 12.5% (p=0.042) in favor of the conservative strategy in the lowest CVP quartile. Conservative fluid management also resulted in more VFDs and ICU-free days in the lowest versus highest CVP quartile (p<0.001).

CONCLUSIONS:
Among ARDS patients, those with the lowest initial CVP demonstrate the greatest difference in VFDs, ICU-free days, and mortality from application of a conservative versus liberal fluid strategy.
STATISTICAL MODELING OF PERIOPERATIVE β-BLOCKADE INITIATION ACCOUNTING FOR HETEROGENEOUS TREATMENT EFFECTS: POSSIBLE LONG TERM MORTALITY BENEFIT WITH AGENTS OTHER THAN METOPROLOL

Derek Smith, Loren Smith, Jeffery Blume

OBJECTIVES: Randomized controlled trials (RCTs) have reported decreased risk of myocardial infarct (MI) with the initiation of perioperative β-blockade, however the POISE trial also reported increased risk of stroke and 30 day mortality. Observational studies suggest metoprolol is more strongly associated with perioperative stroke and short term mortality than other β-blockers. No previously published meta-analysis has accounted for this heterogeneity of treatment effect. The theory tested in this work is that β-blockers other than metoprolol have a different risk profile than metoprolol when used to initiate perioperative β-blockade.

METHODS: A literature search identified applicable RCTs with placebo controls. Outcomes of interest included non-fatal MI, non-fatal stroke, short term (= 30 day) and long term (> 6 month) mortality. Due to the binary nature of these outcomes, it was possible to reconstruct patient level data for analysis, as compared to traditional meta-analyses which utilize published summary statistics. All analyses were completed with mixed-effects logistic regression modeling stratified by metoprolol versus other β-blocker. This statistical model allows control data to be shared across study groups. Random intercepts were utilized to account for differing baseline event rates among studies.

RESULTS: When stratified by medication, a decreased risk of MI (p = 0.001) and an increased risk of non-fatal stroke (p = 0.037) and short term mortality (p = 0.036) were observed with metoprolol treatment. These results are very similar to POISE results, likely due to the large sample size of the POISE trial. A sensitivity analysis for POISE data revealed that the remaining metoprolol data show no significant evidence for decreased MI or increased stroke. No significant short term results were found with other β-blocker treatment. A likelihood ratio test was performed comparing the relative risk of long term mortality with metoprolol versus other β-blocker treatment, resulting in $\chi^2(1) = 3.875$ (p = 0.049). Per Cochrane review guidelines, this test should be interpreted at the p = 0.1 level, suggesting a difference in these treatments. Further analysis shows that β-blockers other than metoprolol are associated with a statistically significant decrease in long-term mortality (OR = 0.50, 95% CI 0.26 - 0.95, p = 0.034).

CONCLUSIONS: These results support the theory that initiation of perioperative β-blockade with β-blockers other than metoprolol is associated with a different risk profile than metoprolol. The failure in past analyses to account for heterogeneous treatment effects has obscured evidence of a possible protective effect on long term mortality of β-blockers other than metoprolol. These analyses highlight the importance of thoughtful statistical model selection by illustrating the possibility of obtaining misleading results if an inappropriate model is employed. Future studies should utilize a range of dose and administration parameters and include long term follow up to allow estimation of the risk/benefit profiles of these agents.
PARASTOMAL HERNIAS AFTER RADICAL CYSTECTOMY AND ILEAL CONDUIT URINARY DIVERSION: RISK FACTORS AND MANAGEMENT

Nicholas Smith, Harras Zaid, Christopher Anderson, Sam Chang, Willie Melvin, Daniel Barocas, Michael Cookson

INTRODUCTION AND OBJECTIVES:
While complications following radical cystectomy and ileal conduit (RCIC) are common, few data exist on the incidence and management of parastomal hernias (PH). We sought to describe the incidence, risk factors and management of this post-operative complication.

METHODS:
We performed a retrospective analysis of all patients undergoing RCIC at Vanderbilt University between 2000 and 2010. Patients with less than 6 months follow-up were excluded. Clinical and demographic covariates were examined including age, sex, race, body mass index (BMI), smoking status, Charlson Comorbidity Index (CCI), and receipt of neoadjuvant chemotherapy. Associated symptoms and operative management of patients with PH were also collected.

RESULTS:
Our analytic cohort included 407 patients that underwent RCIC and had at least 6 months of follow-up (mean 35.9 months, SD 28.8). Of these, 113 (27.8%) developed a PH that was detected on clinical exam. Age was similar between those who developed a PH and those who did not (mean 69.0 vs. 69.2 years). Other demographic and clinical variables are displayed in Table 1. The mean time from RCIC to development of PH was 17.8 months (SD 18.1), although this varied widely (range 0.2-124.3; IQR 6.9-24.1). 61 (53.9%) of patients with PH presented with one or more symptoms. Among the most common complaints were pain (28.3%) and pouching difficult (25.7%). In a multivariable analysis incorporating age, sex, race, BMI, smoking, CCI, and receipt of neoadjuvant chemotherapy, no single variable was independently associated with the development of PH. Operative repair was pursued in 49 (43.4%), of which 44 (89.8%) were elective and 5 (10.2%) were done on an urgent basis.

CONCLUSION:
Patients remain at risk for development of a PH over their lifetime following RCIC. While no single factor predicted PH in this cohort, the development of this complication occurs in almost one-third of patients and is likely multifactorial. Fewer than half of our patients elected for operative management. Our findings suggest that long-term follow-up is necessary to monitor for this post-operative complication.
OLECRANON FRACTURES: FACTORS INFLUENCING REOPERATION

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OBJECTIVE:
Tension band (TB) and plating (ORIF) are two methods of fixation for olecranon fractures. While ORIF is used for comminuted fracture patterns, evidence is inconclusive regarding the best technique for simple fracture patterns. In this study, we evaluate isolated olecranon fractures over a decade at a single level 1 trauma center in order to investigate the factors influencing reoperation in TB versus ORIF.

METHODS:
A retrospective chart review at a level I trauma center identified 489 patients who underwent operative management of olecranon fractures (CPT code 24685) from 2003 to 2013. These patients’ charts were reviewed for gender, height, weight, BMI, ASA score, mechanism of injury, fracture type and classification, and complications (infection, nonunion, malunion, loss of function, or hardware complication requiring surgery). Radiographs were reviewed to identify OTA fracture classification and patients who underwent TB or ORIF. Chi-squared and multivariate analyses were used to determine difference in complication rates.

RESULTS:
177 patients had isolated olecranon fractures. TB was used for fixation in 43 patients (24%) and ORIF in 134 patients (76%). 10 open fractures had TB (grade 1=6, grade 2=4, grade 3=0) and 40 had (grade 1=7, grade 2=23, grade 3=10). No statistical significance was found when comparing complication rates in open (36.0%) versus closed (36.2%) olecranon fractures (p=1). In a multivariate analysis the key factor in outcome was method of fixation. Overall, 23 TB patients had complications (53.6%) compared to 41 ORIF patients (30.6%) with infection and hardware removal being markedly higher in the TB group. Patients with TB were 3.8 times more likely to return to the operating room.

CONCLUSIONS:
Our results demonstrate that the dominant factor driving reoperation in olecranon fractures is the type of fixation. Surgeons must be cognizant of the risk of a potential second operation when using TB fixation.
EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO) USE FOR INFLUENZA-ASSOCIATED ILLNESS

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BACKGROUND:
Influenza virus is associated with significant morbidity and mortality, especially with bacterial co-infection. A portion of these individuals requires ECMO, particularly during the 2009 H1N1 influenza pandemic; however, the overall use and survival rates are not known.

OBJECTIVES:
Determining the frequency of subjects diagnosed with influenza-associated illness requiring ECMO and comparing survivors to non-survivors.

DESIGN/METHODS:
Using the Extracorporeal Life Support Organization (ELSO) registry, all subjects on ECMO with either the ICD-9 code “influenza” (487 or 488) or an organism code for influenza were queried from 1992-2012. Data from the registry were extracted to include demographic information, microbial co-infection, and outcomes.

RESULTS:
893 subjects diagnosed with influenza on ECMO contributed to 2.2% of all ECMO runs (1054 out of 48,627 ECMO runs) over a 20-year period with an overall mortality of 40%. The median age was 22.5 years, 56% were adults, 53% were male, and 63% were white. A sharp increase in ECMO use for influenza-associated illness was noted in 2009. Survivors (n=535) were compared to non-survivors (n=358) based on demographic and clinical characteristics. The median age of survivors was 26.1 years and non-survivors was 16.6 years (p=.038). There was no statistically significant difference in gender proportions for survivors versus non-survivors. The frequency of bacterial co-infection was higher among non-survivors (36%) than survivors (29%) (p=.012). In addition, non-survivors had a higher frequency of fungal co-infection as compared to survivors, 13% vs. 7% respectively (p=.001). The percentage of patients with viral co-infection was similar between the two groups; non-survivors had 6% viral co-infection as compared to survivors who had 4% viral co-infection. In addition, on their blood gas prior to ECMO initiation, non-survivors had statistically significant lower median pH (7.23), higher median pCO2 (59.2 mmHg), lower median HCO3 (23 mmol/L), and lower median PaO2 (120 mmHg) as compared to survivors (p<.05 for all values).

CONCLUSIONS:
The frequency of subjects with influenza on ECMO increased over time, with a sharp increase during the 2009 H1N1 pandemic. Non-survivors were younger, more likely to have either bacterial or fungal co-infection, and had a greater degree of hypoxemia and acidosis prior to ECMO initiation compared to survivors.
INSTITUTIONAL MODIFICATION OF ANTIBIOTIC PROPHYLAXIS PROTOCOL REDUCES INFECTIONOUS COMPLICATIONS FOLLOWING TRANSCRECTAL ULTRASOUND GUIDED PROSTATE BIOPSY

Daniel Z. Sun, Harras B. Zaid, Chad Ritch, Kirk Keegan, Jacob Ark, Roger Dmochowski, Daniel Barocas, Michael Cookson

INTRODUCTION:
There has been an increase in microbial resistance to quinolone antibiotics and subsequent rise in infectious complications following transrectal ultrasound guided prostate biopsy (TRUS pBx) in recent years. We sought to describe post-TRUS pBx infectious complications at Vanderbilt and compare our historic rates to a contemporary series following an institutional effort to modify our standard antibiotic prophylaxis protocol based on our local antibiogram.

METHODS:
We performed a retrospective comparison of a historic cohort of men between 2008-2010 who underwent TRUS pBx following antibiotic prophylaxis with at least 3 days of peri-procedural fluoroquinolone (standard antibiotic protocol - SP), versus a contemporary cohort of men between 2011-2013 who underwent prophylaxis with single dose ceftriaxone or gentamicin plus a single dose of oral fluoroquinolone at the time of biopsy (modified antibiotic protocol - MP). All men who underwent TRUS pBx during these time periods were included. Infectious complications were extracted from the patient chart. Univariate and multivariate statistical analyses were performed to determine significant predictors of infectious complications, in particular use of the SP versus MP.

RESULTS:
A total 2003 patients were included (1175 SP and 828 MP). Age, history of quinolone use, biopsy setting (operating room vs. outpatient), diabetic status, and number of previous biopsies was similar between the two groups. In the SP group, there were 75 infectious complications (6.1%) compared to 18 (2.2%) in the MP group (p < 0.05). 48% and 33% of cultures were fluoroquinolone resistant, respectively. On multivariate analysis, previous quinolone use and TRUS pBx performed in the operating room predicted higher infection rates (OR 1.93 and 2.00, respectively, p < 0.05). Furthermore, patients who underwent TRUS pBx with the MP had a significantly lower likelihood of infectious complications (OR 0.22, p < 0.05) when controlling for other known factors influencing infections.

CONCLUSIONS.
Institutional modification of our antibiotic prophylaxis protocol reduced the risk of infectious complications in men undergoing TRUS prostate biopsy.
IDENTIFYING PARENTAL PREFERENCES FOR CORTICOSTEROID AND INHALED BETA-AGONIST DELIVERY MODE TO OPTIMIZE MEDICATION ADHERENCE IN CHILDREN WITH ACUTE ASTHMA EXACERBATIONS

Sarah Szlam, Donald Arnold

BACKGROUND: Acute asthma exacerbations are the most frequent reason for childhood hospitalization in North America. Standard of care includes inhaled beta agonists and oral steroids, most commonly a 5 day steroid burst. Previous studies demonstrate oral steroid compliance to be poor. Recent studies, however, have demonstrated oral Dexamethasone (DEX) given as a single dose (0.6mg/kg) in the emergency department to be as effective as a 5 day steroid burst. Patients given the single dose of DEX showed improvement in asthma symptoms and no greater rate of relapse in comparison with those treated with the standard 5 days steroid burst. Single dose DEX offers greater compliance rates with steroids as the medication is administered in the hospital and was shown to be cost effective. To our knowledge, parental preference has not been examined. This information can help guide practitioners in the treatment of acute asthma exacerbation in pediatric patients presenting to the emergency department to improve patient compliance and parental satisfaction.

OBJECTIVE: The objective of this study was to evaluate parental preferences in the use of single dose oral DEX versus a 5 day oral steroid burst.

METHODS: We prospectively recruited a cohort of parents of pediatric patients between the ages of 2 years to 18 years with an acute asthma exacerbation treated in an academic, tertiary children’s hospital emergency department with oral steroids and inhaled beta agonists. Parents provided demographic and asthma characteristics of their child, and were then asked to complete a brief (1 page) questionnaire. The questionnaire included items that examined parental preference for use of single dose DEX versus a 5 day steroid course, access to a pharmacy, ability to fill a prescription, and other variables pertaining to compliance with prescribed medications. We examined characteristics of the parent-child dyad and assessed for associations of these characteristics with preferred parental steroid regimen of DEX versus a 5 day steroid burst.

RESULTS: During the period 8/2013 until 2/2013, we enrolled 50 parents. Amongst these, 71% prefer the use of one time DEX administration in the pediatric emergency room to a 5 day course of steroids. There were no associations of this preference with patient demographics, asthma/asthma exacerbation history or ease of filling the prescription.

CONCLUSION: Our study indicates that parents strongly prefer use of single-dose DEX in the treatment of an acute asthma exacerbation. The results of this investigation may inform clinical practice in acute care settings in which pediatric patients with acute asthma exacerbation are managed.
THE SIGNIFICANCE OF L1CAM (CD171) EXPRESSION, EPITHELIAL-TO-MESENCHYMAL TRANSITION, AND STEM CELL PHENOTYPES IN ENDOMETRIAL CLEAR CELL CARCINOMA

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BACKGROUND:
The L1 cell adhesion molecule (L1CAM) is a 200-220kDa membrane glycoprotein of the immunoglobulin superfamily whose expression has been shown to be related to epithelial-mesenchymal transition (EMT). Recent studies have found that activation of EMT pathways eventuate in increased cellular plasticity, 'stem cellness' and tumorigenicity. The purpose of this study is to evaluate the role of L1CAM expression and related EMT and stem cell phenotypes in the pathogenesis of endometrial clear cell carcinoma (CCC).

DESIGN:
54 CCC, 17 endometrial serous carcinoma (ESC), and 49 endometrioid carcinomas (EEC; 18 G1, 19 G2, 12 G3) in a TMA were immunohistochemically assessed for their expression of the EMT-related markers L1CAM, Snail, Slug, E-Cadherin, BMI1, as well as the putative cancer stem cell markers NANOG, NAC1 and Musashi. In addition to conventional microscopic assessment, objective staining scores were also assigned by an automated image capture system that incorporated staining intensity and extent on tumor cells.

RESULTS:
L1CAM expression was present in 81%, 69%, 58%, 26%, and 0% of CCC, ESC, G3 EEC, G2 EEC, and G1 EEC respectively. Analysis of the automatically-generated staining scores showed that statistically significant higher levels of L1CAM were present in CCC as compared with EEC of all grades, G3 EEC, and G1/G2 EEC (p _

CONCLUSION:
These preliminary findings highlight a distinct novelty in the pathogenesis of CCC, whereby a mesenchymal-like phenotype is activated in a manner similar to the other high grade carcinomas (G3 EEC and ESC). However, unlike the latter tumors, and similar to G1 and 2 EEC, there is no concurrent downregulation of epithelial-cadherin.
IMMUNOHISTOCHEMICAL ANALYSIS USING A BRAF V600E MUTATION SPECIFIC ANTIBODY IS HIGHLY SENSITIVE AND SPECIFIC FOR THE DIAGNOSIS OF HAIRY CELL LEUKEMIA

Xuan Julia Wang, Shaoying Li

BACKGROUND:
Hairy cell leukemia (HCL) is usually diagnosed by morphology combined with flow cytometry immunophenotypic studies. However, it can be challenging sometimes to distinguish between HCL and HCL mimics, which include HCL variant (HCL-v), splenic marginal zone lymphoma (SMZL), and rarely other marginal zone lymphomas (MZL). Recently, the BRAF V600E mutation has been described as a disease defining molecular marker for HCL. This specific point mutation is present in nearly all cases of HCL but is virtually absent in HCL mimics. Most of the previous studies used molecular techniques, which although is direct and specific, is usually more expensive, has a relatively longer turn-around-time, and may not be available in all pathology practice settings.

OBJECTIVES:
In this study, we investigated the possibility of using immunohistochemistry to detection the BRAF V600E mutation protein product to differentiate between HCL and its mimics.

METHODS:
A total of twenty-eight formalin-fixed paraffin-embedded tissue specimens were studied, including 12 cases of HCL, 3 cases of HCL-v, 6 cases of SMZL, and 7 cases of nodal and extranodal MZL. Immunohistochemical studies were performed using a mouse monoclonal antibody (clone VE1, Spring Bioscience, CA) specific for BRAF V600E mutation. Molecularly confirmed BRAFV600E mutation positive and negative cases were used as the positive and negative controls.

RESULTS:
All 12 cases of HCL showed cytoplasmic BRAF V600E protein expression in leukemia cells by immunohistochemical study, whereas all the cases of HCL mimics, including HCL-v, SMZL, and MZL,, were negative for BRAF V600E protein. By using this BRAF V600E mutation specific antibody, immunohistochemical study has 100% sensitivity and 100% specificity in the diagnosis of HCL in our study.

CONCLUSION:
Our result suggested that immunohistochemical detection of the BRAF V600E mutation protein is highly sensitive and specific for the diagnosis of HCL. Compared to molecular method, immunohistochemistry is a relatively inexpensive alternative with a short turn-around-time for the differential diagnosis between HCL and its mimics.
MYC/BCL2 DOUBLE-HIT LYMPHOMA (DHL) HAS A WORSE PROGNOSIS THAN MYC/BCL2 PROTEIN DOUBLE-POSITIVE LARGE B CELL LYMPHOMA (DPL) AND MYC GENE STATUS IS AN IMPORTANT FACTOR FOR RISK STRATIFICATION IN DPL

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BACKGROUND AND OBJECTIVES:
Coexpression of MYC and BCL2 protein, identified in about 20-30% of diffuse aggressive B cell lymphomas by immunohistochemical stains, has been considered as a possible surrogate for DHL identified by cytogenetic studies for predicting a worse prognosis. However, DPL and DHL are not completely concordant and little is known if MYC aberrations remain an independent prognostic factor in cases of DPL or if DHL behave worse than DPL.

METHODS:
We studied 242 patients diagnosed with high-grade B-cell lymphoma between 2003 and 2013. MYC and BCL2 status were confirmed by FISH. Paraffin-embedded tissue from 115 patients was available for immunohistochemical assessment of MYC and BCL2 expression. DPL was defined by coexpression of MYC in >40% and BCL2 in >50% of cells. The overall survival of DHL patients was compared to that of DPL patients. The prognostic impact of MYC status was further assessed within the DPL subgroups. Patient survival was analyzed using the Kaplan-Meier method and compared using the log-rank test. Fisher’s exact test was used for comparisons between the two groups.

RESULTS:
63/115 (55%) were identified as DPL. There were 35 men and 28 women with a median age of 63 years (range 6-92 yrs); Among them, 19 (30%) had MYC rearrangement (DPL-MR) with or without BCL2 rearrangement, 14 (22%) with multiple copies of MYC (DPL-MC) and BCL2 rearrangement or multiple copies, 24 (38%) with no MYC abnormalities (DPL-MN), and 6 with unknown MYC status. 79 cases were MYC/BCL2 DHL. Overall, there was no significant difference in clinicopathologic characteristics between the DPL, or more specifically the DPL-MN group, versus the DHL group. However, the DPL-MN subgroup had more cases with CD10- and were treated less aggressively (p<0.05). Overall survival (OS) was not significantly different when the DHL group was compared to all DPL cases (2-year OS 47% vs 59%, p=0.10), but DHL showed worse OS compared to DPL-MN (2-year OS 47% vs 83%, p=0.01). Within the DPL group, an abnormal MYC status correlated with a significantly worse outcome (p=0.02 between DPL-MN vs DPL-MR and between DPL-MN vs combined DPL-MR &MC).

CONCLUSIONS:
MYC cytogenetic aberrations identified a subset of MYC/BCL2 DPL with a significantly worse prognosis. While immunohistochemical assessment for MYC and BCL2 proteins may be helpful for an initial risk screening, FISH analysis for MYC status remains important for further risk stratification in MYC/BCL2 DPL.
DORSAL RAPHÉ FUNCTIONAL CONNECTIVITY IN DEPRESSION

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OBJECTIVES: Deficits in limbic, default mode and cognitive control networks have been implicated in depression and antidepressant response. As antidepressants affect serotonin, we hypothesized that dorsal raphé involvement in these functional networks should be investigated. However, the relationships between neural networks and the raphé have not been previously described. We examined resting state functional connectivity between raphé and known network nodes related to depression, and how modulation of serotonin levels using acute tryptophan depletion changes that connectivity.

METHODS: We obtained two 3T resting state fMRI scans – with and without acute tryptophan depletion - in 15 adults treated with sertraline for depression. We studied connectivity between the raphé and 7 regions implicated in depression. Using CONN toolbox [1, 2], an analysis of correlation between regions was performed for each subject in both diet conditions, and within specific frequency ranges. We contrasted intra-subject functional connectivity for the two diet conditions, while controlling for remission status. Subgroup analysis was also performed to examine whether raphé connectivity differed between the 10 remitters and 5 non-remitters.

RESULTS: Comparing depletion to sham using full bandwidth (0.01-0.1 Hz), functional connectivity analysis of all subjects revealed significantly decreased correlation between raphé and right subgenual anterior cingulate cortex (ACC; beta=0.22, p=0.02). There were no significant correlations between raphé and other regions of interest. When we limited analysis to remitters, depletion decreased connectivity between raphé and right thalamus (beta=0.16, p=0.02). In non-remitters, raphé connectivity with right subgenual ACC was increased (beta=-0.21, p=0.02). When we examined all subjects within narrower frequency band filters, we found that raphé connectivity was significantly altered specifically within low and medium ranges. Within low range (0.01-0.025 Hz), raphé and right thalamus connectivity decreased (beta=0.45, p=0.04). Within medium range (0.025-0.05 Hz), raphé connectivity with right subgenual ACC decreased (beta=0.35, p=0.03), while raphé connectivity with left dorsolateral prefrontal cortex increased (beta=-0.30, p=0.04). We did not find significant connectivity differences between diet conditions within high frequency range (0.05-0.1 Hz).

CONCLUSIONS: In adults treated for depression, alteration of serotonergic function by acute tryptophan depletion appears to alter functional connectivity of dorsal raphé with right thalamus and right subgenual ACC. Narrower frequency band analyses suggest that these differences may be specific to changes in low and medium frequency ranges. Our results are consistent with a frequency-based mechanistic model for serotonergic modulation of mood-related networks. Additionally, functional connectivity changes related to acute tryptophan depletion appear to differ between remitters and non-remitters.