Mechanisms and Molecular Correlates of Seizures Post-Traumatic Brain Injury (TBI)

Introduction: Traumatic brain injury (TBI) afflicts approximately 1.7 million individuals annually in the United States; a third of injury-related deaths in the US report TBI as a contributing cause. TBI results from a wide array of causes, including sporting collisions, motor vehicle accidents, falls, and during combat. Risk for seizures at the population level has been reported as 2% whereas in those with severe TBI the risk for early seizures (<1 week post-trauma) escalates to 14-30%. Seizures post-TBI put one at heightened risk for the development of epilepsy, and the risk correlates with the severity of injury.

Objective: To compare the expression of an ion channel and signaling proteins between control and TBI-injured mice. Also, to compare EEG waves and seizure susceptibility between control and TBI-injured mice.

Background: The Na-K-Cl cotransporter (NKCC1) is an active transport ion channel responsible for moving sodium, potassium, and chloride into and out of cells at a 1:1:2 ratio. NKCC1 is expressed in a wide variety of tissues but notably in the brain where its changing levels during childhood spur key neurodevelopmental processes. As a regulator of three essential ions NKCC1 plays a role in maintaining the electrical activity in the brain and has been shown to facilitate seizures in the developing brain. Interestingly, bumetanide, an NKCC1 antagonist has been demonstrated to reduce the frequency of seizures in patients with temporal lobe epilepsy and also epileptiform discharge in a subset of patients.

Transforming growth factor-beta (TGFβ) has also been implicated as a key cytokine release after neurotrauma. Capable of being released from neurons and astrocytes, TGFβ regulates the expression of a wealth of genes, some believed to impact seizure development. However, there are three isoforms of TGFβ (1-3) which complicate its potential role. TGFβ2 signaling leads to increased production of nerve growth factor (NGF) which has been linked to elevated NKCC1 expression. Thus, a proposed mechanism may be suggested where TGFβ post-TBI may lead to upregulation of NKCC1 expression leading to increased seizure activity.

Methods: Six week old C57/BL6 mice were subjected to controlled TBI to the left skull using a pneumatic TBI device developed by a URMC neurosurgery resident. Mice were sacrificed using CO₂ asphyxiation at pre-determined time points post-TBI (3hr, 1d, 3d, and 7d). Whole brains were sectioned using a Shandon Cryotome FSE at 10 µm. Immunohistochemistry was completed using
primary antibodies (NKCC1, TGFβ1, and TGFβ2) which were conjugated with fluorescent secondary antibodies. Antibodies were co-stained with GFAP as a marker for reactive astrocytes and mounted using a DAPI-containing medium. Images were then taken on a microscope and overlaid.

A second group of mice underwent controlled TBI and were surgically implanted with a myo-electrode and epidural-electrode, each containing three leads. Mice were then injected with pentylenetetrazol (PTZ) to stimulate convulsions, afterwards EEG measurements were taken and seizure activity was observed.

**Results:** At the present stage of data collection from immunofluorescence, there appears to be increased TGF-β2 production in the CA3 region of post-TBI mice at early time points (3 hours and 1 day post-TBI) but no change compared to controls at latter times (3 days and 7 days post-TBI). TGF-β1 and TGF-β3 data analysis is still in process. Likewise, NKCC1’s expression profile is still being completed but preliminary data supports it may be elevated in the CA3 region of the hippocampus as well. EEG analysis and behavioral data are still being collected.

**Conclusion:** While more data is required to make conclusive statements a few general trends arose in the present study concerning NKCC1 and TGF-β expression post-TBI. According to immunofluorescence and microscopy data the CA3 region of the hippocampus seems to be predominantly affected by TBI at three hours and one day post-TBI. The cortex displayed a similar trend but the effect did not appear as strong. Thus, the preliminary data support a proposed mechanism where TGF-B may lead to an upregulation of NKCC1 and increased seizure susceptibility. More data displaying a rescue effect and antagonism of TGF-β would be helpful in determining the causality and direction of the relation. If the basic framework is correct then new treatment options for the management of TBI patients may be warranted, possibly using drugs antagonizing NKCC1.

**References:**

Emergency Room Triage Expectations and Their Effect on Patient Satisfaction

Introduction:
As demands for physician care increase and options for public access to personal health care expand, investigation of patient satisfaction becomes increasingly important.

Objective:
Creation and implementation of a self-triage tool, to be used as an additional vital sign, may allow physicians and nurses to understand the emotional state of the patient before first contact. Patient satisfaction will increase due to increased caregiver awareness of patient’s emotional needs.

Background:
Previous studies have highlighted discrepancies between patient expectations and emergency department interventions. To address this inconsistency, improving interpersonal attitudinal skills has been shown to positively influence patient satisfaction. However, an area that begs further exploration is the direct and standardized assessment of patient’s emotional needs upon arrival to the ER, allowing caregivers to respond in a more empathetic and appropriate manner, thus improving patient satisfaction.

Methods:
This study follows a single center, randomized control study. Patients were randomized into the study on a daily basis at the University of Utah’s Emergency Department, collecting a total of 300 patients. Enrollment of patients alternated daily between control and intervention arms over the period of 2 months. Patients who arrived via ambulance, children, prisoners, and those with altered mental status were excluded from the study. Enrolled patients provided basic identifiers and demographic information for the purpose of stratification. In addition, patients in the intervention group completed self-triage tool. Upon discharge from the ED, all patients received a follow-up patient satisfaction survey in person or by telephone. These surveys are based on the Press Ganey survey model in order to allow comparison of patient satisfaction scores pre and post intervention.
Results:
Statistical analysis has not been completed, however, preliminary results indicate an improvement in patient satisfaction scores with administration of the tool.

Conclusion:
A final conclusion cannot be ascertained due to the study’s ongoing nature. However, based on preliminary results, the implementation of the self-triage emotional assessment tool improves both patient and provider awareness of the patient’s emotional needs and positively influences patient satisfaction.

References:

Abstract:
As demands for physician care increase and options for public access to personal health care expand, investigation of patient satisfaction becomes increasingly important. Creation and implementation of a self-triage tool, to be used as an additional vital sign, may allow physicians and nurses to understand the emotional state of the patient before first contact. Patient satisfaction will increase due to increased caregiver awareness of patient’s emotional needs. Previous studies have highlighted discrepancies between patient expectations and emergency department interventions. To address this inconsistency, improving interpersonal attitudinal skills has been shown to positively influence patient satisfaction. However, an area that begs further exploration is the direct and standardized assessment of patient’s emotional needs upon arrival to the ER, allowing caregivers to respond in a more empathetic and appropriate manner, thus improving patient satisfaction. This study follows a single center, randomized control study. Patients were randomized into the study on a daily basis at the University of Utah’s Emergency Department, collecting a total of 300 patients. Enrollment of patients alternated daily between control and intervention arms over the period of 2 months. Patients who arrived via ambulance, children, prisoners, and those with altered mental status were excluded from the study. Enrolled patients provided basic identifiers and demographic information for the purpose of stratification. In addition, patients in the intervention group completed self-triage tool. Upon discharge from the ED, all patients received a follow-up patient satisfaction survey in person or by telephone. These surveys are based on the Press Ganey survey model in order to allow comparison of patient satisfaction scores pre and post intervention.
Statistical analysis has not been completed, however, preliminary results indicate an improvement in patient satisfaction scores with administration of the tool. A final conclusion cannot be ascertained due to the study’s ongoing nature. However, based on preliminary results, the implementation of the self-triage emotional assessment tool improves both patient and provider awareness of the patient’s emotional needs and positively influences patient satisfaction.
Introduction: The Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) demonstrated that the benefits of CRT also apply to patients with mild heart failure symptoms (NYHA class I or II), with particularly good results in patients with LBBB and those with wider QRS complexes.

Objective: We hypothesized that the response to CRT-D is more favorable than the commonly referenced figure of 70%. An echocardiographic metric was used to evaluate the benefit from cardiac resynchronization therapy.

Background: Several randomized clinical trials have shown that cardiac resynchronization therapy (CRT) is associated with reduction in the risk of death and heart failure in patients with New York Heart Association [NYHA] class III or IV, reduced ejection fraction, and a wide QRS complex. The MADIT-CRT showed that the benefits extended to NYHA class I and II. It is generally estimated that about 70% of patients treated with cardiac resynchronization benefit from this therapy. However, this has not yet been thoroughly investigated in patients with mild heart failure using a control group.

Methods: This study involves the MADIT-CRT study population in which paired echocardiograms from baseline and one-year follow-up were available in 621 ICD patients and 749 CRT-D patients. We pre-specified CRT-D responders as the patients who at one-year follow-up had a reduction in left ventricular end systolic volume (LVESV) that corresponded to the top (best) quintile of LVESV reduction in the ICD-treated patients, i.e., a 17% or greater reduction in LVESV.

Results: Using this metric, 88% of CRT-D patients and 91% of the CRT-D patients with LBBB were identified as CRT responders. Landmark multivariate Cox model analyses revealed a significant interaction (p=0.038) involving LVESV (responders vs. non-responders) and LBBB (present vs. not-present) in risk reduction for heart failure or death. The interaction finding indicates that CRT responders with LBBB have a significantly (p=0.038) lower risk for heart failure or death (HR=0.24) than patients without LBBB (HR=0.62). In the CRT-D patients, LVESV responders were associated with reduction in the risk of death (HR=0.20, p<0.001). An increasing percent reduction in LVESV greater than 17% is associated with progressively lower rates of heart failure or death, a finding consistent with a dose-response relationship.
**Conclusion:** Approximately 90% of CRT-D treated patients have a significant and meaningful reduction in LVESV, and these LVESV responders have significantly reduced rates of cardiac events during long-term follow-up.

**References:**


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A Novel Platform for the Identification of Stromal-Derived Factors that Enhance Acute Lymphoblastic Leukemia Cell Survival in the Context of Maintenance Chemotherapy

Introduction: Childhood B-lineage acute lymphoblastic leukemia (ALL) is the most common form of malignancy in children. ALL is highly responsive to intensive, multi-agent chemotherapy, and most children enter remission; however, 25% of children relapse. Furthermore, cure requires an additional two years of low intensity maintenance chemotherapy with 6-mercaptopurine (6-MP) and methotrexate.

Objective: We are developing a conceptually simple screening system that will identify stromal cell-derived molecules that support ALL cell survival in the setting of 6MP and methotrexate. Our hypothesis is based on the observation that in serum-free conditions, BMSC prevent apoptosis of primary ALL cells. We reason that if we interfere with the production of key BMSC-derived trophic factors, an increase in ALL cell apoptosis in vitro will be seen.

Background: It is known that serum levels of maintenance chemotherapy drugs are not highly cytotoxic for ALL cells, and it is thought that bone marrow stromal cells (BM-SC) provide trophic signals to leukemia cells that result in increased resistance to standard therapy. If anti-apoptotic signals from stromal cells to leukemia cells were known, new molecular targets for leukemia therapy could be developed.

Methods: The system has 3 components: (1) human marrow stromal cells; (2) primary ALL cells (not established cell lines); and (3) siRNAs to knockdown candidate stromal genes. We employ a human mesenchymal stromal cell (MSC) line immortalized with a human TERT gene that has been shown to be representative of primary human stroma. 20,000 BMSC are placed in wells of a 96-well plate and treated with siRNA. 48 hours later, 30,000 primary human ALL cells are added in serum-free media. After 5 days, viable ALL cells are measured by flow cytometry.

Results: (1) The addition of pharmacological concentrations of 6-MP to BMSC/ALL co-cultures does not significantly increase primary ALL apoptosis. Co-cultures were established as above and 6-MP was added at 1 micromolar. ALL survival was measured at 5 days. No increase in ALL survival was seen in the 6-MP containing cultures. On unmanipulated stroma cultured without 6-MP, 1948.8 (±397.0) viable ALL cells were recovered; on manipulated stroma in the presence of 6-MP, 1698.5 (±299.3) (p value = 0.12). (2) Interference with stromal cell protein synthesis significantly increases ALL cell apoptosis. We hypothesize that interference with new protein synthesis might reduce stromal support of ALL cells. To test this we treated BMSC for 6 hours with 25 micrograms of G418 which irreversibly blocks polypeptide synthesis. Wells were then washed with serum-free medium. Stromal cells remained viable for up to 1 week. However, ALL cells apoptosis was much higher on such treated stromal cells (32.7±18.5 viable
Interference with global stromal cell RNA transcription significantly increased ALL cell apoptosis. Triptolide is a molecule that irreversibly inhibits RNA transcription. BMSC were treated for 6 hr with 1 microgram triptolide and washed with serum-free medium. Stromal cells remain viable for up to 1 week. ALL cell apoptosis was significantly reduced by triptolide treatment of stroma. The number of viable ALL cells recovered from triptolide-treated stroma was 252.3±113.2, compared to 996.6±239.2 on unmanipulated stroma. Knockdown of CXCL12 gene expression in stromal cells significantly increase ALL cell apoptosis. For proof of principle, we have started with CXCL12, a gene shown in CLL to contribute to leukemia cell survival. BMSC were treated with 0.3 picomolar anti-CXCL12 siRNA for 24 hr. As measured by quantitative RT-PCR, CXCL12 gene transcription was reduced by 80%. Moreover, there was a 53.5% reduction in ALL cell viability in ALL cells co-cultured with CXCL12 siRNA-treated stroma compared to ALL cells co-cultured with untreated stroma (p value < 0.001).

Conclusion: This BMSC cell/primary ALL cell system can be used to identify stromal cell genes that prevent apoptosis of primary ALL cells. The simple system can be scaled up to allow high throughput screening of candidate genes that have antagonistic or additive effects to maintenance chemotherapy drugs.

References:


Introduction & Objectives:
Patient use of complementary and alternative medicine (CAM) continues to increase in the United States, yet surveys at some medical schools have shown varying comfort levels and attitudes toward CAM among students. This study aims to investigate factors associated with these attitudes by studying medical students at one university from a variety of perspectives. The objectives of this study are (1) to describe attitudes towards CAM using a standardized screening tool, the Integrative Medicine Attitude Questionnaire (IMAQ); (2) to determine whether previous personal or family exposure to CAM, prior knowledge or interest in CAM, exposure to the Double Helix curriculum, interest in or exposure to the biopsychosocial model of medicine, or interest in certain fields of medicine are associated with student attitudes toward CAM; and (3) to describe students’ feelings toward the incorporation of CAM into the curriculum.

Background:
The use of CAM by patients of many ethnicities and with varying illnesses has been and is steadily increasing in the United States. Therefore, health care providers must become familiar with CAM practices that their patients are likely to seek and use. Surveys of CAM attitudes among medical students at a few institutions, including UCLA and the University of South Florida, have shown that females and first/second year medical students are more likely to report personal use of CAM and to have more positive attitudes towards various modalities. It has been hypothesized that the more negative attitudes in more advanced students could be due to the shift from a more academic, classroom-based curriculum in first/second year to a more clinical setting in third year, more experience with allopathic diagnoses and procedures, and interactions with more conventional physicians, all of which may lead students to have a less open-minded view of CAM.

This study investigates the potential influence of the Double Helix curriculum at the University of Rochester School of Medicine and Dentistry (URSMD), which introduces clinical education during the first year instead of the third year and should, therefore, eliminate these differences in CAM attitudes due to clinical exposure. The URSMD’s unique integration of the biopsychosocial model of medicine, with its emphasis on holistic, patient-centered health care, may also have an influence on how open students may be to unfamiliar CAM modalities. Additionally, to our knowledge, surveys at other medical institutions have not examined other factors potentially associated with CAM attitudes, including religiosity, family usage of CAM modalities, and future specialties of interest. However, as far back as 2000, the Society of Teachers of Family Medicine has encouraged the incorporation of CAM education for Family Medicine residents, which may influence CAM attitudes in students.
interested in family medicine or other primary care fields. Therefore, this study will provide an additional perspective on various factors that may possibly have an influence on medical students’ attitudes towards CAM usage.

**Methods:**
We collected data by online survey from the URSMD classes of 2014, 2015, 2016, and the matriculating class of 2017 during June 2013, using the established Integrative Medicine Attitude Questionnaire (IMAQ), which has been validated and shown to be a reliable measurement of attitudes towards CAM and has been used to survey medical students at other institutions. A higher IMAQ score (starting at 117 out of a highest possible score of 203) indicates a more positive attitude towards CAM, as well as more openness to unfamiliar ideas and physician-patient relationships. IMAQ score comparison between current and matriculating students was done with an independent t-test while comparisons among the three current classes were done by one-way ANOVA with Bonferroni correction. Additional data were collected from students to assess possible factors associated with IMAQ scores including sociodemographics, personal and family CAM use, awareness of CAM therapies, and feelings regarding the biopsychosocial model of medical education at the URSMD. Independent t-tests, one-way ANOVAs with Bonferroni correction, and Pearson correlations were used to compare IMAQ scores depending on the various factors.

**Results:**
The overall response rate was 37.8% (158/419). Due to incompleteness, only 34.1% (143/419) were included in analyses, of which 53.8% of respondents were female and 46.2% were male. A majority of the students were Caucasian (70.6%), which reflects the medical school student body. The overall mean IMAQ score was 139, with a total possible score of 203, indicating an overall positive attitude toward CAM. There were no differences in mean IMAQ scores by gender, age, ethnicity, region of the United States in which students grew up, occupation (if any) before medical school, education level (Bachelors versus higher degree), family use of CAM, or whether students have lived abroad.

However, students who identified as religious (Buddhist, Christian, Jewish, or other spiritual) had higher mean IMAQ scores (141.6±14.8) than those who were agnostic or atheist (134.8±16.9) with a p-value=0.01. There was no significant difference in IMAQ scores between different religions. The more CAM modalities a student has personally used, is interested in learning about, or say they would recommend to patients were all associated with higher IMAQ scores (each with p<0.001).

There was no significant difference among the mean IMAQ scores of current medical students, classes of 2016, 2015, 2014 at 139.1, 138.3, and 136.0 respectively (p=0.31). However, current medical students had a higher mean IMAQ score (141.0±15.2) than that of the matriculating class (136.0±16.7), which approached significance with a p-value of 0.07. Students who felt that the biopsychosocial curriculum was important in medical education were more likely to have a higher mean IMAQ score with a Pearson’s correlation coefficient of 0.26 (p=0.002).

In comparing future fields of interest, students interested in the surgical specialties had a mean IMAQ score with standard error (132.6±2.6), which is lower than that of students interested in primary care (138.9±1.6) and the nonsurgical subspecialties (139.3±1.7). However, these differences did not reach significance.
87.4% of students believe education about CAM should be incorporated into medical school curricula. When asked how this education could be added, the top responses were: optional lunch or dinner talks with CAM experts (selected by 66% of students), an afternoon CAM lecture series in one of the clinical courses (55%), more availability of Medical Humanities Seminars centered on CAM (52%), experiential workshops with CAM practitioners (51%), and opportunities to visit and observe CAM practitioners in their offices (49%).

**Conclusion:**
Medical students at the URSMD had overall positive attitudes about CAM. Personal CAM use, religiosity, and feeling that the biopsychosocial model of medicine is important were associated with more positive attitudes toward CAM. Attitudes were similar among classes of current medical students, suggesting that the Double Helix curriculum of introducing clinical medicine during the first year instead of the third year may equalize attitudes toward CAM for students across all four years. There was no significant difference in CAM attitudes between current and matriculating students or by future field of interest. A majority of students believes that education about CAM should be incorporated into medical school curricula. Future studies comparing the URSMD to other medical schools with different curricular emphases would further our knowledge of factors associated with medical student attitudes toward CAM.

**References:**
7. Schneider CD, Meek PM, Bell IR. Development and Validation of IMAQ: Integrative Medicine Attitude Questionnaire. BMC Medical Education 2003; 3-5.
A Survey Study of Barriers to and Enablers for Prehospital Pediatric Analgesia

Objective. Oligoanalgesia is common in the prehospital care of children. A recent hypothesis-generating qualitative study identified previously unrecognized barriers to and enablers for prehospital analgesic administration in children. This study aimed to more broadly characterize those factors in an emergency medical services (EMS) system.

Methods. A cross-sectional survey study of a convenience sample of advanced life support (ALS) providers was conducted in a northeastern EMS region. Survey items were derived from barriers and enablers identified from a previous study. ALS providers were identified during training sessions or while on duty at their bases and given written surveys to complete. Pediatric patients were defined as those <9 years of age. Descriptive statistics were calculated. Differences in survey responses between new providers (≤5 years of ALS experience) and experienced providers (>5 years ALS experience) were assessed using Chi-square tests and Fisher’s exact test where appropriate.

Results. Of the 130 providers surveyed, 65% were experienced and 22% were female. Overall, 88% responded that they consider treating pain in children to be important. Most providers reported feeling comfortable with pediatric patients (92%) and the pediatric pain protocol (85%). They agreed that analgesic administration is important (98%) and is supported by their agency leadership (87%) and that their education has prepared them to administer analgesics (87%). Top barriers to pediatric analgesic administration were concern regarding pain of intravenous placement (60%) and allergic reactions (47%) as well as difficulty in assessing pain in children (48%). Previously reported barriers, including discomfort with pediatric patients and pain protocol, insufficient education, negative responses from emergency department staff or superiors, avoidance of excessive paperwork, and avoidance of quality assurance scrutiny were not demonstrated. Significant differences were not noted between experienced and new providers.

Conclusions. ALS providers in this region did not confirm all of the novel findings of the previous qualitative study. Providers reported the traditional reasons for not providing children analgesia, despite reporting comfort with treating pediatric patients, believing that treating pain in children is important, and feeling that their education has prepared them to administer analgesics to this population. Further measures are needed to address oligoanalgesia in children.
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Retrospective Review of Gastrostomy Tube Insertion in Children at URMC

Background & Introduction:
Gastrostomy tube is a device used to establish an artificial opening in the stomach to provide a route for enteral feeding. It is useful in pediatric patients with prolonged inadequate or absent oral intake resulting from a variety of medical conditions. The methods of gastrostomy tube placement have evolved over the years from open1 to endoscopic2,3 to laparoscopic4,5 to a combined laparoscopic and endoscopic technique6. There are also a variety of catheters available for use. Malecot or Pezzer catheters have a malleable internal bolster that is used as an anchor. They are most commonly used in open procedures. PEG tubes are catheters with rigid internal bolsters that have attached wires that facilitate the endoscopic placement. Skin-level gastrostomy tube, such as a MIC-KEY button, is a balloon-based catheter that is known for its low profile.

While the indication for the procedure is dictated by the patient’s underlying medical diagnosis, overall condition, and ability to tolerate laparoscopy or endoscopy, the gastroenterologist and surgeon preference determines the choice of tube and the method of placement. Until recently, skin level button gastrostomy tubes were not commonly used in initial tube placement. Gradually, primary button gastrostomy tubes started being used in laparoscopic gastrostomy tube placement and then moved toward being used in endoscopic gastrostomy tube placement using a “push” technique. There is a general impression that using skin level gastrostomy tubes as the primary tube placed increases tube longevity, reduces the number of tube check studies and lessens the number of postoperative emergency department visits associated with gastrostomy tube complications. However, these claims have never been critically evaluated.

This study is a retrospective review of gastrostomy tubes placed in pediatric patients at the Golisano Children’s Hospital, University of Rochester Medical Center and the associated patient outcomes.

Objective:

1) To determine if primary percutaneous endoscopic button gastrostomy tube placement is a safe approach to establish enteral access in children.

2) To compare the complication rates for primary percutaneous button placement with open gastrostomy or traditional PEG.
**Methods:**
All patients between ages 0-14 years of age who underwent gastrostomy tube placement at the Golisano Children’s Hospital, University of Rochester Medical Center from 1/1/2011 to 12/31/2012 were identified through Department of Surgery billing database. Patients who had undergone concomitant GI operations such as Nissen fundoplication or enterectomies were excluded from the study in order to avoid confounding factors from additional procedures. All demographic information including age, gender, weight at the time of gastrostomy tube placement, procedure notes/operative reports, subsequent emergency department visits, clinic follow-up visits and inpatient admissions within 6 months of tube placement were reviewed using eRecord. All gastrostomy-related complications and the need for imaging studies, surgical procedures or hospital admissions related to gastrostomy tube complications were recorded. The complications were classified as minor and major. Minor complications included tube dislodgements, leakage around the insertion site, clogs, granulation tissue requiring cauterization, erythema requiring intervention or any problem requiring bedside replacement or adjustment without sedation or anesthesia. Major complications included any G-tube related problems requiring imaging studies, hospitalization, endoscopy or operations.

All data points were recorded in Microsoft Excel program (Redmond, WA) and analyzed using GraphPad Software (La Jolla, CA). Categorical data was analyzed using Chi square test, and continuous variables were analyzed using unpaired t tests. Statistical significance was defined as \( p \) value less than 0.005.

**Results:**
A total of 122 patients were identified. After excluding those who underwent concomitant GI operations, 63 patients remained. Six additional patients were lost to follow-up. Our analysis includes 57 patients. Patients are segregated based on insertion technique or type of tube placed. Patient characteristics are summarized in Table 1.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age at time of G tube insertion (months)</th>
<th>Weight at time of G tube placement (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Male</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Female</td>
<td>14</td>
<td>18</td>
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<tr>
<td></td>
<td>9</td>
<td>10</td>
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<td>21</td>
<td>17</td>
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</table>

There is no significance found in patient gender. When comparing open to the minimally invasive group, patients who underwent open technique were younger and weighed less. However, when comparing MIC-KEY to Non-MIC-KEY group, such differences are not statistically significant. Analysis of the outcome is illustrated in Table 2. Patients who underwent open technique or those who had Non-MIC-KEY button placed needed their gastrostomy tube replaced much earlier after the operation. Of note, we were not able to identify the first tube replacement dates on all patients. Of the 25 patients who underwent open technique, only 21 had first tube replacement dates identified. Only 19 of 32 patients who underwent minimally invasive techniques had their first tube replacement dates noted. Similarly, only 10 of 18 MIC-KEY patients and 29 of 38 Non-MIC-KEY
patients had their first tube replacement dates noted in our review. The only other outcome difference identified is that patients who underwent minimally invasive techniques had a significantly greater number of major complications than those who underwent open techniques. This difference, however, is not observed when we compare MIC-KEY and Non-MIC-KEY groups. This is probably due to the fact that these complications took place in patients who underwent laparoscopic or endoscopic placement of Non-MIC-KEY tubes.

<table>
<thead>
<tr>
<th></th>
<th>Open Mean</th>
<th>SD</th>
<th>Min Invasive Mean</th>
<th>SD</th>
<th>MIC-KEY Mean</th>
<th>SD</th>
<th>Non-MIC-KEY Mean</th>
<th>SD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days before first tube replacement</td>
<td>47.0</td>
<td>25.11</td>
<td>85.26</td>
<td>48.33</td>
<td>0.0007</td>
<td>94.91</td>
<td>49.16</td>
<td>53.90</td>
<td>33.63</td>
</tr>
<tr>
<td>ED visits per patient</td>
<td>0.84</td>
<td>1.52</td>
<td>0.31</td>
<td>0.54</td>
<td>0.0729</td>
<td>0.32</td>
<td>0.48</td>
<td>0.658</td>
<td>1.30</td>
</tr>
<tr>
<td>Clinic visits per patient</td>
<td>1.32</td>
<td>1.22</td>
<td>0.94</td>
<td>0.88</td>
<td>0.1732</td>
<td>0.68</td>
<td>0.75</td>
<td>1.316</td>
<td>1.12</td>
</tr>
<tr>
<td>Imaging studies per patient</td>
<td>0.48</td>
<td>0.96</td>
<td>0.16</td>
<td>0.37</td>
<td>0.0859</td>
<td>0.16</td>
<td>0.37</td>
<td>0.368</td>
<td>0.82</td>
</tr>
<tr>
<td>Minor complications per patient</td>
<td>5.16</td>
<td>4.91</td>
<td>3.34</td>
<td>3.10</td>
<td>0.0933</td>
<td>3.47</td>
<td>2.87</td>
<td>4.474</td>
<td>4.54</td>
</tr>
<tr>
<td>Major complications per patient</td>
<td>0.12</td>
<td>0.33</td>
<td>0.34</td>
<td>0.65</td>
<td>0.0004</td>
<td>0.05</td>
<td>0.23</td>
<td>0.342</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Conclusion:
In a comparable patient population, gastrostomy tube placement is equally safe using a skin level gastrostomy tube, such as a MIC-KEY button, versus other types of catheters. There is a propensity for minimally invasive methods of gastrostomy tube placement to be associated with more major complications. However, most minimally invasive methods utilized PEG tubes or Non-MIC-KEY button tubes in our study population. Such difference in number of major complications is not seen when comparing MIC-KEY vs. other types of catheters. The significant difference in number of major complications associated with open versus minimally invasive methods of gastrostomy tube placement may be attributable to the use of Cook catheters with rigid internal bolsters within the PEG group. This will require further review.

References:
Background: There are many autoimmune diseases, like systemic lupus erythematosus in which B cells play an important role (1). Discovering in detail how B cells are activated and their downstream effects will play an important role in the understanding of disease pathology and possibly offer more specific treatments. B cells possess many surface markers and receptors (1). Toll-Like Receptor 9 TLR-9 is an important mediator of B cell activation (1). Stimulation of TLR-9 has been shown to enhance the ability of B cells to act as antigen presenting cells (2). While the natural ligand for TLR-9 is microbial DNA with unmethylated CpG motifs, it has been found that the synthetic ligand ODN 2216 can mimic that activation (1). Another TLR-9 ligand used to activate purified B cells is ODN 2006 (1). ODN 2006 has been shown to induce naïve B cell expansion as well as to protect them from apoptosis. (2). Once B cells are activated by TLR-agonist(s) there are many downstream effects including increased expression of activation-induced cytidine deaminase (AID), (3). AID is an enzyme that is responsible for class switch recombination and somatic hypermutation. In a normal immune reaction, AID deaminates cytosines. This deamination in turn activates somatic hypermutation and class switch recombination, introducing variation among B cell receptors. Some variants will bind antigen better than the original receptor (3).

However, increased production of AID has been implicated in causing B cells to escapes tolerance, allowing the B cell present an auto-reactive antibody (3). Unregulated expression AID could lead to alterations in the immune response including production of several auto-reactive antibodies. It has been shown in recent experiments that mice with overexpression of AID had a severe form of SLE, while those that were AID deficient had a delayed onset of disease (3). When B cells are stimulated with estrogen and LPS (lipopolysaccharide), AID induction becomes highly active (3). Recent publications have demonstrated a role for estrogen in enhancing AID expression in mice (3). It has been shown in mice that estrogen causes a 7-fold increase in the production of AID (3). This could implicate that sex hormones like estrogen have an effect on the severity of diseases like SLE.

The autoantibodies produced in systemic lupus erythematosus or directed against antigens to stimulate TLR7or TLR 9. In mice knocking out TLR 9 prevents the development of anti-DNA antibodies and lupus prone mice. Similarly, knocking out TLR 7 events and development of antibodies against RNA binding proteins. Thus, TLR 7 and TLR 9 are critical for the development of autoantibodies in lupus prone mice. The pathogenic autoantibodies in lupus are somatically mutated IgG antibodies with a high affinity for autoantigen. AID is critical for the development of these pathogenic autoantibodies. Since lupus is much more prevalent in women than in men, we hypothesized that estrogen would be particularly important for induction of AID when B cells are stimulated by TLR 7 or TLR 9.

The goal of this project is to investigate estrogen’s role in activating AID in presence and absence of molecules that mimics in vivo TLR9 stimulation in human naïve B cells. This project involved setting
up an assay to determine the effect of estrogen and TLR agonists on activated induced deaminase. Tonsilectomy specimens were used for collection of naive B cells, which were then treated with estrogen and TLR9 agonist to determine the amount of AID induction by PCR. This is relevant because many autoimmune diseases are B cell mediated and involve the formation of autoantibodies. With many of these diseases having a female bias, estrogen could be a possible factor in the activation of the B cells.

**Methods and Materials**

**Tissue and Cells.** Tonsil tissue was obtained from routine tonsilectomies. Isolation of lymphoid cells from tonsil tissue occurred according to standardized protocols (Johnston CP7.8). Mononuclear cells were suspended in PBS and separated by ficoll density gradient centrifugation. B cells were isolated by negative selection using a naïve B cell isolation kit (Miltenyi Biotech) according to the manufacturer’s instructions. Naïve B cells at 1.0 x 10⁶ cells/mL were incubated in RPMI 1640 (no phenol red) + 10% charcoal stripped FBS, 100 U/mL penicillin and 100 µg/mL streptomycin (invitrogen).

**Reagents.** Estrogen (17-β-estradiol; Sigma) was dissolved in DMSO at 100mM; this solution was used to prepare 0.5, 5 and 50uM stocks in DMSO. These working stocks were then diluted 1:1000 followed by 1:5 in media to achieve the final concentrations indicated in the figures. The final concentration of DMSO was constant at 0.02% and the concentration of ODN 2006 (invivogen) was 0.5µM.

**Real-Time qRT-PCR.** Six hours after treatment cells were; washed briefly with cold PBS, pelleted and stored at -80°C prior to mRNA extraction using an RNeasy mini kit (Qiagen). mRNA was reverse transcribed using iScript and cDNA was amplified using iQ SYBR green supermix(Bio-Rad) using AID and HPRT1 primer pairs published previously (4)(5). Real-Time qRT-PCR used the RotorGene 6000 instrument and results were calculated using the two standard curve method.

**Results**
Incubation of naïve B cells in media containing 0.1 - 10nM estrogen had little effect on AID expression. Likewise, stimulation with toll-like receptor 9 ligand ODN 2006 resulted in an approximate doubling in AID expression. However, the increases in expression that result from TLR9 stimulation in the presence of estrogen far exceed the additive effect of TLR-9 agonist or estrogen alone.
Figure 1. Expression levels of activation induced cytidine deaminase (AID) normalized to housekeeping gene HPRT1. Naive B cells were incubated in media containing physiological concentrations of estrogen or DMSO control. Expression of AID after treatment with estrogen and/or 0.5uM ODN 2006 is relative to DMSO control. Each chart is a single independent experiment.
Figure 2. Expression levels of activation induced cytidine deaminase (AID) normalized to housekeeping gene HPRT1. Naïve B cells were incubated in media containing physiological concentrations of estrogen or DMSO control. Expression of AID after treatment with estrogen and/or 125ng/ul ODN 2216 is relative to DMSO control.

**Discussion:** The results showed that when B cells are stimulated with TLR9 agonists in the presence of estrogen there is a significant increase in the amount of AID production. This finding could be significant in the context of developing autoimmunity. In mice, it has been shown that the overexpression of AID can cause severe autoimmune disease, while blocking AID delays the onset of autoimmunity (3). In a normal cycling woman there is a time in her menstrual cycle where there is high estrogen and low progesterone. If at this time there is AID stimulation, there could be production class switched, somatically mutated, high affinity, pathogenic antibodies rather than non-switched, non-somatically mutated protective IgM antibodies. This B cell can become a memory cell and potentially survive for the duration of the patient’s life producing autoantibodies. In the general population, there are 10 female lupus patients to every one male lupus patient. Estrogen and TLR enhanced AID expression could provide a logical reason for the sex bias in autoimmunity. The plan moving forward would be to start looking at interventions. Depo-Provera and Nexplanon are progesterone based birth controls. Currently the dose of these birth controls given is solely to prevent pregnancy not autoimmunity. The question would be could you give enough progesterone to drive down estrogen levels and inhibit the presentation of clinical disease. Taking females with some autoimmunity as represented by a positive ANA or interferon-α signature, if you give them hormone replacements could you remove some elements of autoimmunity?
Works Cited


Endochondral ossification is the process by which most long bones develop from a cartilage template. Specifically, chondrocytes within the cartilage initially proliferate, but ultimately exit the cell cycle and begin the process of chondrocyte hypertrophy and terminal maturation. As chondrocytes reach terminal maturation, the cells undergo apoptosis and the cartilage matrix scaffold is utilized by osteoblasts to lay down bone. The process of chondrocyte hypertrophy and maturation is critical for inducing osteoblast differentiation and bone formation.1 Previously, we have demonstrated that Notch signaling regulates the process of endochondral ossification at least partially via the transcriptional control of Sox9 and chondrocyte hypertrophy.2,3 Much of Notch function is imparted via the direct regulation of repressor type basic helix-loop-helix (bHLH) proteins, such as the HES/HEY factors and their regulation of both tissue specific and ubiquitous bHLH activator proteins (ie. ASCL, ATOH, and other E-proteins).4 The Tcf3 gene encodes two ubiquitous type I bHLH proteins, E12 and E47, that are capable of homo- or heterodimerization and regulation of gene transcription via the binding of E-box consensus sequences.5,6

To determine whether E12 and/or E47 are important regulators of endochondral ossification, we developed Prx1Cre; Tcf3fl/fl mice in which the E12 and E47 proteins would be eliminated from mesenchymal progenitors that give rise to chondrocytes and osteoblasts of the limbs. We also transfected E47 plasmids into ATDC5 chondrogenic cells and then induced maturation to determine whether E47 could change the course of chondrocyte maturation in this cell line.

Comparing Alcian blue stained tibias from Prx1Cre; Tcf3fl/fl and littermate controls at embryonic day 13-14.5, we found that the hypertrophic lengths in elements from Prx1Cre; Tcf3fl/fl animals were shorter. Furthermore, tibia elements from Prx1Cre; Tcf3fl/fl animals closer to embryonic day 13 are shorter in length and preliminary data shows an increase in proliferation after BrdU staining. Lastly, in situ hybridization showed expression of ColX, a marker for hypertrophy, was delayed in Prx1Cre; Tcf3fl/fl animals. These differences were not as pronounced at embryonic day 16.5. Alcian blue staining of ATDC5 cells transfected with E47 and subsequently induced to undergo maturation show more proteoglycan matrix deposition compared to control treated ATDC5 cells at days 5, 7, and 14 post maturation induction.

These results suggest that Tcf3 has an early pro-maturation role in chondrocytes, which disputes claims in a previous publication.7 While these differences are subtle, the differences are observed in multiple litters. Furthermore, the in vivo and in vitro results are consistent in suggesting that Tcf3 has a pro-differentiation role in chondrocytes. Knockout of the Tcf3 gene in vivo results in a delay of hypertrophy at embryonic
stages 13-14.5. Over expression of E47 in ATDC5 cells in vitro results in earlier and increased proteoglycan deposition, which is consistent with an accelerated rate of maturation. Further work will focus on how Tcf3 gene products interact with the Notch signaling pathway to fine-tune chondrocyte maturation, specifically through Hey/Hey factors.6

References:


Disasters from Physicians’ Perspectives

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7 Years and Counting: A Qualitative Study of Louisiana Healthcare During Natural Disasters

Background and Introduction: The many actions that have been taken during natural disasters such as Hurricane Katrina and Rita, and Hurricane Gustav, demonstrate the constant need to learn from previous disaster experiences and to continue to make improvements to the health care system and patient care. Issues of evacuation strategies, medical funding, care for low income patients, and adequate access to healthcare for the chronically ill are even more critical during a natural disaster (Rathbun, 2006.) While much research and time has been dedicated to understanding how devastating natural disasters have affected Louisiana socially, politically, and medically, very few other studies have focused on understanding the needs of the medical system through the perspective of physicians and other medical administrators who were employed before and after devastating hurricanes and the changes that they have seen and would expect for the future of medical care. This research revisits these issues to develop a better understanding of what changes are taking place and what may be needed in the future.

Objective: We hypothesize that, as result of tragic natural disasters such as Hurricanes Katrina and Gustav occurring in Louisiana, physicians’ and medical professionals or administrators’ perspectives on healthcare management and disaster preparation have changed and continue to evolve.

Main Study Aims:
・ To review similar research which was conducted during the immediate post Katrina period in order to evaluate medical services and practices that existed during that time, including the 2008 study that was performed by Louisiana State Medical Society.
・ To formulate and apply an interview instrument to address our specific research questions. We will incorporate questions from previous studies to allow comparison of data over time.
・ To use this data to compare changes in perspectives and medical systems since Hurricane Katrina and the succeeding storms.
Methods and Procedures: The study coordinators will perform face-to-face or web/teleconference interviews. All interviews were audio recorded for transcription and analysis. No audio or video will be released in any publication or report. The primary method of data collection for this study will be semi-structured, in-depth interviews. Each participant will be interviewed for one to two hours at a place of the participants choosing. Questions used for the interview will be similar to and consistent with the LSMS study from 2008.

Data Analysis and Monitoring: In a phenomenological study, data analysis procedures begin with horizontalizing the data. Horizontalizing is the process of laying out all of the data for examination and treating the data as having equal weight. The data is then organized into clusters or themes and from these clusters and themes a composite description of the essence of the phenomenon is developed. The description represents the structure of the experience being studied and the reader should come away from the phenomenology with the feeling “I understand better what it is like for someone to experience that”. The data will be also be verticalized, to gain an understanding of how medical professionals' attitudes and opinions have changed regarding healthcare since 2008 and subsequent hurricane disasters.

Results: Congruent themes were consistent among many of the medical professionals that were interviewed. An emphasis on the following categories was expressed. They included medications, hurricane preparedness on the individual, physician, and government level. A few changes have been made with regard to national disaster planning in Louisiana. More adequate levee systems have been engineered, a new hospital has been created that fosters to poor and uninsured patients. Improvements have also been made to the evacuation plan during future hurricane disasters. Though these changes have occurred, many medical professionals indicated that more adjustments need regarding the previous categories. Greater preparation for disasters are needed. Resources for medications, water, food, and other supplies should be determined prior to the natural disaster. Mandated evacuation may need to be implemented if the disaster is predicted to be very severe. Many medical professionals believed that portable health records or an intrastate database for electronic records would be helpful. More cohesive cooperation from government and medical entities are required for better implementation of any protocols during natural disaster. The current protocol for natural disasters should be expanded to also include plans for post evacuation health care needs.

Conclusion: Although there were varying accounts concerning important changes for future natural disasters, many of the medical professionals agreed that multiple areas still need to be explored in order to better facilitate an effective protocol. The occurrence of natural disasters are inevitable in Louisiana. It is imperative that federal and local government, medical professionals, and autonomous patients each fulfill their role in a cooperative manner.

References:
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Social Functioning in Youth with Tourette Syndrome

Introduction: Tourette Syndrome (TS), is a neuropsychiatric disorder affecting up to 1% of the population worldwide. It is characterized by motor and phonic tics often accompanied by comorbid attention-deficit hyperactivity disorder (ADHD), anxiety, obsessive-compulsive disorder (OCD), and challenges in socialization (1). Although some tics do result in self-injury, it is more often the psychosocial toll of TS that affects patients' quality of life (2). Peak tic severity typically occurs in the pre-teen to early teenage years, coinciding with a critical period for social development.

Objectives: To investigate differences in social functioning between children with TS and matched controls and to identify factors that predict decreased social functioning in children with TS.

Background: Social functioning affects a child’s day to day wellbeing and research indicates that tic related psychosocial stress is associated with poor psychiatric health in adulthood (3). Comorbid symptoms and tic severity have been proposed as possible mediating factors, yet published literature shows a lack of consensus on this topic (4, 5). Comorbid symptoms are categorized as internalizing (e.g. OCD, anxiety) or externalizing (e.g. ADHD, disruptive behaviors), with greater evidence supporting the contribution of externalizing symptoms (4, 5, 6, 7).

Methods: A multidimensional data set was collected over the course of a three-year CDC funded study to assess the impacts of TS on children, families, and communities (Principal Investigator; Jonathan Mink, MD, PhD). From Rochester, NY and surrounding areas, 93 children with TS and 101 age- and sex-matched controls ages 6-17 years were recruited along with a parent for participation. Each parent-child pair completed an extensive battery of assessments. Cross-sectional data from the CDC study were used in the current project. The Social Skills Rating System (SSRS) completed by parents in regard to their child, was used to assess overall social functioning; number of friends and the Friendship Activities Questionnaire (FAQ) measured the quantity and quality of friendships. Tics, family functioning and internalizing/externalizing behaviors, possible mediators of social functioning, were measured with the Yale Global Tic Severity Scale (YGTSS), the Family Assessment Device (FAD) and the Child Behavior Check List (CBCL) respectively. TS versus control group comparisons of social functioning were conducted using Mann-Whitney U Tests. The relationship between SSRS score and possible mediating factors were assessed using Spearman rank order correlation.
**Results:** SSRS scores for children with TS were significantly lower than those of their peers (p<0.001). Additionally, parents of children with TS reported that their children had significantly fewer friends (p=0.0027), however there was no significant difference in FAQ scores between groups. Among children with TS, a significant positive correlation between family functioning and social functioning was found. Internalizing/externalizing behaviors and tic impairment but not tic severity were negatively correlated with social functioning.

**Conclusion:** As anticipated based on existing literature, our results indicate that children with TS are more likely than their peers to encounter difficulties in social functioning. However, there is a wide range of social functioning among children with TS. Clarifying factors associated with poor social functioning will allow clinicians to identify children at greatest risk. This study indicates that ADHD and OCD type behaviors are identifiable risk factors where as higher family functioning may be protective factor. Interestingly, tic severity, as assessed by the interviewing clinician, was not associated with social dysfunction however tic impairment, a subjective measure reported by the patient and their family, was negatively related to social functioning. This finding highlights the importance of eliciting a subjective description of tic impairment in clinical practice.

**References**


Androgens Alter the Period of Clock Gene Expression in Cultured Ovarian Granulosa Cells

Circadian clocks play an intricate role in the timing of female reproductive physiology. Clock gene expression has been described in each tissue of the mammalian hypothalamo-pituitary-ovarian (HPO) axis and its’ function is linked to steroid hormone synthesis, ovulation and implantation. Despite the fact that the clock plays a role in the timing of events like ovulation, diseases that disrupt the clock have not yet had the true scope of their impact on fertility revealed. One such disease is polycystic ovary syndrome (PCOS), an exceptionally devastating endocrinopathy that produces infertility and metabolic disease in roughly 10% of women. PCOS presents with a polycystic ovarian morphology, hirsutism and amenorrhea or anovulation. Excess androgen, most likely of ovarian origin, plays a primary role in the etiology of PCOS. We have previously determined that excess serum androgen during fetal gestation or puberty alters the internal timing system. Though not known, it is presumed these effects in the clock are mediated by a direct action of androgens on clock gene expression in target tissues like the ovarian follicle.

To address this hypothesis, we have determined the effects of androgen on rhythms of clock gene expression in granulosa cells collected from immature gonadotropin primed female Period2::Luciferase (PER2::LUC) transgenic mice. Briefly, 3-4 week old mice were given an i.p. injection (5IU) of pregnant mare serum gonadotropin to induce follicular growth. Forty-eight hours later mice were euthanized and granulosa cells were removed via needle puncture and cultured in 35mm dishes. After a period of incubation (72hr) cells were synchronized with a 1h pulse of dexamethasone (200nM) followed by culture in the presence of the non-aromatizable androgen 5α-dihydrotestosterone [DHT] at 0.1, 0.5, 1 and 10 µM concentration (n=3-5 cultures per conc.).

DHT treatment dose-dependently shortened the period of PER2::LUC expression in the cells, although this trend was not significant at p<0.05. These data suggest that abnormally high androgen levels may affect clock gene expression directly in target tissue via classic androgen receptor signaling.
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Analyzing the Pathogenicity of the m.G14710A mutation

Introduction:
Dysfunction in mitochondria, the cellular organelle required for aerobic energy metabolism, is responsible for an array of disorders with varying manifestations that collectively pose a significant burden on human health. Most of the enzymes involved in respiration are complexes consisting of nuclear and mitochondrial DNA-coded subunits. Mitochondrial DNA (mtDNA) is circular, maternally inherited, and encodes 13 subunits of the electron transport chain and ATP synthase. Each mitochondrion contains several copies of mtDNA, and each cell can have thousands of mitochondria. Despite these and other differences, as with nuclear DNA, mutations in the mitochondrial genome have been linked to human disease (1, 2).

Our understanding of mitochondrial mutations can be complicated by the presence of multiple mtDNA sequences within one individual, a condition known as heteroplasmy. Methods have been developed to investigate the pathogenicity of mitochondrial DNA alterations and have advanced the current understanding of the inheritance of mitochondrial-based disorders (3). Further study into individual mtDNA mutations and their effect on mitochondrial function will improve understanding of the pathophysiology of mitochondrial dysfunction and may lead to the development of new therapies to treat patients.

In our studies, we aim to look at the effect of a mutation, m.G14710A. The potential consequence of this mutation is that glutamic acid may be inserted in place of lysine during mitochondrial translation because the mutation changes the anticodon of the tRNA. This mutation was identified in a small for gestational age infant presenting to The Children’s Hospital of Philadelphia with an array of problems including cardiomyopathy, global amino aciduria, ventricular septal defect, sepsis, and cardiac arrest. This same mutation was first identified in a 41 year-old female patient with mitochondrial myopathy and marked retinopathy (4). She exhibited many symptoms consistent with a mitochondrial disorder, including ptosis, abnormal fundus pigmentation, pigmentary retinopathy, progressive external ophthalmoplegia, easy fatigability with muscle weakness and pain on exertion, and occasional syncopal episodes associated with hyperventilation. While Anitori et al has provided convincing evidence that the m.G14710A mutation is associated with mitochondrial disease, the actual mechanism behind the pathogenicity has not been defined.

Objective:
The purpose of this project is to generate cybrid cell lines with varying levels of heteroplasmy of the m.G14710A using a constant nuclear DNA background. These cell lines can be used in future experiments to investigate the pathogenic mechanism of this mutation.
Background:

In order to synthesize the 13 proteins encoded for by mtDNA, mitochondria have their own protein synthesis machinery distinct from that used to translate nuclear-encoded genes. While some of the components of this machinery are encoded for by nuclear genes and require import of the proteins into the mitochondria (such as ribosomal proteins and tRNA synthetase), all of the RNA components (tRNA, rRNA) are supplied in the mitochondria. Thus any defect in mitochondrial tRNAs has the ability to cause significant problems with mitochondrial protein synthesis.

The G14710A mutation is located in the anticodon of tRNA^{Glu}, changing the specificity from Glu (CUU) to Lys (UUU). There are several ways in which mutations in mitochondrial tRNA have been shown to cause disease. For instance, mutations can affect tRNA synthesis, maturation, stability, aminoacylation, or interactions with translational components (5).

The first step in investigating the pathogenic mechanism of this particular mutation is to generate cybrid cell lines harboring varying levels of the mutation but with a constant nuclear genome. Cybrids are cells generated by the fusion of a patient’s enucleated fibroblasts with 143B p0 osteosarcoma cells which lack mitochondria (3). Creating these cybrid lines allows study of the effects of the patient’s mitochondrial mutation without the influence of the patient’s nuclear genome. Subsequent experiments using these cybrid lines can shed light on the precise mechanism by which the G14710A mutation is causing mitochondrial dysfunction.

Methods:

Identification of m.G14710A mutation in fibroblast cells
To detect low levels of mitochondrial mutation in the patient’s fibroblasts, we used PCR-RFLP with a mismatch forward primer designed to introduce an NlaIII restriction site at nucleotide 14710 in the wild-type sequence but not in the mutant sequence. PCR amplification of the patient’s mitochondrial DNA was run at standard conditions and PCR products were digested with NlaIII at 37° for 2 hours and resolved by non-denaturing PAGE (12% polyacrylamide). Fragments of 149 and 68bp were produced in mutated mtDNA, while in wild-type DNA the 149bp fragment was cleaved into 125 and 24bp products. The cleavage patterns of the patient DNA and wild-type DNA were compared to determine the presence or absence of the mutation.

Fibroblast culture
Fibroblasts were obtained by skin biopsy and cultured in DMEM, supplemented with 10% fetal calf serum, pyruvate (110ug/mL) and uridine (500ug/mL).

Generation of cybrid cell lines
Cell culture was used to generate cybrids from the patient cells harboring the m.G14710A mutation. Genotyping of cybrid lines can be used to identify those that have all wild-type sequence (homoplasmic wild-type), all mutant m.G14710A sequence (homoplasmic mutant) or heteroplasmic lines.

Determination of cybrid genotype
The mitochondrial sequence from nt 14460-15350 was amplified and sequenced with forward primer GCTGTAGTATATCCAAAGACA and reverse primer GTGCAAGAATAGGAGGTGGAGT to determine the genotype at m.14710.
**Results:**

*Heteroplasmia in patient fibroblast cells*

PCR-RFLP of the DNA derived from the patient’s fibroblasts confirmed low-levels of the m.G14710A mutant allele (Figure 1).

*Cybrid generation and genotypes*

Nine cybrid clones were generated from the fusion experiment (Figure 2). Through sequencing, several were found to be homoplasmic for the wild-type sequence (G at m.14710) while one was found to be heteroplasmic for the mutation (Figure 3). The heteroplasmic clone and one of the homoplasmic wild-type clones can be used in future proteomic studies and compared to determine the effect that the mutation has on protein synthesis.

**Conclusion:**

There are two potential mechanisms through which this mutation is causing disease. The first is that the aberrant tRNA is inserting a glutamine rather than a lysine at AAA codons, potentially altering the stability of mitochondrial proteins. This misincorporation can result in the loss of function of some of the resulting proteins. An alternate explanation is that the mutation in the anticodon loop is affecting the aminoacylation of the tRNA by altering its ability to be recognized by aminoacyl-tRNA synthetase, preventing the tRNA\(^{\text{Glu}}\) from being charged with an amino acid. Rather than causing misincorporation of lysines for glutamic acids, the inability to charge the tRNA\(^{\text{Glu}}\) with an amino acid would potentially cause more drastic defects in the translation of mitochondrial proteins. These two mechanisms can be distinguished using a variety of experiments on the cybrid cells.

In this experiment, we successfully generated cybrid cell lines using enucleated patient fibroblast cells and 143Bp\(^{0}\) osteosarcoma cells. Clones harboring the mutation will be used to investigate the pathogenicity of the m.G14710A mutation. Proteomic analysis studies of tRNA levels will give us insight into how this particular mutation causes mitochondrial dysfunction and disease.

**REFERENCES**


Increased TSPO Expression in Cerebrospinal Fluid from Patients with Subarachnoid Hemorrhage

**Introduction**: Translocator protein 18 kD (TSPO) is a multifunctional protein whose expression (in astrocytes) increases following brain injury and in various neurological diseases. Localized to the outer mitochondrial membrane of cells, TSPO is not normally present in cerebrospinal fluid (CSF). Exposure to general anesthesia in the young causes diffuse neuroapoptosis in rodents, and has been linked with possible developmental learning impairment in children. Since diffuse brain injury is associated with increased cellular TSPO expression, we tested the hypothesis that CSF TSPO expression may increase in humans experiencing diffuse neurological injury.

**Objective**: A predictive biomarker for anesthesia-induced neurotoxicity would be of great utility in monitoring long-term consequences in children exposed to anesthesia during critical periods in brain development. Our short-term objective was to test for increased TSPO expression in CSF in patients experiencing subarachnoid hemorrhage (SAH), a type of diffuse central nervous system injury. Since TSPO is an intrinsic membrane protein, its occurrence in CSF in SAH would be novel, and would validate our long-range objective of testing for its presence in CSF following anesthesia in children.

**Background**: Subarachnoid hemorrhage is a complication of ruptured cerebral artery aneurysm which has substantial morbidity and mortality. The aim of the ICHOP study was to evaluate outcomes following SAH.

**Methods**: CSF was obtained in the morning (5-7AM) from 5 SAH patients consented to the ICHOP study. Samples were centrifuged at 14,000 g for 10 minutes and the resulting supernatant and pellet fractions were stored at -80 °C and analyzed for the presence of TSPO immunoreactive bands using specific anti-TSPO and control antibodies. Homogenates of microglial cells containing 18 kD TSPO served as a positive control.

**Results**: An 18 kD apparent TSPO immunoreactive (IR) band was detected in the pellet fraction in CSF from 1 of 5 SAH patients tested. The CSF supernatant fraction from 2 of 5 SAH subjects tested contained a ~32 kD TSPO-IR band. No 18 kD TSPO IR was detected in concentrated or unconcentrated CSF supernatants from 5 of 5 SAH patients tested. TSPO immunoreactivity (18kD) in the CSF pellet occurred in the only one of five SAH subjects tested who experienced symptomatic cerebral vasospasm following SAH.
Conclusion: These are the first data to suggest that 18 kD TSPO is expressed in CSF from a subset of SAH patients. More study is needed to determine if TSPO could be a novel marker for the occurrence of life-threatening cerebral vasospasm in a subset of SAH. The 32 kD TSPO immunoreactivity (in supernatants) may represent a dimeric form of TSPO which results from exposure of the hydrophobic protein to an aqueous, CSF environment.

References:


Epithelial Cells Exert Anti-Fibrotic Effects via PGE₂ and TG2 in Pulmonary Fibrosis

Introduction:
Idiopathic Pulmonary Fibrosis (IPF) is a progressive interstitial lung disease characterized by epithelial cell dysfunction, accumulation of fibroblasts and myofibroblasts and deposition of extracellular matrix (ECM) resulting in disruption of normal architecture. There are few efficacious therapies and for the majority of patients, death due to respiratory insufficiency occurs within 5 years of diagnosis. The current belief is that repetitive injury to type II alveolar epithelial cells (AECs) results in increased AEC apoptosis, deficiencies in regeneration of normal alveolar structure and fibroblast activation via the production of pro-fibrotic mediators and is therefore responsible for the pathobiological changes seen in IPF. However, it is suggested that healthy epithelium might have protective effects on underlying fibroblasts. The mechanisms by which the epithelium exerts these effects are currently unknown.

Objective: Test the hypothesis that normal lung epithelial cells are capable of exerting anti-fibrotic effects on surrounding fibroblasts, and that epithelial TG2 regulates the anti-fibrotic effects via increasing PGE₂ production.

Background: Transglutaminase 2 (TG2) is a multifunctional protein expressed on different cell types, including epithelium. TG2 regulates eicosanoid biosynthesis, including prostaglandin E2 (PGE₂) an arachidonic acid cyclooxygenase metabolite. PGE₂ inhibits human lung fibroblast proliferation, migration, and differentiation into myofibroblasts. PGE₂ has also been shown to reverse the differentiation of fibroblasts into myofibroblasts, a process which was previously was believed to be irreversible.

Methods: Primary human small airway epithelial cells (hSAECs) and primary human lung fibroblasts (HLFs) were used for in vitro experiments. Cells were treated with TGF-β, a major pro-fibrotic cytokine and/or exogenous PGE₂. Protein expression in cell lysates was analyzed by Western blot and PGE₂ in the cell supernatants was analyzed by EIA. For the scratch wound migration assay, hSAECs and HLFs were grown in a trans-well co-culture system where cell-to-cell communication occurs through soluble mediators. HLFs were grown in to a confluent monolayer in a six well dish. HLFs were scratch wounded
with a pipet tip, washed with PBS, and then returned to their respective treatment conditions in the presence or absence of hSAECs. Migration was tracked over 48 hours on a Zeiss Axio Observer A.1 microscope (Zeiss).

**Results:** Two different stains of hSAECs up-regulated total TG2 protein expression and PGE2 production when treated with the pro-fibrotic cytokine TGF-β. Fibroblasts co-cultured with hSAECs showed significant reduction in migration compared to fibroblasts cultured alone. This was true for both untreated fibroblasts, and cells treated with TGF-β. HLFs that were grown in the presence of PGE2 showed a marked decreased expression of α-smooth muscle actin, a marker of differentiation to the pro-fibrotic myofibroblast phenotype.

**Conclusion:**
Human small airway epithelial cells inhibit fibroblast migration. PGE2 produced by hSAECs inhibits fibroblast differentiation into myofibroblasts. When treated with TGF-β, hSAECs up-regulate the expression of TG2 and increase production of PGE2. These data support the hypothesis that healthy lung epithelial cells exert a protective effect on lung fibroblasts even in the presence of a strong pro-fibrotic signal, and suggest that the pathogenesis of pulmonary fibrosis must involve epithelial as well as fibroblast dysregulation. Further experiments with TG2 inhibitors will help define the mechanisms and role that TG2 serves in the development of pulmonary fibrosis.

**References:**
Introduction: Screening the pediatric population for hypertrophic cardiomyopathy (HCM) is a topic often debated, but relatively few studies have extensively considered alternative screening tools, such as electrocardiograms (ECGs). Current discussions are based on the use of echocardiograms (ECHOs), the gold standard for the diagnosis and management of HCM. However, electrocardiograms (ECGs) have shown to be useful in the context of HCM, increasing sensitivity of a cardiac exam to 90.9% for HCM when added to a history and physical. In addition, for HCM patients, abnormalities in ECGs can appear before detectable ECHO abnormalities. Furthermore, some studies have effectively shown correlations, though sometimes limited, between ECGs and ECHOs for the diagnosis of cardiac hypertrophies. It is important to note that many of these studies did not focus on HCM, and criteria for suspecting HCM on an ECG are based on a population of Canadian Caucasian children. Therefore, these results cannot be confidently generalized to a more diverse population.

In order to understand the feasibility and ramifications of HCM screening in a pediatric population, one must know if ECGs could be used as a specific and sensitive test. To determine this, ECHO and ECG results must be obtained from a more diverse population and specifically for the diagnosis of HCM. From these results, comparisons could be made between ECG and HCM-specific ECHO parameters to see if a relationship exists.

Objective: To determine which individual or set of ECG measurements correlates best to ECHO abnormalities in patients with HCM. In addition, those ECG measurements will be compared to control ECG findings in order to identify the most sensitive, specific, and predictive ECG abnormalities associated with HCM.

Background: HCM is an autosomal dominant disease characterized by thickening of the left ventricle of the heart, often involving the ventricular septum. This can lead to left ventricular outflow tract (LVOT) obstruction, diastolic dysfunction, myocardial ischemia, and mitral valve regurgitation. HCM occurs in approximately 1 in 500 within the United States, and it is the leading cause of sudden cardiac death in young athletes. Death predominately occurs due to ventricular tachycardia and fibrillation, and sudden cardiac arrest can be the first presentation of disease. The current method of diagnosis is through ECHOs, where a left ventricular (LV) wall thickness of ≥ 15 mm suggests significant hypertrophy. Common ECHO findings in HCM patients also include systolic anterior motion (SAM) of the mitral valve and LVOT obstruction. In addition, the ECGs of HCM patients often show prominent Q waves in the left ventricle leads, ST-segment alterations, and T-wave inversion.

Methods: 157 HCM cases were previously collected with complete ECG and ECHO data on file. A gender- and age-matched set of ECHO, ECG, and clinical data was collected from printed medical records, CardioIMS, and XML exported data. A Pearson’s correlation was performed on the cases to identify associations between the ECG and ECHO data. Further statistical analysis will compare cases
and controls to determine the best parameters with respect to specificity, sensitivity, and predictive values.

**Results:** Preliminary results show a significant correlation (p ≤ 0.001) between multiple ECG parameters to ECHO findings. The highest rho-correlations were seen in the following pairs: QRS area of lead V6 and LV mass (ρ = 0.527), V6 lead R wave duration and LV Diastolic Dimension (ρ = 0.503), QRS area of V1-V6 and LV mass (ρ = 0.499) and V6 lead R wave duration and LV mass (ρ = 0.495).

**Conclusion:** The preliminary data suggest that certain ECG measurements are highly correlated to specific ECHO findings in HCM, and therefore ECG parameters could be used as an indicator of disease. Specifically, the R wave duration in lead V6, and the QRS areas of V6 or combined leads all highly correlate to ECHO measurements of LV mass, LV diastolic dimension, and LV wall thickness. This is expected, as these components on ECG represent left ventricular size and function, which is abnormal in patients with HCM. Further studies isolating each ECG lead, and other combinations, are currently in progress. In addition, results are pending regarding the comparison of control to HCM case data in order to determine the statistical specificity, sensitivity, and predictive values of ECG findings. This data will specify the way in which ECGs can be used in the diagnosis and management of HCM, and supply additional information to be considered in the discussion of screening the pediatric community for HCM.

**References:**

Clinical efficacy, safety, and feasibility of using video glasses during interventional radiologic procedures

Introduction and background:
Over the past few years, portable, hands-free audiovisual devices have been used in a variety of clinical settings as a method of distraction to improve patient care. These devices provide high-quality picture and stereo sound to create an atmosphere where patients can watch movies, cartoons, or television shows of their choice as a way to tune out their surroundings during a medical procedure.

The use of video-glasses has been shown to be a safe and effective method of distraction in certain outpatient clinical settings. Harned et al [1] explored the effects of a video goggles system in pediatric patients undergoing magnetic resonance imaging (MRI) and found that patients required less sedation during the procedure leading to lower adverse risk and cost. Lee et al [2] demonstrated that utilizing audio and visual distraction with a video glasses system significantly decreased the use of patient controlled sedation and overall pain scores during routine colonoscopy. Similarly, studies have showed that an audiovisual eyeglass system led to a reduction in anxiety, discomfort and procedure time for patients undergoing routine dental prophylaxis [3,4].

Currently, there is no research that has investigated the safety, feasibility, or clinical efficacy of using video glasses in patients undergoing interventional radiologic procedures. This study tests the hypothesis that video-glasses can be implemented safely in interventional radiology to reduce anxiety without disturbing the physician or support staff performing the procedure.

Objective:
The purpose of this study is to evaluate the clinical efficacy, safety, and feasibility of implementing video-glasses in a variety of interventional radiologic procedures.

Materials and Methods:
Outpatients undergoing elective interventional radiologic procedures at Strong Memorial Hospital during August 2012 to August 2013 were prospectively randomized to either the intervention group (video glasses) or the control group (no video glasses). Patients in the intervention
group chose from a pre-set list of videos and movies. Patient anxiety levels were measured using the State-Trait Anxiety Inventory (STAI) pre- and post- procedure [5]. The amount of sedation (Midazolam) and analgesia (Fentanyl) administered during the procedure were recorded. The patient’s average mean arterial pressure (MAP), heart rate (HR), respiratory rate (RR), and pain score were recorded before, during, and after the procedure. Post-procedure complications and any adverse events related to video glasses were recorded. Attending physicians, residents, and nurses completed a post-procedure survey evaluating the safety and feasibility of using the video glasses. A subset of patients in the intervention group filled out post-procedure satisfaction surveys.

Results:
A total of 50 patients (16 females and 34 males) were enrolled in the study (control (n=24) and intervention group (n=26)). The mean age was 55 years with an age range of 18 to 82 years. The percent change in STAI score between the two groups was significant with patients in the intervention group having a greater reduction in STAI scores compared to the control group (18.2 vs. 5.5; p=0.023). There was no significant difference in amount of sedation (p=0.77) or analgesia (p=0.30) administered between the two groups. Video glasses did not have a significant effect on the change from baseline in MAP (p=0.09), HR (p=0.88), RR (p=0.45) or pain score (p=0.59). None of the patients experienced any adverse events related to the use of video glasses. Post-procedure surveys showed that 93% of attending physicians and 100% of residents agreed that using video glasses did not interfere or pose a safety issue during the procedure, were not distracting, and did not interfere with the patient-physician relationship. One hundred percent of nurses reported that video glasses did not interfere with the preoperative or post-operative procedure. Patient satisfaction surveys showed that 95% enjoyed using video glasses, 85% enjoyed the video content, 95% stated that the video glasses did not interfere with the procedure, 100% enjoyed their overall experience, and 100% stated they would use the video glasses again for a future procedure.

Conclusion:
Video-glasses reduce patient anxiety and can be implemented safely in a variety of interventional radiologic procedures without disturbing physicians and support staff or interfering with the normal physician-patient interaction. This device may be used to improve a patient’s experience and overall satisfaction with their procedure without posing adverse risks. As healthcare policies, like the Affordable Care Act, shift towards a patient centered system, identifying methods of improving patient satisfaction becomes more important.

References:
Changes in lung function in cross-country touring bicyclists

Introduction: Exercise-induced bronchoconstriction (EIB) affects 10% of the general population, with a higher prevalence among Olympic athletes. Physical symptoms manifest similar to pollutant-induced asthma and may often go undiagnosed. Elite cyclists are susceptible to both EIB and air pollutant exposure, but it remains unclear as to whether air quality may influence amateur cyclist lung functioning and EIB development in a short period of time.

Objective: The purpose of this study is to determine whether participants in the Big Ride Across America, a 48 day, 3300 mile charity bike ride from Seattle, WA to Washington DC, experience changes in lung functioning over the duration of the ride related to physical exertion and/or pollutant exposure.

Background: Exercise-induced bronchoconstriction is an acute transient narrowing of lower airways triggered by a period of intense physical exertion that occurs as an indirect result of the dehydration of larger airways\(^1\,^2\). As water is lost and cells begin to shrink, a compensatory mechanism seeks to restore cell volume. Inflammatory mediators, such as bronchial smooth muscle contraction, are triggered and ultimately lead to narrowed airways\(^3\). Although the general population has a 10% prevalence of EIB, many patients show no symptoms or misinterpret their symptoms as falsely being out of shape\(^4\). Recently, several studies have shown that elite endurance athletes have a 34% prevalence of EIB, with 73% of these athletes having no prior asthma diagnosis\(^5\). While EIB causes shortness of breath, chest pain, and cough\(^6\), similar symptoms have been observed in those with pollutant-induced bronchoconstriction due to oxidative stress. It has yet to be determined if these pollutants can affect the development of EIB in outdoor amateur athletes.

Methods: The Big Riders rode for 7 consecutive weeks with 40 days of riding and 8 days of rest, averaging 83 miles per day with daily mileages ranging from 59 to 113 miles. Each ride lasted between 4-8 hours, depending upon weather and road conditions. 14 participants agreed to take place in the study and used handheld spirometers to record lung function every morning before riding and every evening after the ride. The riders were split into 3 groups to undergo peak flow measurements one time per week at each checkpoint around mile 20 of each ride. This was done to represent an exercise challenge stimulus. A GPS navigation system was used to determine the exact location of measurements and air quality was obtained using the U.S. Environmental Protection Agency's Air Quality System databases.

Results: There seems to be no evident overall trend in changes in lung functioning among the riders. A few riders showed improvement in peak flow, FVC, and FEV1 readings within the first two weeks of the ride and consistently held this improvement while other riders showed an initial increase followed by a
return to baseline. Other riders showed no evident changes throughout the entire ride. Data concerning air pollution is still being analyzed.

**Conclusion:** The effect of endurance exercise on the lung functioning of amateur athletes seems to depend on individual stamina, baseline, and athletic performance and thus vary between each cyclist. Data regarding the effect of air pollution on lung functioning and cyclist performance will be presented at the poster session.

**References:**


Clarifying the effect of bone surface morphology on mesenchymal stem cell differentiation and bone growth

Introduction: Osteogenesis is a vital physiological process to maintain stable bone structures, bone development, and in the healing of bone after fractures. The bone regeneration process is a complex process initiated by the differentiation of mesenchymal stem cells (MSC) into osteoblast cells. There have been many In vitro studies illustrating the positive effect of rough surface textures on biomaterials to the stimulation of MSC differentiation and bone regeneration. By translating these findings to bone, surface textures may be used in a similar manner to improve clinical results for delayed or non-union fractures, as well as bone grafts.

Objective: To develop an in vitro model to study fracture repair in order to elucidate the role of surface morphology on MSC differentiation and bone growth.

Background: Mesenchymal stem cells are present in bone marrow and most connective tissue. They have the capability of differentiating into mesenchymal tissues (fibroblasts, chondrocytes, osteocytes, etc.). Osteogenesis occurs when MSC progress into the osteoblast lineage. It has been shown that supplementation of induction factors into the media MSC are grown with can influence differentiation into various cell lines. More specifically, by supplementing common cell culture media with ascorbic acid, b-glycerophosphate and dexamethasone, differentiation into the osteoblastic lineage is favored. Osteoblasts synthesize and secrete bone matrix on growing surfaces. The matrix is then mineralized under the regulation of osteoblasts by the secretion of calcium-phosphorous vesicles into the extracellular matrix. The fracture site of bone is a well-known stimulus for new bone formation, and bone topography has been shown to play a role in this formation. However, the specific stimuli for new bone formation are still relatively unclear.

Methods: Bone disks were cut from bovine tibia, and split in half by an osteotome creating a fractured surface. Equal proportions were kept as a fractured surface, polished, or textured in a striated pattern. Titanium alloy disks were used as a control and had polished, striated, or grit blasted surfaces. Human MSC were cultured on the various disks with either common culture medium or osteogenic differentiation medium. Histological analysis was done at 28 days, and Mineralization assays were done at 21, 28, and 35 days.

Results: Data collection and analysis is still ongoing at the time of this abstract publication.

Conclusions and Discussion: Pending results from this study, future directions could proceed in small and large animal models testing bone textures at fracture sites and bone grafts.
References:


Evaluating the Impact of Surgical Management on Trauma Patient Infection Rates

Introduction: Infections in individuals with liver injuries are an important clinical complication for adult trauma patients. With an end goal of improving patient outcomes, this study aimed to determine how mechanism of injury and management of injury contribute to infection rates.

Objective: We hypothesized that patients with penetrating trauma compared to patients with blunt trauma have higher rates of infection, as defined as a positive bacterial culture, due to a physical breach in skin barrier. Additionally, trauma patients managed surgically either receive a vacuum-assisted wound closure or primary closure of the abdomen. Therefore, as a secondary question, this study explored whether different types of surgical closure are associated with variable rates of infection.

Methods: We evaluated both these questions using a retrospective chart review of trauma patients at University of Rochester Medical Center (n = 283) and The Johns Hopkins Hospital (n_total=331).

Results: The data indicated that blunt (M: 22.1, SD 12.7) and penetrating trauma (M: 18.2, SD 12.7) patients present to Strong Memorial Hospital with similar Injury Severity Scores (t(269) = 1.12, p=0.26). At Strong, blunt trauma patients are managed operatively as frequently as penetrating trauma patients (15% vs. 31.2% operative, p=0.1, respectively). Blunt trauma patients managed operatively have equal rates of positive bacterial cultures compared to blunt trauma patients managed non-operatively, (χ² = 0.001, df = 1, p = 0.9). Operative management of penetrating trauma patients also does not contribute to the rate of infection (χ² = 0.008, df = 1, p= 0.9). Furthermore, there was no difference in the rate of positive culture between surgical patients receiving a vacuum closure compared to a primary closure (χ² = 2.7, df = 3, p=0.4). In fact, one of the only differentiating factors between blunt and penetrating trauma patients in our analysis is length of hospital stay (11.8 vs. 23.3 days respectively, p=0.01).

Conclusion: When looking at our results, it is important to note that our data is currently heavily influenced by a small sample size (n_total=283, n_blunt = 267, n_penetrating = 16). It is likely that our results will change significantly when we supplement URMC data with traumatic liver injuries data from Johns Hopkins Hospital (n_total=331, n_blunt=112, n_penetrating= 218).
The Impact of the Hospital Elder Life Program Based on Residence Prior to Admission

Abstract:
Purpose: Hospitalized elders admitted from assisted living facilities (ALF) are a frail population with a high risk of functional decline and nursing home admission.1 This study sought to determine the utility of the Hospital Elder Life Program (HELP) as an intervention targeted toward reducing rates of incident delirium in hospitalized ALF patients.

Methods: This non-concurrent cohort study of QI data collected for the HELP program at Highland Hospital in Rochester, NY included 384 patients age 70 and over, at risk for delirium admitted during an eleven-month period from 2012 - 2013. We categorized patients by residence prior to admission, and used χ² and Logit Regression to compute incident delirium before and after implementation of the HELP program.

Results: Among ALF patients, incidence of delirium decreased from 50% prior to the program, to 6.1% after the program (p=0.0007). By comparison, rates for community dwellers and skilled nursing facility residents went from 11.4% to 5.6% (p=0.08) and 9.5% to 12.5% (=0.74), respectively. The effect of the program on incident delirium in the sub-population residing in ALFs prior to admission remained significant after adjusting for multiple population characteristics (OR = 34.17, p = 0.01). The program was also independently predictive of decreased incident delirium (OR = 2.82, p = 0.007).

Implications: This study confirms the effectiveness of HELP in preventing delirium in hospitalized seniors, and demonstrates that individuals from an ALF may be particularly likely to benefit from the program. Through the non-invasive, cost-efficient interventions of the HELP program at Highland, rates of delirium in this vulnerable geriatric population can be substantially reduced.

Survivorship analysis in patients undergoing femoroacetabular osteoplasty with microfracture

Introduction:
Femoroacetabular impingement (FAI) is a significant cause of hip pain in younger patients, where abnormal contact between the hip acetabulum and femoral head has been recognized as a potential cause of premature osteoarthritis. In an attempt to preserve the joint and improve long-term outcomes, hip arthroscopic techniques (including femoroacetabular osteoplasty, or FAO) have been developed to re-shape the components of the hip, with microfracture as the method of choice to treat full-thickness chondral lesions if they arise.

Contemporary use of microfracture in hip arthroscopy has been adapted from similar procedures in the knee, where results and long-term outcomes have been investigated in more detail. Outcomes in patients undergoing hip microfracture are poorly defined, as research has not focused solely on microfracture patients, has focused on professional athletes, or has not been considered in the diagnosis of FAI. Because FAI is a joint-preserving surgery, it is important to know how FAO patients with microfracture perform in the long-term.

Objective:
By using the modified Harris Hip Score (mHHS) and conversion to total hip arthroplasty (THA) as outcome measures, we sought to determine the long-term survivorship of patients undergoing femoroacetabular osteoplasty (FAO) with microfracture.

Background:
Chondral lesions, due to poor blood flow, rarely heal spontaneously. By creating small holes into the bone marrow (or “microfractures”), leaked hematopoietic cells have demonstrated the ability to differentiate into fibrocartilaginous material that can substitute for lost cartilage. An analysis of second-look hip arthroscopies has shown that microfracture can produce approximately 95% coverage of the lesion with an above-average repair grade, and case series have shown improvement in 86% of hip microfracture patients at 2-year follow-up. It should be noted, however, that multiple studies have demonstrated a relationship between intraoperative cartilage condition and quality of outcomes. Poorer cartilage condition is a predictor of poorer outcomes (including THA), although this has not focused solely on patients with full-thickness chondral defects.
Methods:
A retrospective chart review was performed using an electronic medical record system. Patients who underwent FAO with microfracture, had no previous pre-operative diagnoses other than FAI, and had no previous surgery on the repaired hip were identified. For FAO surgery, the mini-direct anterior approach was utilized in all patients.
Charts were reviewed to re-ensure validity of inclusion criteria. Post-operative status was determined depending on THA status. THA patients were identified through the presence of THA in a post-operative or clinic note. Non-THA patients had no mention of prior THA in clinic notes. Modified Harris Hip Scores were obtained either through in-clinic surveys, through phone interviews, or through online surveys. More qualitative measures, such as patient satisfaction, were sampled to provide other subjective measures to define “success” and “failure.”
Using THA and mHHS, outcomes were defined. Since FAO is considered a joint-preservation surgery, THA was considered a failed outcome. Remaining patients were to considered to have failed outcomes if the mHHS was below 80, a criteria used previously to determine outcome quality. Patients with mHHS only within 6 months of surgery were not able to be included in combined THA/mHHS survivorship analysis to allow for sufficient time for rehabilitation.

Results:
After chart review, 77 FAO patients (80 hips) meeting inclusion criteria were identified. Surgeries took place between July 2007 and March 2013. Average age at time of index surgery was 37.69 years, and 53 were male. Of the 80 hips, 50 surgeries were performed on the right hip, 30 were performed on the left (3 were bilateral cases). All hips had labral lesions, and 25 had either partial or complete resection of the labrum.
Survivorship analyses using THA/mHHS criteria (n= 36) and THA-only (n=77) criteria were performed. Average years of follow-up for these analyses were 1.96 and 1.22 years, respectively. Patient survivorship to THA was 78.6% at 3 years, with an average of 1.13 years until THA. When including mHHS criteria, this falls to 48.1% over the same time period.

Conclusion:
Survivorship to THA among FAO/MF patients with more serious cartilage defects was approximately 80% at three years. However, when non-THA definitions of failure are included, less than half of patients report successful outcomes over the same time period, suggesting that surgical conversion is not the only thing to consider when advising FAO/MF patients. Further data collection is ongoing, and more subjective definitions of success are currently being investigated.

References:


Erg Transcription Factor Expression in Cardiac Neural Crest Cells

Introduction:

Erg, a member of the ETS family of transcription factors, is a key player in the normal regulation of vascular development. It exists in seven isoforms; 3 of these share a common translational start site in exon4 (Ex4) and are expressed primarily in endothelial cells (EC), while the remainder utilize a separate start site in exon3 and are expressed in chondrocytes (1). Expressed in EC, Erg has been shown to be essential in maintaining endothelial tube formation and preventing EC apoptosis during angiogenesis through binding to the VE-Cadherin promoter (2). It also serves as a transcriptional repressor of the pro-inflammatory cytokine interleukin 8 (3). More recently, Erg has been shown to be essential to normal cardiac development. Erg Ex4 null transgenic mice die mid-gestation due significant defects in cardiac morphogenesis, including Erg-dependent failure of proper endothelial-mesenchymal transition (EnMT) and valve morphogenesis. (1). Defects in these processes underlay some of the most common congenital heart defects including cardiac valve and outflow tract abnormalities. The full scope of Erg’s novel role in effecting successful cardiac morphogenesis remains to be elucidated and could ultimately lead to a better understanding of congenital heart defects.

Objective:

The objective of this study was to ascertain at a cellular level whether Erg is expressed in the cardiac neural crest cells that help give rise to the outflow tract in the developing murine heart. These studies will help further clarify the mechanism by which Erg deletion produces significant cardiac developmental defects.

Background:

In the mouse, the heart and cardiovascular system is among the first organ systems to develop. Myocardial progenitor cells migrate from the primitive streak to begin forming the cardiac crescent at embryonic day 6.5 (E6.5). By E8, the cardiac crescent has fused to form the cardiac tube which during the ensuing 48 hours undergoes looping to form the nascent 4 chambered heart. At this point, the septum of the outflow track and the cardiac valves have yet to form. This process begins with the formation of cardiac cushions. The cushions are bulges of tissue composed of a dense extracellular matrix termed the cardiac jelly and a population of mesenchymal cells (4). Some of these cells are derived from endocardial cells through the process of EnMT, a process which requires Erg expression.

Another important source of these mesenchymal cells are the cardiac neural crest (NC) cells. Neural crest cells originate in the neural tube, delaminate, and migrate to sites throughout the embryo where they differentiate and contribute to a variety of structures. Cardiac NC cells migrate via branchial arches 3,
4, and 6 and contribute to cardiac structures via the secondary heart field, an embryonic source of cardiac cells distinct from the cardiac crescent (5). They contribute to the mesenchyme of the outflow tract cardiac cushions, are required for tract septation, and are important for myocardial function (6). Previous studies have offered evidence that Erg mRNA may be diffusely present in murine neural crest, though to date Erg protein expression in NC has not been shown (7). We were therefore interested in exploring a potential link between Erg expression and cardiac NC contribution to the developing heart and aimed to ascertain whether focal, nuclear Erg protein is expressed in cardiac NC cells.

**Methods:**

For immunohistochemistry we isolated embryos at day e10.5 and fixed them in 4% paraformaldehyde overnight. We then submersed the embryos overnight in 30% sucrose for cryoprotection and then embedded them in Tissue-Tek O.C.T. Compound (Sakura Finetek). We collected 8µM thick serial cryosections for staining. To detect expression of Pax3 and Erg we used mouse anti-Pax3 and mouse anti-Erg monoclonal antibodies (DHSB, and CM421A, Biocare Medical respectively). We carried out immunostaining using the Vectastain Elite R.T.U. kit (PK7200, Vector laboratories) and DAB horseradish peroxidase substrate (SK4100, Vector laboratories) as follows. We allowed cryosections to thaw at room temperature, and washed them 3 times for 5 minutes in 1X PBS. To antigen retrieve we boiled the slides in 1L of 0.1 M sodium citrate buffer (29.4 g/L Sodium Citrate in diH2O adjusted to pH 6.0 diluted 1:10 in di H2O) for 30 minutes. Following cooling and a 1X PBS wash, we treated slides for 30 minutes with 3% H2O2 (30% H2O2 diluted 1:10 in MeOH) to quench endogenous peroxidases. Next, we coated each slide with 500 µL of protein block composed of 36µL/mL M.O.M. blocking reagent (MKB 2213, Vector Laboratories), and 0.1% Triton x-100 detergent diluted in 1XPBS, allowing slides to incubate for 1 hour at room temperature in a humidified box. Following an additional 3 PBS washes, we incubated overnight in primary antibodies (1:100 dilution of anti-Erg into 10% Fetal Goat Serum, 1:200 of anti-Pax3 into PBS + 1g/100mL bovine serum albumin), or normal mouse IgG diluted 1:100 in 10% FGS for negative controls (20009-1, Pharmingen) overnight at 4˚C. We then washed the slides 3X5 minutes in PBS and applied 500µL of M.O.M. biotinylated secondary antibody (MKB 2225, Vector Laboratories) diluted 1:100 in fetal goat serum and incubated 1 hour at room temperature in a humidified box. Following 3X5 minute washes in 1XPBS we incubated the samples for 30 minutes in the ready-to-use ABC reagent and then washed in 1XPBS again. We developed stains for Pax3 and Erg for 6 minutes using a DAB peroxidase substrate according to manufacturer’s instructions (SK4100, Vector Laboratories). Imaging was performed using a Zeiss microscope and AxioVision software.
To assess for Erg expression in neural crest cells, we performed immunostaining for both Erg protein and Pax3 protein, which migrating neural crest cells express highly, on separate serial sections murine E10.5 embryonic sections. Immunostaining for nuclear Erg protein expression revealed the expected nuclear expression patterns surrounding vascular structures and the endocardium (A). Interestingly, we also detected nuclear Erg expression in single cells radiating from the neural tube (B). We observed groups of these populating the branchial arches of the embryonic sections as well (B, C). A cluster of 32 Erg+ cells appears in the area of the right branchial arch shown above (C). We compared these results to the results of Pax3 staining in adjacent embryonic sections. Pax3 immunostaining revealed dense Pax3 expression in the neural tube, and in diffuse groups of cells surrounding the tube (D). Two pockets dense pockets of Pax3-expressing cells populated the branchial arches (E,F). A dense cluster of 44 Pax3-expressing cells is present in the right branchial arch shown (F). This corresponds with the expected NC migratory pattern.

**Conclusion:**

Results of the immunostaining revealed an interesting pattern of Erg expression beyond the expected expression of Erg in EC cells of vascular structures and the endocardium. This pattern is similar to the pattern of cardiac NC cell migration towards the secondary heart field. Comparing this result with the expression of Pax3 in adjacent embryonic sections for Pax3, it appears that expression of Erg and Pax3 surrounding the neural tube and within the branchial arches overlap. Moreover, Erg-expressing cells in these regions are not associated with vascular structures, and appear morphologically different than Erg-expressing EC or endocardial cells. This suggests that they are cells of a separate lineage, and based on their location are likely to be Erg-expressing cardiac neural crest cells. Thus, the results of this experiment offer evidence on a cellular level that a population of cardiac NC expresses nuclear Erg protein.
While the overall pattern of Pax3-expressing and non-vascular Erg-expressing cells was similar, Pax3 was expressed in more cells and in a denser pattern in the branchial arches than Erg. Thus, it is also possible that Erg is expressed in a subset of cardiac NC or that non-vascular Erg-expressing cells are mesenchymal cells of another origin. Future experiments utilizing immunofluorescent staining on serial sections or simultaneous staining of Erg and Pax3 may help clarify this. Future studies of Pax3 expression in Erg Ex4 null embryos will also be of interest. Such studies would allow us to ascertain whether Erg is a necessary factor for normal cardiac NC migration and contribution to the secondary heart field and could suggest a functional role for Erg transcription factor in Erg-expressing cardiac NC. Should such an effect be detected, further follow-up studies could include evaluation of BMP signaling in Erg-null cardiac NC; several BMP signaling pathways have been shown to be necessary for cardiac NC migration (7), and we have recently uncovered evidence that Erg may be involved in mediating BMP signaling during the process of EnMT (unpublished data). In conclusion, evidence of Erg expression in cardiac NC opens up intriguing new avenues for research into the role of Erg in NC function and cardiac development as a whole. Further illumination of these subjects may ultimately lead to a better understanding of some of the most common congenital heart defects including cardiac valve defects and malalignment syndromes (8).

References:


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**Accuracy of EMS-Recorded Medical History and Medications**

**Introduction & Background:** A crucial aspect of prehospital emergency medical services (EMS) care is identifying and documenting accurate patient data, particularly medications and medical history. Data recorded and reported by EMS providers can influence the care delivered to patients by EMS and providers in the emergency department (ED).

EMS providers must know their patient’s medical history, as that information may influence differential diagnoses, treatments, and transport decisions. However, no studies have examined the accuracy of medical histories collected by EMS. If accurate and complete, the EMS data can assist healthcare providers in caring for patients as well as researchers in risk adjusting between populations.

Over 25% of hospital prescribing errors have been attributed to incomplete medication histories at the time of admission. Because EMS providers frequently come into contact with family members or caregivers and can often visualize the patient’s medications and their bottles at the site of pickup, EMS providers may be able to generate a more complete medication list than other sources. This list, when accurate and complete, can assist EMS, ED, and hospital providers in caring for these patients most effectively.

**Objective:** This study aimed to examine the accuracy of EMS-recorded data on the past medical history and current medications of older adults (age ≥ 65 years), as compared to a comprehensive “gold standard” compiled from other available sources.

**Methods:** We performed a cross-sectional survey study of a convenience sample of older adults transported by EMS to the Strong Memorial Hospital ED in Rochester, NY between June and July 2013. Verbal informed consent was obtained from patients or proxies. A survey was developed and administered, which included patient demographic data, chief complaint, Emergency Severity Index score, and EMS level of care. For each patient, current medications and past medical conditions were also recorded from four sources: the patient and/or proxy, the patient’s PCP, eRecord, and EMS medical records. A “gold standard” was created by combining the PCP and eRecord lists.

Survey data was analyzed with descriptive statistics using SAS 9.3 (SAS Institute, Inc., Cary, NC). For both medical conditions and medications, we calculated a number of metrics to describe the accuracy of the EMS medical history and medication lists.

**Results:** 200 subjects were enrolled and 106 of these subjects had complete data for analysis. EMS reported notably fewer medications than the gold standard (median of 5 vs. 12) and medical...
conditions (3 vs. 9) (Table 1). Only 20% of subjects or their proxies were able to provide the research staff with names of medications and 63% were able to provide names of medical conditions. EMS reported a median of 51% of the gold standard medications and 41% of the gold standard medical conditions (Table 2). Patients or their proxies reported a median of 0% of the gold standard medications and 14% of the gold standard medical conditions.

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<th>Table 1: Medications &amp; Medical Conditions Identified</th>
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<td>Medications</td>
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<th>Table 2: Comparison of Gold Standard Lists vs. EMS &amp; Patient Lists (n=106)</th>
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<td>Medications</td>
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<td>On patient list but not gold standard list</td>
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<tr>
<td>On EMS list but not gold standard list</td>
</tr>
<tr>
<td>Percentage of gold standard reported by patient</td>
</tr>
<tr>
<td>Percentage of gold standard reported by EMS</td>
</tr>
</tbody>
</table>

**Conclusion:** EMS documented approximately half of the number of medications and medical conditions that are recorded in the gold standard comprised of PCP and eRecord medical records. However, the range of the proportion of EMS-recorded data compared to the gold standard is vast, with instances of EMS collecting both significantly less and significantly more data than is available from other sources. Interestingly, patients and their proxies were able to provide very little information about the patients’ medications and medical conditions.

These findings demonstrate a significant potential information gap. EMS, ED, and hospital providers may lack critical patient information unless they have access to consolidated electronic medical records. Although it is unclear if this gap reflects poor documentation or impacts care of the acute illness, these findings do highlight that EMS providers need better access to medical records, and that ED and hospital providers cannot rely on a single source of information.

**References:**
Risk Factors for Postoperative Venous Thromboembolism in Orthopedic Spine Surgery, Hip Arthroplasty and Knee Arthroplasty Patients

Introduction/Background
Orthopedic surgery is a major risk factor for venous thromboembolism (VTE) manifesting as deep vein thrombosis (DVT) or pulmonary embolism (PE). Prior epidemiologic studies in elective hip and knee arthroplasty patients have demonstrated their rate of symptomatic VTE to be between 1.1-10.6%1-6, and in orthopedic spine surgery patients from 0 to 31%, depending on patient population, method of surveillance and type of prophylaxis7-27. Furthermore, various risk factors alter the likelihood of individual patients having a VTE, including a history of diabetes28, cigarette smoking29, malignancy30, dyslipidemia31,32, obesity33,34, history of DVT or PE35, the use of general versus regional anesthesia36, time to prophylaxis37, coronary artery disease38 and genetics39,40. Despite rigid adherence to current VTE prophylaxis guidelines, VTE events still occur, possibly due to substantial variability between guidelines. These significant discrepancies warrant further investigation of the most optimal VTE prophylaxis regimen following orthopedic surgery.

Objective
To determine if particular patient characteristics are risk factors for VTE following major orthopedic surgery.

Methods
Data was reviewed from 201 patients presenting with either a PE or DVT following spine surgery or joint replacement from October 2009 through June 2013. The following characteristics were reviewed for each patient: VTE event date, surgery date and type, comorbidities and pre-existing conditions, calculated comorbidity level, body mass index, prophylaxis type, time to initiation of chemoprophylaxis, time to spinal epidural removal and VTE event type. The comorbidities and pre-existing conditions included were diabetes, hypertension, coronary artery disease, hyperlipidemia, hypercholesterolemia, smoker status (current or former), cancer, history of VTE and Factor V Leiden disorder. The control patients were randomly selected from a group of 13,782 patients during the equivalent period, and the same information was reviewed.
**Results**

A history of VTE (p<.0001), Factor V Leiden disorder (p=.04) and the use of general anesthesia (p=.05) were significant risk factors for postoperative VTE (Table 1). The frequency of VTE decreased following hip and knee arthroplasty and remained constant for spine surgery during the study period. Over 90% of PEs were diagnosed within the first week of surgery and zero PEs were diagnosed after the second week. 33.3% to 75% of DVTs were diagnosed within the first week following surgery, and DVTs occurred 14.2 days later after surgery than PEs (p<.0001).

**Table 1. VTE and Control Case Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>VTE Cases Mean (n=96)</th>
<th>Controls Mean (n=80)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>31.3</td>
<td>31.9</td>
<td>0.2</td>
</tr>
<tr>
<td>Time Epidural Removed Post-Operatively (min)</td>
<td>1167.7</td>
<td>1176.2</td>
<td>0.45</td>
</tr>
<tr>
<td>Time to Prophylaxis (min)</td>
<td>994.5</td>
<td>929.5</td>
<td>0.13</td>
</tr>
<tr>
<td>Time to Prophylaxis for Patients with Epidurals (min)</td>
<td>1236.1</td>
<td>1175</td>
<td>0.22</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>VTE Case Frequency (n=201)</th>
<th>Control Frequency (n=201)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-Operative Epidural</td>
<td>0.48</td>
<td>0.4</td>
<td>0.05</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.13</td>
<td>0.24</td>
<td>0.003</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.64</td>
<td>0.58</td>
<td>0.13</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>0.08</td>
<td>0.07</td>
<td>0.42</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.22</td>
<td>0.16</td>
<td>0.08</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>0.2</td>
<td>0.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>0.04</td>
<td>0.11</td>
<td>0.002</td>
</tr>
<tr>
<td>Former Smoker</td>
<td>0.27</td>
<td>0.27</td>
<td>0.5</td>
</tr>
<tr>
<td>Cancer (Active malignancy or considered cured≤1 year)</td>
<td>0.01</td>
<td>0.01</td>
<td>0.5</td>
</tr>
<tr>
<td>History of DVT or PE</td>
<td>0.15</td>
<td>0.01</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Factor V Leiden Disorder</td>
<td>0.01</td>
<td>0.01</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*a n=201 for cases and controls

*b n=173 for cases and controls

*c According to Revised Geneva Scoring System

**Conclusion**

This study demonstrates that a prior history of DVT or PE and Factor V Leiden Disorder significantly increases a patient’s risk of VTE. Anesthesia administered via an epidural significantly reduces the risk of VTE as long as it does not delay chemoprophylaxis initiation and it appears that VTE prophylaxis reduces the impact of other risk factors. Initiating chemoprophylaxis sooner after
surgery may decrease the risk of VTE postoperatively, but the known increased risk of bleeding must be taken into consideration. Additionally, the likelihood of a PE beyond the second postoperative week is low. Orthopedic surgeons should consider the results of this study when providing the most optimal VTE prophylaxis regimen and general postoperative care for individual patients.

References


Investigating arrhythmogenic mechanisms using an in-silico model of the Human Heart

Abstract title: Preliminary results on the development of an in-silico human wedge

Introduction:
Accurate prediction of drug safety when a new compound exhibits inhibitory properties of the HERG channel remains one of the major challenges of the pharmaceutical industry. The current preclinical and clinical safety assays are not satisfactory. In clinical safety studies, a dose-dependent prolongation of the QT interval is used as the surrogate marker of an increased risk for drug-induced torsades de pointes (TdPs), a life-threatening ventricular arrhythmia. Yet, QT prolongation is an imperfect surrogate marker of the risk for TdPs. There is strong interest in developing the next generation of safety assays to improve the assessment of drug cardiotoxicity at an early stage of development.

Objective:
We plan to assess whether an in-silico modeling technique could be used to improve the assessment of drug safety. In this preliminary work, we investigated the ability of the model to generate electrograms (EGs) recorded from an in-silico human heart wedge. We designed an experiment including specific pacing protocol and recorded the resulting voltage gradient at different locations on and inside the wedge.

The in-silico model is based on high throughput calculation. IBM donated a Blue Gene/Q supercomputer to URMC and, in collaboration with the Lawrence Livermore National Laboratoty (DC), developed the Cardioid software. This modeling tool relies on high-performance computing resources to generate a 1D cable, 2D patches, 3d wedges , and 3-D heart/torso model.

In this work, we present our preliminary results describing the sequences involved in the normal excitation of heart muscle and the impact of modifying the pacing rate and location of the pacing site(s) to the front of excitation inside the wedge.

Methods:
A stimulus was applied to the endocardium at specific intervals. The stimulation period was adjusted by 200 ms for each of five tests. The stimulation period for test one was 200 ms. Test five pacing was set at 1,000 ms. All wedges used identical recording locations and stimulation boxes.

By studying the visualization and EG, we determined the point at which re-entry did not interfere with T-wave completion. We visualized and quantified re-entrant arrhythmias through the generation of EGs.
Results:
Preliminary results show that enhanced automaticity interferes with repolarization completion at periods less than 800 ms in this ventricular wedge.

Conclusion:
By adjusting automaticity, we were able to create realistic depolarization and repolarization fronts inside an in-silico wedge model. These preliminary results are crucial to the design of the next development of the in-silico heart model and more precisely the impact of the location and distribution of the different type of myocardial cells (epi-, endo-, and M-cells) into the in-silico Cardioid model.

References:


Introduction: Repetitive mild traumatic brain injury (mTBI) has become an epidemic among athletes and military personnel, but the pathophysiologic processes leading from trauma to chronic neurodegeneration remain unclear.

Objective: The purpose of this study was to examine, in a dose-response manner, the relationship between the number of mTBI events and the induction of a pathologic process leading to neurologic changes.

Background: Repetitive mTBI, encompassing concussive and sub-concussive brain injury, has shown a propensity to induce neurologic sequelae beyond the acute or sub-acute phase, most notably chronic traumatic encephalopathy (CTE). However, the mechanisms underlying this transformation remain unclear. At present there is no widely accepted animal model of CTE (1).

Methods: In adapting our laboratory’s previously characterized ‘Hit & Run’ model to a clinically relevant model of repetitive mTBI, mice were restrained in a suspended plastic cone without anesthesia. The mice were then subjected to an impact over the left temperoparietal lobe by a pneumatic controlled cortical impact (CCI) device with a rubberized tip. Mice received 3 hits every 2 hours for 1, 2, 3, or 4 consecutive days, totaling either 3, 6, 9, or 12 hits. Neurological severity scores (NSS) were assigned one hour after injury, confirming that all mice underwent mild injury (NSS < 5/10). Immunohistochemical staining of cerebral tissue was performed to assess levels of glial fibrillary acidic protein (GFAP), an established biomarker for astrogliosis following TBI.

Results: Immunostaining revealed a dose-dependent response in GFAP+ area across tissue sections from the ipsilateral and contralateral hemisphere, cortex, white matter, and subcortex. When compared to sham-injured controls, GFAP+ area was not significantly elevated in the 3-hit or 6-hit groups, but was greatly increased in the 9-hit and 12-hit groups.

Conclusion: These data suggest that the degree of astrogliosis correlates closely with the number of repetitive mTBI events, and that there may be a threshold number of traumatic events, which when reached will initiate a pathologic pathway leading to long-term neurologic injury. Future work must be done to investigate this question further.

References:

Introduction: In the management of pain, physicians are often faced with the complex and broad etiology of their patients’ complaints. Perception of pain is influenced by several inputs including the limbic system, nociceptive neurons, cognition, and memory. Pain’s multifaceted nature has given researchers difficulty in designing experiments and tools required to further treatments for our patients. Commonly, the study of pain focuses on nociception, and its transduction to an electrical signal at a molecular level. However, this approach largely eliminates the modulation of pain perception by higher order centers of the nervous system. Therefore, the goal of our study is to cultivate a better research base for pain in the context of higher order modulation.

Objective: To develop a high-throughput behavioral assay in zebrafish to model nociceptive behaviors modulated by higher order processes.

Background: This tool can be used by researchers to test more complex forms of behavior requiring higher cognitive centers in response to pain. Whereas, previous studies tested reflexive responses and escape behaviors not requiring higher cognition, our assay tests fish preference between a zones that contains a noxious stimulus (such as higher water temperature) compared to a zone of non-noxious stimulus. Preference requires the fish to explore both zones in the arena, decipher differences between the two stimuli, and choose one zone over the other.

Methods: I developed a 4 minute place preference assay able to test up to 20 fish simultaneously. Fish arenas are divided into two zones and their water temperatures are controlled using thermal plates. One zone is always set to the non-noxious incubation temperature of 28.5˚C. The testing zone can be altered from 28.5˚C (control) to a semi-noxious water temperature (31.5˚C). 4dpf AB* embryos were used for the test. During this project, I screened through 15 known compounds that interact centrally to alter the perception of pain. 1% DMSO in EM was used as the drug vehicle and acted as the control condition during drug trials.

Results: Wild type fish (4dpf AB* embryos) choose a non-noxious water temperature (28.5˚C) over a semi-noxious water temperature (31.5˚C) 70.6% (SEM= ± 3.6%, n=50) of a four minute trial. This is compared to when both zones are set to equal non-noxious temperatures and duration on either side is approximately 50% of the trial (49.6 ± 4.7%, n=50). Several hits during drug screen decreased or increased the choice of zebrafish in response to heat stimuli. For example, when fish larvae are given 10µM clonidine, choice between the noxious and non-noxious temperatures is abolished and fish spend time equally between both conditions (48.5% ± 3.9%, p<0.001, n=50). Conversely, when a low concentration of allyl isothiocyanate (2 µM) is added to the water, the larvae spend a significantly larger proportion of time in the zone with non-noxious temperature (88.1 ± 4.0%, p<0.001, n=30).
**Conclusion:** We are able to model hyperalgesia and analgesia in a complex behavior and in a high-throughput manner. My assay can be applied to advance the treatment of pain by discovering novel drugs or genes involve in pain. This may translate to more specific and safer treatments or modify the framework through which we approach pain in the clinic.

**References:**
Title: A Propensity Score Matched Analysis of Asymptomatic Patients Undergoing Carotid Endarterectomy (CEA) vs. Coronary Artery Bypass Graft (CABG) vs. Combined CEA-CABG in the ACS-NSQIP

INTRODUCTION:
Carotid endarterectomy (CEA) and coronary artery bypass graft (CABG) may be combined to treat concomitant coronary artery and carotid artery atherosclerotic disease. Previous reports on combined CEA/CABG have shown wide variation in adverse event rates for asymptomatic patients and have often been limited by small sample size and/or lack of granularity.

OBJECTIVES:
We aim to compare stroke and death after CEA-CABG with CEA or CABG alone in asymptomatic patients using the ACS-NSQIP.

METHODS:
All patients undergoing CEA, CABG or CEA-CABG from 2005 to 2011 in the NSQIP database were identified. NSQIP documented neurologic symptoms lack laterality and temporal detail for assignment of positive current neurologic symptoms while asymptomatic patients are captured with excellent accuracy. Accordingly only asymptomatic patients were analyzed. Propensity score matched groups of asymptomatic patients were based on age, sex and ASA class 4. Chi-square, ANOVA and multivariable logistic regression were used to compare stroke, death and stroke/death across procedures.

RESULTS:
We identified 47,667 patients; 42,474 CEA (89%), 5,018 CABG (11%), 175 CEA-CABG (<1%). Forty percent of all patients had a history of neurologic symptoms and were omitted from consideration: 43% CEA, 12% CABG, 28% CEA-CABG. Unmatched rates of stroke/death in asymptomatic patients were: 1.4% (CEA), 3.3% (CABG) and 6.7% (CEA-CABG). Propensity score matching identified 1,332 asymptomatic patients; 606 CEA, 607 CABG, 119 CEA-CABG. Stroke, death and stroke/death rates are compared across procedures in the Table. Independent risk factors for stroke/death among matched asymptomatic patients were: recent myocardial infarction OR: 4.0 (95% CI: 2.0-8.0), COPD OR: 4.7 (95% CI: 2.4-9.2) and age > 70 years OR: 2.7 (95% CI: 1.4-5.2); CEA-CABG, as compared to CABG alone, did not have increased risk of stroke/death (OR: .6, 95%CI: .2-1.4). No significant difference was seen between the stroke/death rate of CEA-CABG (6.7%) as compared to the aggregate of CEA and CABG alone (2.1% + 4.2%).
CONCLUSIONS:
In asymptomatic patients CEA-CABG does not confer increased risk for stroke/death as compared to the combined risk of CEA and CABG alone. CEA-CABG should be considered a safe approach in asymptomatic patients requiring both CEA and CABG.

<table>
<thead>
<tr>
<th></th>
<th>CEA (N=606)</th>
<th>CABG (N=607)</th>
<th>CEA-CABG (N=119)</th>
<th>p value (CABG vs. CEA/CABG)</th>
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<tbody>
<tr>
<td>Death (%)</td>
<td>1.2</td>
<td>2.3</td>
<td>3.4</td>
<td>.516</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>1.2</td>
<td>2.0</td>
<td>3.4</td>
<td>.314</td>
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<tr>
<td>Stroke/Death (%)</td>
<td>2.1</td>
<td>4.1</td>
<td>6.7</td>
<td>.227</td>
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</table>

REFERENCES:


**UR Well is a Cost-Effective Option in Comparison to the Emergency Department**

**Introduction:** UR Well is a student-run medical clinic that provides free health care services to uninsured and under-served adults. It provides services including screening for hypertension and diabetes, ongoing care for chronic conditions, physical exams, referrals, health education, and preventive medicine. On Tuesday evenings, ongoing primary care is offered at St. Joseph’s Medical Center, while on Thursday evenings, acute care is provided at Asbury First United Methodist Church. This clinic is mutually beneficial to patients and students, both supplementing students’ medical training and providing patients with quality care for little to no money, thus relieving cost burdens on hospitals as well as on patients. The aim of this project was to determine the amount of money saved by patients who sought care at UR Well instead of going to an emergency department.

**Objective:** To compare prices spent by patients at UR Well clinic nights to prices that would have otherwise been incurred at an emergency department visit.

**Background:** Visits to the emergency department can be extremely expensive, especially for the patient who is uninsured. An alternative route for healthcare provision can be difficult to find however, as almost all private medical providers require insurance. Thus, the uninsured often go without any preventative healthcare, receiving medical care only when the need is acute. Not only does this have a negative impact on the health and financial well-being of the patient but it also has negative implications for the public healthcare system as well – namely hospitals. Hospitals must address both the consistent overcrowding in the emergency department as well as the rising cost of uncompensated healthcare. The most recent statistics show that uncompensated healthcare costs for US hospitals has been more than $367 billion since 2000, and was $41.1 billion in the year of 2011 alone.

Free clinics such as UR Well relieve some of the pressures placed on both the uninsured patient and hospitals. In allowing patients to be seen in both chronic and acute situations, UR Well is able to enhance continuity of care given to patients in an affordable manner while also decreasing crowding and costs that would have otherwise been incurred at hospitals.

**Methods:** The total cost incurred by all patients seen at the clinic between December 2012 and May 2013 was calculated. The cost to be seen at an emergency department for the same complaint addressed at the clinic was then determined for each individual patient and the total was calculated. In calculating the cost to an emergency department visit, the only cost considered in this study was the consult with a physician. Not included in price calculations were additional assessments that were provided, lab work, and cost of treatment. Furthermore, in calculating the estimated price to an emergency department visit, the minimum potential cost was used. These considerations avoid an over-estimate of costs saved. Finally, in determining the price of physicals, the cost of a physical was compared to the cost of a physical received at a WorkFit Medical provider. The results therefore reflect the absolute minimum saved in a six-month period.
### Results:

<table>
<thead>
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<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients seen at UR Well</td>
<td>357 patients</td>
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<tr>
<td>Total cost incurred by patients at UR Well</td>
<td>$1,550</td>
</tr>
<tr>
<td>Minimum total cost of equivalent visits to ED</td>
<td>$171,208</td>
</tr>
<tr>
<td>Total amount saved</td>
<td><strong>$169,958</strong></td>
</tr>
</tbody>
</table>

### Conclusion:

The cost of healthcare is clearly detrimental to an uninsured patient’s health and finances in addition to being a significant burden to US hospitals. UR Well is a productive and highly utilized program, seeing over three hundred and fifty patients in a six-month period. This study demonstrates that the clinic is a cost-effective option for patients and hospitals. Moreover, it is extremely beneficial to students, not only supplementing their medical training, but also connecting students with the difficulties and real-life situations that the uninsured face. Overall, UR Well is a valuable resource to its students and is an integral part of healthcare in our community.

### References:


ADDRESSING THE RESOURCE NEEDS OF ROCHESTER'S CHRONICALLY HOMELESS THROUGH MEDICAL STUDENT OUTREACH

Introduction: The Street Outreach program conducts nightly street rounds including regular visits to homeless camps, public parks, and downtown parking garages to personally engage Rochester’s homeless and tend to their individual health needs. Our teams consist of medical and nursing students, physicians, social workers, and a formerly homeless guide. The team seeks to provide treatment, including appropriate medications, for acute medical concerns as well as providing counseling and resources to address long-term needs.

Objective: Improve the physical, mental, and social wellbeing of Rochester’s unsheltered homeless through direct outreach to the community and by engaging in advocacy activities to work to improve the infrastructure of local homeless services.

Background: The Civic Center parking garage downtown has long been a place of refuge for a significant number of Rochester’s unsheltered homeless. However, the owners of the garage plan to secure the premises and prohibit individuals from living there starting November 1st. A homeless task force was formed by the City of Rochester Manager of Housing to discuss viable solutions for those who will be displaced by the closing of the garage.

Methods: Our outreach team conducted a qualitative needs assessment at St. Joe’s House of Hospitality with a focus group of six homeless men to elucidate the specific concerns of those that use the Civic garage as a nightly safe haven. We conducted a site visit to the Oxford Inn in Syracuse, NY to explore the possibility of adapting a similar model to better serve the needs of Rochester’s homeless.

Results: Many barriers exist to accessing existing resources in Rochester. According to our focus group, the highly stringent regulations imposed by shelter staff act to deter homeless individuals from seeking services. These include mandatory religious activities, strict curfews, and no leniency in alcohol use policies. In addition, there were concerns about poor safety, lack of personal space, and maltreatment.

The operations at the Oxford Inn in Syracuse are markedly different than the majority of shelters in Rochester. The Oxford Inn allows for intakes at all hours of the night, has no mandatory religious activities, and allows guests to stay under the influence of alcohol as long as they are not disruptive.

Conclusion: Rochester’s current temporary shelter options are not sufficient to meet the needs of a significant number of chronically homeless individuals. The City of Rochester could better serve their homeless population by adopting a model similar to the Oxford Inn in Syracuse. Additional temporary housing programs should be explored in order to expand the coverage of social services to all Rochester residents.
UR Well Summer Internship: Rapid HIV Testing Project

Introduction: UR Well is a student-run medical clinic that operates out of two centers, providing medical care to the uninsured population of Rochester. Every Thursday night a free acute care clinic takes place at Asbury Methodist Church, and once a month physicals are offered there. On Tuesday nights, UR Well takes over St. Joseph’s Neighborhood Center, providing primary care. Both clinics serve those who otherwise would not have access to care. The UR Well Summer Internship allows students to serve this community in several ways. First, as a summer intern, I functioned as an administrative coordinator for the weekly UR Well clinics. Second, I worked at the front desk of St. Joe’s during the day, continuing my administrative duties and getting to know the clinic better. Finally, I worked on an ongoing improvement project suggested by senior leadership at the clinic. My project was to look at implementing rapid HIV testing at the Asbury acute care clinic.

Objective: To develop a framework for implementing rapid HIV testing at the UR Well Asbury site that is sustainable and feasible.

Background: Rapid HIV testing has been discussed and attempted in various capacities at UR Well for years. While many good ideas had been proposed in the past, UR Well’s faculty advisors were rightly worried about the sustainability of the program and the capacity of UR Well to provide adequate counseling and access to services. These concerns are valid and this project aims to address them. Meanwhile, the need for HIV testing is real. While more investigation needs to be carried out to identify the needs of the target community, current statewide and nationwide numbers are startling. The CDC estimates that more than 1.1 million people in the US are infected with HIV; even more startling, 1 in 5 are unaware of their infection. In order to increase awareness, the CDC has recommended that community centers of all types adopt rapid HIV screening. Importantly, knowledge of HIV positive status has been shown to reduce risky behavior by about 50%, which may help to prevent further spread of disease.

Methods: This project required me to work with a number of different individuals to collate resources and establish plans for turning Asbury into a clinic that offers rapid HIV screening. First, I examined several previous proposals for rapid testing at UR Well, evaluating them for their strengths and weaknesses. From this, I was able to gain insight into what worked and what needed to be improved. I then reached out to a number of possible partner organizations to pool
resources and identify how to best help the at-risk community. Finally, I gathered, tested, and utilized online resources from the NYS Department of Health and the CDC.

**Results:** I developed a testing protocol based on Kathryn Chenault’s 2012 CHIC project, as well as a plan for how to put this protocol into place. I collected documentation forms for testing from the NYS Department of Health. I identified a CDC online training course for providers of HIV as the best way to train students. This training course is free, takes about 5 hours to complete, and is comprehensive, handling point of care, facility guidelines, and counseling. I myself completed the course and obtained a training certificate. Additionally, I completed the paperwork from the URMC Labs Point of Care testing, to be submitted at a later date. Finally, I re-established a partnership with Trillium Health, a provider of HIV/AIDS services, to provide confirmatory testing.

**Conclusion:** While my summer project has ended, and rapid HIV testing is not yet in place at UR Well, I have developed the framework to enact it. The next step is to achieve advisor approval of the plan. I am continuing to work on this project with other URMC students. I personally believe that rapid HIV testing can be implemented at Asbury in a thoughtful, appropriate way. Furthermore, I believe that it is a necessary service to provide to the community, in accordance with the CDC goals.

**References:**

Introduction: A primary goal of improving healthcare quality is to better manage and prevent chronic illness. Chronic disease management and prevention can be complicated in the setting of vulnerable patient populations, especially those without adequate healthcare insurance. The St. Joseph’s Neighborhood Center (SJNC) is a community health center that provides inexpensive care to those without insurance. Supported by the Sisters of St. Joseph, the SJNC provides an excellent opportunity to improve the health of the uninsured Rochester community through the implementation of specific programs that best utilize community resources. A growing concern is the increasing prevalence of diabetes mellitus and other chronic metabolic disorders. This trend parallels the rising prevalence of metabolic and cardiovascular risk factors implicated in many chronic and degenerative disorders. Preventing the transition from prediabetes or metabolic syndrome to type 2 diabetes mellitus is a cost-effective intervention that has the potential to save patients and the community significant disease and financial burden.

Objective: As a summer intern working closely with the SJNC, I developed a translational program aimed at obtaining a weight reduction with a clinically significant decrease in risk of type 2 diabetes in people with prediabetes through healthy eating, increased activity, and self-monitoring. This program was designed to utilize the resources available to the SJNC and the UR Well Student Outreach Clinic of the University of Rochester School of Medicine for the uninsured population that these clinics serve.

Background: Diabetes is one of the most rapidly increasing worldwide epidemics, threatening the resources of healthcare systems across the globe. Diabetes affects 26 million people in the United States alone, amounting to 8.3 percent of the US population\(^1\). The incidence of diabetes has increased from 5.6 million new cases in 1980 to 20.9 million new cases in 2010\(^2\). The cost of diagnosed diabetes in the United States in the year 2007 amounted to $174 billion\(^2\). Monroe County is not immune to this trend. An estimated ten percent of adults in Monroe County have ever been told by a physician that they have diabetes\(^3\). This is greater than the eight percent average for the state of New York\(^3\). While most attention is paid to the treatment of diagnosed diabetes and its sequelae, the importance of prevention in decreasing disease and financial burden cannot be understated. About 79 million adults 20 years and older in the United States
have prediabetes\(^4\). While most professional diabetes educators are trained in self-management education for diagnosed diabetes, they are generally not used in the context of prevention. Programs directed at preventing diabetes and lowering risk factors have already been proven effective, including a landmark study, the Diabetes Prevention Program (DPP)\(^5\). The DPP demonstrated that in people with prediabetes, losing 7% of initial body weight through healthy eating and moderate activity decreased the risk of developing type 2 diabetes by 58% (compared to those taking a placebo pill), whereas taking metformin resulted in a risk decrease of only 31%\(^5\).

**Methods:** The program design was based on two previously successful models: (1) The Group Lifestyle Balance\(^{TM}\) program created from the Diabetes Prevention Program\(^6\) and (2) The Five A’s model of behavior change\(^7\). The evidence-based Group Lifestyle Balance\(^{TM}\) program aims to lower risk of diabetes in prediabetics by achieving a 7% reduction of body weight through healthy eating and doing 2.5 hours of brisk physical activity each week. This model attempts to accomplish these goals through education and empowerment with self-monitoring skills. The 5 A’s model explores the patient’s perceptions and motivations through a collaborative partnership. Modifications of these two models were made to create a pilot program design that is practical, applicable to the practice setting of the SJNC, and clinically successful. Program design was aimed at utilizing available resources, including the community-based St. Joseph’s Neighborhood Center and medical student volunteers from the University of Rochester School of Medicine. The initial pilot design of the program will be based on provider recruitment of candidates for one-on-one appointments with a trained student volunteer. Continuity will be emphasized by encouraging weekly or bi-weekly visits and by tracking key measures, including weight and BMI, and by documenting important topics covered in each visit. The program will be free of charge to patients of the SJNC.

**Results:** With the initiation of a pilot phase that will last 6-12 months, data will be collected with two objectives. First, it will be imperative to assess the practical integrity of program implementation through program evaluation data. Second, outcome data will be useful in interpreting the clinical applicability and success of this modified program design.

**Conclusion:** The SJNC provides an exciting opportunity to assess the feasibility and success of developing a program tailored to a community’s needs and resources. Clinical translation is an important aspect of any intervention and many times can be a barrier to implementation in a primary care setting. The success of this project would demonstrate hope that highly-structured evidence-based interventions aimed at disease prevention can be modified to fit the needs and resources of a community while maintaining clinically significant outcomes. Specifically, success will demonstrate that the Diabetes Prevention Program (DPP) and the Group Lifestyle Balance (GLB) program can be modified for the purpose of effecting change in a community-based program for high-risk patients without insurance.

**References:**


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Why ED? Investigating Expectations and Decisions in Choosing the ED in a Public Hospital in Lima, Peru

Introduction: Over 100 million patients visit Emergency Departments in the United States each year (Cowan and Trzeciak 2004). This high patient volume was the basis for creating the specialty of Emergency Medicine in the United States. Since that time, annual visits to the emergency room have only increased in number. A 2011 survey done by the American College of Emergency Physicians found that 80% of physicians stated that the number of patients visiting their ED had increased in the past year and over 90% believed that number would increase again in the following year (ACEP 2011). A 2003 article by Trzeciak and Rivers stated that because “the role of the ED is crucial for public health…any threat to the ED’s ability to provide quality emergency care constitutes a public health crisis”. Understanding the reasons behind the growing amount of patients utilizing the ED is thus of critical importance. Many articles have cited that the biggest problem resulting from the increased patient flow into waiting rooms in Emergency Departments all over the country has been overcrowding (Derlet 2000, 2001, Trzeciak and Rivers 2003). Continued investigation into the reasons why patients choose to come to Emergency Departments, including whether they have access to care and if they use it regularly, could provide insight into the problem of overcrowding.

However, most of the studies on patient flow have been done in Europe, Canada and the United States (Kellermann 2000, Derlet 2000, 2001, Olsson 2001, Gordon 2001, Trzeciak and Rivers 2003, Cowan and Trzeciak, 2004, Cowan 2004, Cooke 2006, Muntlin 2006, Raven 2011). We hoped to investigate the reasons that patients choose to come to the Emergency Department, and their expectations of their visit, in an overcrowded urban Emergency Department in Lima, Peru.

Objectives: This study aimed to look at some of the reasons why patients chose to come to the ER, whether they felt as though they had any alternatives, and how their relationship was to their usual source of care if they had one. Our survey had four sections that each attempted to answer a different question: 1) Demographics, 2) Usual source of healthcare, 3) Decision to come to the ED, and 4) Expectations of the visit.
The first section attempted to understand the characteristics of the patient population and identify any trends. The second section aimed to understand who the primary healthcare provider was for each patient (and if they had one), as well as understanding the nature of the relationship. The third section measured the patient’s choice in coming to the ED rather than an alternative source of care, and what factors were involved in making that decision. The final section sought to understand the patient’s expectations of time (such as how often they felt they should be updated about their status) and the severity of their complaint compared to the average of others during their wait.

**Background:** Lima, Peru is the largest city in Peru, and with a population topping out above 8 million people, it holds over a quarter of Peru’s entire population. The poorest and most underserved area of the city is in the “Cono Norte”. Cayetano Heredia National Hospital is a leading academic hospital in Lima, and is one of a small handful of hospitals that serves this densely populated area. Dr. Raul Acosta, former director of the Emergency Department at Cayetano Heredia and our on-site mentor during the summer, noted that the hospital regularly sees high patient flow and overcrowding. This hospital was the ideal location to survey a diverse patient population in a country that had not yet been studied with regard to patient expectations of Emergency Medicine.

**Methods:** The survey was professionally translated by MAS Translation Services, Rochester, NY. In addition to receiving approval by the RSRB, the survey was approved by the Office of Training and Research at Cayetano Heredia. We worked with the Emergency Department staff at Cayetano Heredia to identify the most appropriate time to recruit participants. All surveys were distributed in the “observation room” of “Tópico de Medicina,” the functional waiting room of the Emergency Department. After explaining the purpose of the survey and obtaining verbal consent from the patients, paper copies of the survey were distributed to patients in the waiting room that met the inclusion criteria. If there appeared to be particular questions that patients did not understand or were not willing to complete, they were left out. If patients did not understand the study or were not capable of participating due to an altered mental state, extreme pain, dementia, psychosis, or other such factors, they were excluded from the study.

**Results:** We conducted 113 surveys on patients in the “observation room” of Tópico de Medicina in the Emergency Department. Our patient population was relatively balanced in terms of age, and 59% of the patients were women. Only 23% (95% CI ±7.76%) of patients described their general health as poor. However, only 19% (95% CI ±7.23%) described their health as good or better. Over half of patients (59% (95% CI ±9.11%)) had been to the ER at least one other time (7% having visited 6 or more times) within the past year. The “posta” was the most utilized primary source of healthcare for patients (40% reported using a local clinic), though it remains unclear how in depth the care is at those sites. 16% (95% CI ±6.86%) of patients used the ER as their primary source of care, and 68% of patients reported an average (3 out of 5) or above relationship with their primary source of care (whether it was the ED or a posta). In 87% (95% CI ±6.12%) of cases, the decision to come to the ED was made either by the patient or a family member. Only 40% of patients considered alternative care before coming to the ED. Among patients who considered other care first, the most common reason for coming to the ER instead was that they thought their condition was very serious. In terms of severity, 69% (95% CI ±8.72%) of patients reported their condition as being a 4 or 5 (out of 5) on a Likert scale of self-description of severity. 35% (95% CI ±9.01%) believed their condition was much more severe than others in the same waiting room. Finally, 44% (95% CI ±9.40%) of patients believed that those with the most serious condition should be seen first.
**Conclusion**: In conclusion, our survey data has begun to offer some insight into the demographics and expectations of the patient population visiting the ER at Cayetano Heredia. The observation that only 19% of patients described their health as good or better may indicate some degree of chronic conditions that might require treatment in the ER periodically, and may reflect limited access to care in general. We did not record the actual conditions due to HIPAA regulations, but we met many patients with poorly controlled chronic conditions including diabetes and asthma.

Our results suggest that there are many repeat visits to the ED, and perhaps finding a way to reduce the return rate of patients may alleviate some of the overcrowding in this hospital as well as others. Additionally, our data on perceptions of severity suggest that many patients believe their condition is more serious than that of the other patients and that they should be seen first. Perhaps patient education about the severity of their own conditions would help patients cope better with their wait time. The fact that 68% of patients felt that they had an average or above relationship with their primary care provider suggests general satisfaction and trust in the healthcare system. Finally, since only 40% of patients considered alternative care before coming to the ER, patient education about when it is appropriate to choose the ER may further reduce overcrowding.

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Expatriate Physicians: A Qualitative Investigation of Experiences Practicing Medicine in Cambodia

Introduction and Background: With the expansion of global travel, spread of infectious disease, and rise in public health epidemics, global health is an increasingly pertinent area of study for medical students within the United States. [Drain, P.K, et al. 2007, Haq, C. et al. 2000] In 2009, approximately 25% of all medical students in the United States participated in an international training - a three-fold increase over the last decade. [Jeffrey, J. et al. 2011] With the dramatic rise in the pursuit of global medicine, opportunities to incorporate international medicine into the traditional medical school curriculum has been demonstrated nationwide and by the University of Rochester School of Medicine and Dentistry. In spite of the increase in education and opportunities to experience medicine hands-on in a global setting, little has been officially documented from the perspective of long-term practicing expatriate physicians in developing countries. One study of American physicians working in the Asia-Pacific Region has found that tax requirements, paying back medical school student loans, and visa and medical licensing can prove to be challenging while working overseas. [Elliot, V. 2009].

Cambodia is one of many developing countries that has attracted both seasoned physicians and medical students aspiring towards a career in global health. From the aftermath of the genocide and subsequent unrest to the current growth in development, the changing health needs has seen expatriate physicians’ roles in Cambodia shifting from that of providing emergency relief care to addressing long-term health needs, including infectious disease, vector-borne illness, and diseases associated with very low socioeconomic status. Many other developing countries have experienced, or are in the middle of, similar struggles relating to their tumultuous pasts, to which many expatriate physicians have also mobilized in hopes of making a difference. Furthermore, citizens of many of these countries are migrating to developed countries, which presents unique biopsychosocial considerations for which both physicians and medical students are hoping to prepare.

Objective: This study aimed to qualitatively examine the experiences of expatriate physicians working in Cambodia. Key areas of research include: training in global health, cross-cultural competency, work/life balance, and recommendations for students and clinicians interested in global health. Given the
exploratory nature of this study, the primary goal was to develop a broad understanding of the various aspects involving practicing medicine overseas. Furthermore, it was hypothesized that the insights gleaned from this study will offer a valuable contribution to an area of global health research that is currently lacking, inform the vision of the newly established Global Health pathway in the University of Rochester Medical School, and to better guide students’ passions in pursuing careers in global health.

Methods: In June and July of 2013, qualitative interviews with 15 expatriate physicians working in Cambodia were conducted in the capital city of Phnom Penh and four rural provinces. Recruitment for the study was based on the following criteria: physicians must have graduated from a medical school outside of Cambodia, must have worked in Cambodia in the field of medicine for at least one year, and best fit a representative sample of the expatriate physicians working in the country. Physicians were contacted by means of email, telephone, or in-person at their places of work. An information letter detailing their rights and involvement in the study was presented prior to each interview. A qualitative interview guide was developed based on considering professional issues related to working as a clinician overseas and was shaped by mentor and physician feedback. The average duration of interview was approximately two hours and interviews were recorded and analyzed for key themes.

Results and Conclusion: Results were separated according to the four key areas of research, with the recommendations from participants serving as concluding remarks:

Training in Global Health

Participants represented eight separate specialties and eight countries, with public health and tropical medicine representing the most common types of additional training. A thorough medical education background was frequently cited to be sufficient to work in Cambodia, but participants often had to stretch outside one’s specialty due to frequent exposure to novel scenarios, which involved “learning on the job” by frequently using resources such as the internet for filling knowledge gaps over time. Most started work in global health through affiliations with non-governmental organizations when they arrived, then some set up a private operation once they were established. Most kept licensure in their home countries; they reported that working in Cambodia does not require licensure, but practitioners did need a loosely defined, and financially incentivized, sponsorship with a local Cambodian physician.

Culture and Context

There were many cited cross-cultural differences that affect the work of expatriate physicians. Cambodian patients often expected pills or IVs for their problems, and were not accustomed to asking the doctor
questions due to the strong hierarchical nature of the doctor-patient relationship. For expatriate doctors, there was often favorable discrimination from both patients and Khmer doctors alike. Often times Cambodian patients consulted traditional healers or monks first, visited a pharmacy to self-medicate, visited several Khmer doctors, and finally visited expat doctors. Additionally, it was reported that the Buddhist outlook of karma sometimes influenced patients’ beliefs on illness, such that they “deserved” the illness and ought not treat it as it is their predetermined fate.

The most commonly cited contribution made by expatriate physicians was at a micro-level by treating patients at a low cost with good care who had previously seen many bad doctors. Those involved with capacity building often felt great frustration and were overwhelmed with working within a corrupt and poorly trained system, but often felt impactful regarding their role in shaping the country’s future at a macro-level.

Work/Life Balance

A majority of physicians interviewed reported having a work-day that began at 7:30 AM and finished between 4 PM and 6 PM with a 2 hour lunch break. Several clinicians reported seeing between 25-30 patients each day, but a majority placed staunch limitations on their working hours and patient volume and refrained from advertising their clinic due to high patient demand. Most clinicians saw an equal mixture of Cambodian and expatriate/tourist patients, and sliding scale fees were implemented in many clinics and hospitals appropriate for the means of the patient. Physicians working in the public health sector spent on average 8 hours at the office each day, attending to administrative needs, training preparations, and policy meetings. Physicians reported that the most fulfilling elements of their lives were working with patients and watching their health improve, which was combined with a meaningful life outside of work through nurturing their relationships with family and friends in Cambodia, and immersing themselves in their communities.

Recommendations for Students

Interviewees most frequently offered the following advice for future global health physicians:

Pursue as broad of a medical education as possible, with a focus on primary care and an understanding of public health. Specialties particularly recommended (in order of frequency) were: Family Medicine, Pediatrics, Internal Medicine, General Surgery, and Psychiatry.

Go overseas as much as possible during medical school, residency, and fellowship training. Learn tropical medicine through an intensive course or through self-study and experiences on the job. Visit a country before you make a commitment to work there. Take the time necessary to learn about their history of medicine, political history, and language as those will inevitably shape the current culture of medicine and will allow a better connection with patients.
Avoid the mentality that you are working to “save the world”. Set boundaries on your work to maintain your work-life balance. Take advantage of the lessons that international medicine affords: the importance of being flexible, doing a lot with very few resources, and the opportunity to learn that education goes both ways.
Maintain strong relationships with partners, family, and friends to help make living in a foreign context easier and more enjoyable.

References:


Food Insecurity in Rural Malawi

Introduction
Food insecurity is a significant issue in many countries in Sub-Saharan Africa. Access to adequate nutrition and calories is often affected by farming issues such as unpredictable rainfall, the limited income of subsistence farmers, and the seasonality of staple foods. Another factor contributing to food insecurity has been the introduction of new varieties of staple foods with the goal of increasing yields. This can result in short term gains, but farmers often become increasingly reliant on these foods in the long term. This causes them to become more vulnerable to market forces surrounding these crops (1). It can also lead to increased economic stress through the purchase of inputs such as fertilizer that are often necessary to grow these new crop varieties (3). Unintended consequences of development projects have also played a role. For example, mechanized farming efforts lead to increased costs for fuel and spare parts, and they can deplete the soil of needed nutrients (3).

Food insecurity is a growing problem in Malawi. The World Food Programme reports that the number of food insecure people in Malawi jumped from .2 million to 1.6 million from 2011 to 2012. This study also reports that one in four households nationally have inadequate food consumption to maintain a healthy and active life (4). Our study focused on food insecurity in the Ntcheu district of Southwest Malawi with the purpose of gaining a better understanding of these issues.

Objective
The main goal of our study was to assess how people perceived food insecurity on both an individual level and a community level. Another goal was to assess seasonal changes in food availability.

Background
Malawi is a landlocked country in Southeastern Africa. It is one of the world’s most densely populated nations. Agriculture comprises the majority of the economy with 80% of the population living in rural areas (2). The population is estimated to be 15 million. Approximately half the population lives in poverty, and nearly half of the population is energy deficient. Previous studies have shown that food insecurity in Malawi is often a direct effect of climate factors such as inadequate rainfall or flooding and that there is a seasonal nature to food insecurity in the country (4). Our goal for this project was to add to this existing body of knowledge by focusing on perceptions of individual and community-wide food insecurity, analyzing the seasonal availability of food, and studying strategies that people employ to deal with food insecurity.
Methods
The study was conducted between June and July of 2013 in the Ntcheu District of Southwest Malawi, where the primary language is Chichewa. A one-page survey was utilized which included questions regarding food insecurity. The survey was translated from English to Chichewa by a translator on-site in Malawi. It was then back-translated from Chichewa to English by a different translator to make sure that the questions had been worded appropriately. The first section of the survey involved asking about demographics. The next section consisted of asking people ten questions on their perceptions of food insecurity in their individual households. Participants were then asked the same ten food insecurity questions, but this time the questions pertained to their perceptions of food insecurity in households within their communities as a whole. Another section of the survey consisted of questions on seasonal changes in the availability of food. Questions from the survey were developed from literature on food insecurity. Pilot interviews were conducted with several community members who were not in the sample population before the survey was finalized.

Fifty two individuals were selected from different villages in the Ntcheu district. Criteria for inclusion consisted of being head of household and being eighteen years of age or older. These individuals were drawn from a sample of ninety people that had been formed previously. They were selected by convenience sampling in that they were at their homes and available to be interviewed. Interviews took place at participants’ houses where privacy was protected. The survey was administered after the purpose of the study was explained and consent was obtained verbally by an interpreter. The survey was administered orally with the help of the interpreter, and answers were handwritten by the interviewers.

Results
Results are currently pending. Current analysis suggests that individual households perceive themselves as less food insecure than their surrounding community during April, May, and June. Households surveyed also reported that food insecurity is increased during the months of October through March.

Conclusion
The definition of food in Malawi culture is very complicated and therefore food insecurity cannot be adequately assessed through generalized food insecurity surveys. In order to accurately assess a community's access to nutrition and calories, it is critical to have a knowledge of both the culture's definition of food as well as the local methods of obtaining food (farming, purchasing). Further study is needed in this region of Malawi to obtain a complete annual assessment of food insecurity.

References
Consequences of malnutrition on norovirus susceptibility in children of a peri-urban Peruvian community

Introduction: Globally, diarrheal diseases cause 1.2 million deaths per year with the highest numbers recorded in developing countries. A number of viruses contribute to diarrheal diseases, including norovirus, a virus belonging to the calicivirus family. Norovirus accounts for approximately 200,000 deaths per year in developing countries and is considered the leading cause of diarrhea worldwide. The high morbidity and mortality associated with norovirus likely persists due to the frequency with which norovirus is contracted and spread in developing countries, and the lack of adequate health care available in these impoverished locales. Additionally, norovirus transmission risk factors including environmental contamination and children’s nutritional status are poorly understood in developing countries, highlighting the need for additional research into these areas.

Objective: Our project will explore malnutrition as a risk factor for norovirus infection in a cohort of peri-urban Peruvian children under two years of age. We hypothesize that those children determined to be more severely malnourished are more susceptible to NV infections compared to children who are less malnourished or are considered to be adequately nourished. In addition, we further suspect that malnourished children who contract a NV infection are more likely to experience associated diarrhea compared to appropriately nourished children.

Background: Norovirus is predominantly spread via contamination of food or water with fecal material, although it may be transferred as an aerosol or through vomit. Clinical manifestations may include diarrhea, nausea, vomiting, and low-grade fever. The virus is capable of surviving outside of a host for extended periods and remains resistant to heating, freezing, and detergents. In addition, norovirus transmission has been noted to occur for a median of twenty-eight days following infection even after symptoms have subsided. This asymptomatic spreading of the disease, coupled with its low dose requirement for infection, accounts for the high degree of secondary infection and explains the clustering of the disease evident within families.

Malnutrition has been shown to have a depressing effect on the immune system leading to increased morbidity and mortality. For instance, vitamin A deficiency affects epithelial membranes, and thus, can increase the incidence of respiratory tract infections and diarrhea. Research by Checkley (2002) found that Peruvian children who were malnourished exhibited increased incidence and severity of diarrheal episodes. However, further research into the effect of malnutrition on norovirus susceptibility and subsequent diarrhea has yet to be conducted.
This increased incidence of diarrheal episodes in developing countries is particularly worrisome due to the long-term effects on children’s development. A study by Checkley (2003) found that Peruvian newborns less than six months of age with frequent diarrheal episodes often experience permanent growth stunting. Multiple studies have reaffirmed that growth during infancy is critical for optimal growth during adolescence and is a crucial determinant of adult size.

**Methods:** Forty-five children were selected under the age of two years old who were then further partitioned three participant groups: 1) fifteen randomly selected children who do not contract norovirus; 2) fifteen randomly selected children who contract norovirus and associated diarrhea; 3) fifteen randomly selected children who contract norovirus without associated diarrhea. A symptom history along with biweekly stool samples will be collected from these participants. Concomitantly, they will be evaluated daily for diarrhea. Stool samples were collected on the day any diarrheal episode was detected. A “diarrhea episode” was defined as a 24-hour period during which the child was reported to have three or more liquid or semi-liquid stools. Each stool sample was tested by real-time RT-PCR to detect the presence or absence of norovirus antigen. Nutrition status was assessed using WHO malnutrition guidelines and the requisite anthropometric data collected from the participants. Statistical software was utilized to determine the significance between the three participant groups in regards to frequency of diarrheal episodes and positive norovirus infections in nourished/malnourished individuals.

**Results:** Data regarding norovirus susceptibility in our cohort of peri-urban Peruvian children under the age of two years old will be further analyzed and statistical analysis will be applied to determine significance. A t-test will be performed between each cohort to determine if statistical significance exists with regards to the frequency of norovirus infection and nutrition status.

**Conclusion:** Based upon initial analysis of the data, children who have been found to be more severely malnourished are more susceptible to NV infections compared to children who are less malnourished or are considered to be adequately nourished. In addition, malnourished children who contract a NV infection are more likely to experience associated diarrhea compared to those appropriately nourished children. This data coincides with the work of Checkley et. al. in which he similarly found that malnutrition contributes to increased diarrheal frequency. This research advocates for a more holistic approach to treating infectious diseases in developing countries. Socioeconomic factors may play a vital role in how the body responds to infection in addition to physiological processes.

**References:**


TB Drug Importation into Viet Nam

Introduction/Background:
In a high burden tuberculosis country like Vietnam, capturing the true incidence and prevalence rates in the country is crucial to understanding the changing face and impending challenges posed by the disease. In lieu of a reliable vital registration and disease monitoring system, proxies need to be used, like the market demand for TB drugs outside of the National Tuberculosis Programme (NTP). With multi-drug resistant (MDR) TB, and extensively drug resistant (XDR) TB increasingly jeopardizing TB control efforts, characterizing the availability of TB drug outside of the closely monitored and quality assured program becomes more important as well. In 2011, the notification rates in the country hovered at 100,000 new cases, but the estimated incidence that year was 130,000. The gap between incidence and notification rates indicates that many patients are unaccounted for in the current national program. This study looks at drug importation data from the Drug Administration of Vietnam (DAV) and analyzes the imported TB drugs over the course of 2008 to 2010.

While major strides have been made in Tuberculosis control in Viet Nam, with the incidence declining at about 2.6% per year, in order to reach the STOP TB Partnership goal of eliminating the disease by 2050, incidence needs to decrease almost seven times the current rate. In order to assess the success of TB control programs, reliable data on incidence and prevalence rates needs to be regularly obtained. The incidence rate quoted above was found in a review of the National TB Programme data done by the WHO, and “included an assessment of the surveillance and vital registration systems using a WHO checklist of TB surveillance standards and benchmarks and a reassessment of trends in estimates of TB disease.” The National Tuberculosis Programme (NTP) is a government-run organization under the Ministry of Health, which is responsible for the identification and treatment of TB cases in Viet Nam; however, the current system for reporting cases of TB remains underdeveloped. Data reliability is a constant concern in a country lacking a robust health infrastructure. As assessed in 2012, the prevalence rate of TB was 323 per 100,000 in 2011, but reassessment done in 2013 indicated an incidence rate of 188 per 100,000 (Global Tuberculosis Report, WHO 2012).

Until a reliable notification system exists in Viet Nam, the data can be bolstered by other indirect measurements, for example the amount of TB drugs imported into the country. In 2011 around 100,000 patients were notified to the National Tuberculosis Programme, of these patients, over 90% received appropriate, evidence based care, using the DOTS framework. However, 130,000 new cases were estimated to have arisen that year. This 30,000 patient gap is not insignificant, and this study attempts to shed light on the availability of TB drugs to this population. The National TB Programme uses only domestic products; therefore imported drugs reflect demand for TB drugs outside of what is being used to
treat tuberculosis cases through the NTP. The demand for TB drugs reflects a demand to treat those 30,000 who are not notified each year and/or the use of these drugs outside of their medical indications. While we cannot distinguish between the two in this study, both pose problems in TB control. The WHO advises, and the Vietnamese government endorses the recommendation that all TB cases should be reported to the NTP in order to maintain an accurate account of incidence and prevalence rates in the country and for better control of the disease. Unfortunately many health providers and centers do not report confirmed cases; therefore the true incidence rates do not mirror the notification rates in the country. In addition, TB drugs can be bought without a prescription in Vietnamese pharmacies, and therefore, patients may acquire antibiotics without a physician order, and physicians prescribe TB drugs outside of approved clinical purposes. This practice allows drugs to be used for purposes outside of their medical indications. Characterizing the market trends in the TB market can give better insight on the availability and demand for TB drugs. In order to identify trends in the TB drug market, drug importation data was analyzed over the course of 2008 to 2010.

Hypothesis/Objectives:
There exists a market for TB drugs outside of what is needed for the conventional TB management system in Vietnam. This study attempts to characterize the market trends for imported TB drugs.

Methods:
Raw data was obtained from the Drug Administration of Vietnam (DAV). The data contained information regarding the drugs that have been imported into Vietnam during the period of 2008-2010. From this vast database, drugs used for the treatment of TB were separated into a different spreadsheet. For first line treatment of TB, the following drugs were included: pyrazinamide (Z), ethambutol (E), isoniazid (H), and rifampicin (R). For second line treatment of TB, the following were included: kanamycin (Km), ethambutol (E), pyrazinamide (Z), prothionamide (Pto), levofloxacin (Lfx), and cycloserine (Cs). The amount that was imported was extracted, in terms of milligrams per dose, number of doses per unit, and number of units per shipment.

For first line treatment of tuberculosis, conventional treatment dosing for a person 40-55kg was used to calculate the number of people who would be able to be treated with available fixed dose combination (FDC) drugs. This included 2 months of RHZE and 4 months of RH, or 2 months of RHZ+E and 4 months of RH, or 2 months of RHE+Z, along with 4 months of RH.

For second line treatment of drug resistant tuberculosis, conventional treatment regimen used in 90% of multi-drug resistant (MDR) TB was used to determine the number of MDR-TB cases that would be able to be treated. Finally, the price of TB treatment was calculated for first and second line treatment.

Results:
Using first line fixed dose combination therapy, an average of 12,000 people with TB could be treated using imported drugs. The number of patients able to be treated with second line TB drugs, usually reserved for drug resistant TB, is on the rise, increasing nearly six fold from 2008 to 2010, with enough drugs to treat 100 patients in 2008 to nearly 600 patients in 2010. Cost of first line drugs is on the rise in the private sector and may reflect an increase demand to TB drugs to treat tuberculosis.
Conclusion/Recommendations:
These results are alarming and public policy needs to be refocused on regulating the tuberculosis drug market and increase public-public and public-private partnerships in order to gain a better handle on this deadly disease.

The fixed dose combination drugs (RHZ, RHE, and RHZE) are not indicated for treatment of diseases outside of TB. Therefore, since the government of Viet Nam has control over the drugs that are imported into Viet Nam, and they endorse the goals of the National TB Programme, stricter controls over this importation need to be enforced. Immediately revoking the allowance of these drugs into the country is probably unwise, since there are potentially patients who are being treated effectively with TB drugs. However, in order to ensure that they are being prescribed and used in appropriate and effective manners, pharmacies to which these drugs go need to be identified, and be encouraged to participate in public-private/ public-public partnerships. Treatment for TB is a long road, and too often patients default on treatment after a few weeks because they feel better. Direct observational therapy (DOT) has been proven effective in facilitating adherence to treatment and therefore cure of the disease. With private pharmacies and physicians distributing the drugs, there is no way of monitoring the adherence of patients on TB drugs. With a demand for TB drugs outside of the NTP Programme, the monitoring and evaluation of the disease and programs implemented to eliminate tuberculosis is compromised if cases are not reported and treated with evidence-based medicine.

The cost of a treatment is rising, using the imported price of the drugs, cost ranges from a low of 42.30 USD in 2008 for the 2RHZE/4RH treatment, to a high of 76.90 USD for the same treatment in 2010. The regimen reflects the majority of the FDCs that are imported into Vietnam for a full first line treatment of a new case of tuberculosis. There was a slight decrease in the supply of fixed dose RHZE importation in 2009 to 2010. If price of drugs reflects a growing demand but dwindling supply of TB drugs, then there needs to be a redoubling of efforts to ensure that quality assured TB drugs are widely available in NTP clinics and associated pharmacies. Though there may be other factors that are driving up the price, an increased demand may mean an increase in TB.

The amount of TB drugs that are imported reflects a market demand for these drugs and therefore trends that happen in the market may reflect trends in TB incidence in the country or misuse of these drugs for other purposes. In either case, this reflects a significant obstacle in the management of tuberculosis in the country. If these drugs are being used inappropriately for other illnesses outside of TB, the chance of MDR-TB emerging increases as well.

The availability of the drugs in private markets may actually be a boon, and serve as a reserve in the chance TB drugs stock outs, like what is currently happening in India. However, collaboration between public-public and public-private partnerships needs to be initiated for the benefits to be realized, otherwise, the repercussions of availability of TB drugs outside of a regulated and monitored program may hinder TB control efforts in the country.
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http://www.nebi.nlm.nih.gov/pmc/articles/PMC3278873/
Clinical Improvement with Reconstructive Surgery in Patients with Advanced Spinal Disease in Ethiopia

**Introduction:** Spinal disease due to congenital spine deformity as well as due secondary tuberculosis is a common and serious problem in Ethiopia. These spinal deformities can result in severe vertebral kyphoscoliosis with respiratory insufficiency and neurological, musculoskeletal, and psychological deficits. Dr. Richard Hodes in Addis Ababa, Ethiopia has arranged for corrective spinal surgery in nearly two-hundred children and young adults whom he has seen with end-stage spinal disease. An example of the spinal deformity seen in one patient is presented in Figure 1. During the summer of 2013, two of us (HN and MB) conducted an evaluation on 36 patients. We report the findings from a questionnaire that we helped develop and then applied to the patients to evaluate their functional and psychological status from before to after surgery. At an average cost of $18,000 per patient, Dr. Hodes was able to provide transportation and corrective surgery including pre- and post-operative care. Those patients with spinal deformity secondary to tuberculosis were medically treated prior to the surgery.

**Objective:** The purpose of this survey was to administer a questionnaire developed last year to postoperative patients and their families to assess the quality of life of individuals who have undergone
corrective spinal surgery for kyphoscoliosis. The survey explores the physical, social, and emotional effects of the spinal surgery.

**Background:** The World Health Organization estimates 200,000 existing cases of TB in Ethiopia in 2011, with a prevalence rate of 237 per 100,000 population. Although the lungs are the major sites of damage caused by tuberculosis, the spinal column can also be affected. TB with involvement of the spine is seen at much higher rates in Ethiopia, than it is worldwide for unknown reasons. If left untreated, it can result in severe vertebral scoliosis. In Ethiopia, the prevalence and severity of congenital scoliosis is also extremely high for unknown reasons.

**Methods:** We personally interviewed the patients and evaluated their response to the questionnaire regarding general health, activity, pain, respiration, and emotional state before and at 6 months or more after surgery. The recorded data were entered into an Excel file and analyzed using routine statistical tests. The study was approved by the URMC Research Subjects Review Board.

**Results:** The frequency distribution of the age at spinal surgery is presented in Figure 3. The average age at surgery was 14.0 years ± 4.4. A summary of the responses to 7 of the 28 questions used when interviewing the 38 patients regarding their health and functional status is presented in Table 1. In brief, the subjects reported a good to excellent improvement with minimal residual symptoms post-op when compared to their pre-op status when they were severely physically and emotionally incapacitated.

Figure 3. Frequency distribution at age of spinal surgery.
Table 1. Health Status in 38 patients with spinal surgery.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean Value ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-perception of health as compared to before surgery</td>
<td>1.26 ±0.50</td>
</tr>
<tr>
<td>Change in the shape of your backbone after surgery</td>
<td>1.34 ±0.48</td>
</tr>
<tr>
<td>Ability to bath or dress self</td>
<td>1.29±0.69</td>
</tr>
<tr>
<td>Shortness of breath after surgery</td>
<td>1.08 ±0.27</td>
</tr>
<tr>
<td>Pain interference with daily activities</td>
<td>1.3 ±0.61</td>
</tr>
<tr>
<td>Amount of bullying/teasing experienced</td>
<td>1.24 ±0.49</td>
</tr>
<tr>
<td>Ability to sleep without back discomfort</td>
<td>1.3 ±0.61</td>
</tr>
</tbody>
</table>

Scale: 1.0 = good to excellent improvement with minimal symptoms; 2.0 = moderate improvement with significant residual symptoms; and 3.0 = minimal or no improvement

**Conclusion:** This study shows that physicians can improve the human condition of children and young adults with medical and surgical therapy in patients living with end-stage spinal deformity in a third-world country.

**References**
Introduction: Schizophrenia remission is positively associated with factors such as strong social support (Albert et al., 2011) but is hindered by negative societal mental illness attitudes, particularly if these attitudes are internalized by those who have schizophrenia (Yanos et al., 2008). Common negative attitudes include beliefs that people who have severe mental illness are dangerous and do not belong amongst others (Hayward & Bright, 1997). Since both social support and mental illness attitudes are associated with schizophrenia recovery, studying these factors in different cultures would give insight into how the environment influences schizophrenia outcomes. Research has found that Greek populations tend to have more negative attitudes about serious mental illnesses than other Western cultures (Papadopoulos et al., 2012). In particular, Greek rural populations were found to have more negative schizophrenia attitudes than Greek urban populations in a quantitative study conducted by Economou et al. (2009). Interviews consisting of open-ended questions could provide more in-depth information on schizophrenia perception in rural Greece as well as reveal cultural elements that play a role in illness attitudes.

Objective: The goal of this exploratory study was to utilize structured interviews to learn more about mental illness, particularly schizophrenia, attitudes in rural Greek villages.

Methods: In-depth interviews were conducted with 16 participants (10 females, 6 males) from two villages in Laconia, Greece. Open-ended questions were asked about schizophrenia and the Greek term ψυχοπαθής (the direct translation of this term is "psychopath"). Clinically, ψυχοπαθής in Greece does refer to someone who has antisocial personality disorder, but in conversation the term can be used to refer to psychosis or severe mental illness. Participants were presented with a schizophrenia medical scenario ("An individual who has schizophrenia lives in your neighborhood"), and were asked questions in regards to this scenario. The interviews were transcribed and subjected to inductive content analysis.

Results: Open-Ended Questions: Participants had diverse views on what the terms ψυχοπαθής and schizophrenia mean. While some participants had a view of ψυχοπαθής that is consistent with antisocial personality disorder, other participants stated that ψυχοπαθής refers to anyone who has a mental illness. Some participants stated that the term ψυχοπαθής refers to individuals who have more serious mental illnesses
or "craziness." In regards to the term schizophrenia, some participants stated that schizophrenia referred to an innate tendency to commit evil, particularly murder and suicide. Other participants referred to schizophrenia as being a "split personality" or the existence of a "bad self." Participants also described schizophrenia as the crossing of a mental line where a person socially withdraws and enters his own diseased world.

When asked about what causes schizophrenia, participant responses fell into three categories: (1) environmental factors, (2) biological/genetic factors, (3) or a combination of environmental and biological factors (stress-diathesis). Environmental factors participants emphasized as being causes included childhood trauma, relationship troubles, and the Greek financial crisis. Overall, participants stated that the best way to help individuals who have schizophrenia is through medical treatment. Some participants stated that close monitoring and institutionalization should also be part of the treatment, particularly if an individual is dangerous. While some participants stated that, with medical treatment, an individual who has schizophrenia should have a normal standing in society, others said that regardless of whether someone is on medication, individuals who have schizophrenia should not have the same opportunity to hold high responsibility positions in society, such as educating children, because of the danger they pose.

Schizophrenia Medical Scenario: Overall, participants expressed fear about living close to someone who had schizophrenia but said they would feel better if this individual lived together with family and/or had good behavior. While some participants said they would socialize with the individual and try not to ostracize him from the community, others said they would avoid contact with him. Some participants said they would be willing to obtain medical help for the individual if they sensed he was losing control or becoming dangerous. Participants had diverse views about what the village should do in response to this situation. Some participants stated that the village should be supportive and work to include the individual in the community, while other participants stated that village would be overstepping if it intervened because this matter is a family matter. When asked how they would feel if a family member of theirs married this individual, most stated they would be opposed to this marriage, would express their views to their relative, but ultimately, it would be the relative's choice whether to stay in the relationship.

Conclusion: While most participants were not comfortable with living close to someone who has schizophrenia, this study helped to reveal the complexity and diversity of opinions that exist within rural Greek communities. Participants had differing definitions of both schizophrenia and ψυχοπαθής and also had different opinions about the causes of schizophrenia and how mental illness fits into society.

Reference:
Maternal Characteristics as Determinants of Breastfeeding Practices

**Introduction:** Breast milk is proven to confer a wide range of benefits to infants, including decreased rates of infection, increased growth, and lower blood pressure and cholesterol.\(^1\) The World Health Organization (WHO) recommends exclusive breastfeeding for six months and continued breastfeeding with complementary foods for at least two years.\(^2\) As knowledge about the benefits of breastfeeding has grown, a number of Latin American countries have shown an increase in breastfeeding duration. Data shows that between 1986 and 2004, breastfeeding duration increased by 9.7 months among urban Peruvian women. However, the same data surprisingly shows a decrease of 0.6 months in rural Peruvian communities. This disparity is troubling considering that infants born to rural women have greater risks of morbidity and mortality when not breastfed.\(^3\) Therefore, while it is important to promote the practice of breastfeeding for all women, additional efforts are required to specifically target the rural population of Peru.

**Objective:** The purpose of this study was to both quantitatively and qualitatively assess the maternal characteristics and beliefs that determine the breastfeeding practices of women living in Yantaló, Peru. Specifically, we hoped to answer the following questions: (1) What maternal sociodemographic characteristics have a significant impact on breastfeeding duration? (2) Are there any prevailing beliefs held by women that may influence their decision to breastfeed? (3) What types of resources are available to help women breastfeed?

**Background:** Yantaló is an underserved, rural community in the San Martín region of the Peruvian Amazon with “very little access to health care and the highest infant mortality rate in the country.”\(^4\) Additionally, Yantaló has a high rate of dietary deficiencies and infectious diseases among young children, which lead to stunted growth in late infancy and toddlerhood.\(^5\) Although a government clinic exists in Yantaló, its residents must travel to hospitals in the nearest city of Moyobamba to fully address their health needs. This task often proves challenging due to transportation limitations.\(^6\)
Currently, the Yantaló Clinic and Diagnostic Center is being constructed with the goal of giving everyone in the community access to comprehensive care.\textsuperscript{7} In particular, this clinic will focus on maternal and infant health. One area of interest concerns breastfeeding practices. Both the clinic in Yantaló and hospitals in Moyobamba promote breastfeeding through regular prenatal and postnatal checkups, during which women are given advice on breastfeeding, regarding physical technique, hygiene, frequency, duration and potential problems (Yantaló Obstetrician, personal communication, June 25, 2013). However, the effectiveness of these methods in promoting breastfeeding by women in Yantaló is not documented. Such information would prove helpful in guiding the new clinic’s efforts at enhancing breastfeeding practices in this community.

**Methods:** Surveys were administered in the Spanish language to 100 women in Yantaló who were between 12 and 50 years of age and had had at least one live birth. For women who were unable to read and write effectively, the survey was conducted orally. A map of the Yantaló community was referenced to determine how households would be selected for systematic sampling. The community was divided into geographical regions of similar housing density, and within each region, every other house was surveyed. The survey included both quantitative and qualitative data. Quantitative data was analyzed using Microsoft Excel and chi-square analysis. Qualitative data was coded and classified under common themes.

**Results:** Of the 100 women surveyed, the average age was 33 years and 83\% self-identified as married or cohabitating. The average age at first child birth was 19 years and the average number of births per woman was 3. Concerning breastfeeding practices, 98\% of participants reported having breastfed at some point, with the median duration of breastfeeding being between 12 and 18 months per child. With regard to their youngest child, 90\% of women stated having gone to prenatal checkups, and 72\% breastfed exclusively for the first 6 months.

Data collected on the women’s sociodemographic characteristics were analyzed with relation to whether they breastfed their youngest child exclusively for the first 6 months. Although not statistically significant through chi-square analysis using SAS® software, a number of trends were observed. The survey data demonstrated that women who did not own farms were more likely to have breastfed exclusively for 6 months than farm owners (78\% vs. 67\%, p = 0.24). Women who were less than or equal to 34 years of age at the time of the survey were also more likely than older women (77\% vs. 63\%, p = 0.14). Further, the percentage for married or cohabitating women was greater than for single women (74\% vs. 60\%, p = 0.28). Finally, whether the youngest child was born at the clinic, home or hospital correlated with breastfeeding exclusivity (77\%, 71\% vs. 65\% respectively, p = 0.50). Other characteristics that were surveyed but showed no notable trends were the woman’s age at first birth, BMI, education level and total birth number.

With respect to women’s breastfeeding beliefs, an overwhelming majority of women cited the importance of breastfeeding for their child’s development and nutrition (66\%). Over a quarter of women expressed beliefs that they could make their children sick through poor milk quality induced by factors such as their own illness or consumption of acidic food (27\%). Interestingly, 24\% of women stated that breastfeeding conferred no effects on the mother.

Of the 20 women who reported needing help with breastfeeding in the past, 75\% sought assistance from family or neighbors and 25\% turned to a medical professional. The most common form of
support provided was instruction or demonstration (45%). When asked hypothetically who a woman having problems with breastfeeding might be able to seek help from, almost twice as many women responded with medical professional compared to family or neighbor. The most common forms of assistance woman desired from medical professionals were education or advice (38%), individualized medical treatment such as vitamins or medicines (30%) and free milk for their children (23%).

**Conclusion:** Nearly 100% of the women surveyed reported having breastfed for at least some duration of time. An overwhelming majority received prenatal care and almost three quarters met the WHO guideline concerning breastfeeding exclusivity for 6 months. Despite these positive statistics, there appear to be notable discrepancies between certain groups of women. Groups that could be specifically targeted include farm owners, single mothers, women older than age 34 and women who gave birth at home or at the hospital. Markedly, a majority of women were knowledgeable of benefits conferred on their children through breastfeeding. A sizable proportion, however, was unaware of any maternal health benefits or held false beliefs regarding their milk quality that may have hindered their breastfeeding. Consequently, breastfeeding promotion efforts may prove to be more successful by speaking to the positive effects of breastfeeding for mothers and dispelling these false beliefs.

When surveyed about resources, three times as many women cited receiving help from family or neighbors compared to health professionals. In contrast, twice as many women asserted that they thought a woman could seek help from health professionals compared to family or neighbors. Thus, a discrepancy exists between the resources that women believe are available and those that they actually access. As expressed by these women, clinics may be able to increase their ability to fulfill the needs of women experiencing difficulties with breastfeeding through the offering of advice, medical treatment and provisional milk. Overall, the women surveyed appeared to be quite receptive to intervention by medical professionals. As such, health clinics in Yantaló may find it useful to focus on incorporating the aforementioned recommendations into practice, although future studies with greater power are necessary to strengthen these suggestions.

**References:**
Comparative Study of Kawasaki Disease in Infants Younger than Six Months of Age with Infants/Children Older than Six Months of Age

Introduction & Objectives:
Kawasaki disease is an acute pediatric vasculitic disease. Currently the main diagnostic method for the disease rests on clinical findings developed by the American Heart Association. In this study, we compare the clinical manifestations, laboratory findings, and echocardiograph findings of children younger than 6 months with older children. We hypothesize that the two groups will exhibit different characteristics. These differences may allow a better understanding of the diagnosis of Kawasaki Disease.

Background:
Kawasaki disease (KD) is an acute pediatric vasculitic disease. It is the leading cause of acquired cardiovascular disease among children; however, the etiology of the disease remains unknown. KD is most common among Asian and Pacific Islander children but can affect children of all other ethnicities. According to the American Heart Association and the Centers for Disease Control and Prevention, KD diagnostic criteria include high fever lasting from four to five days and four or more of the following symptoms: (1) polymorphous rash, (2) nonexudative conjunctivitis, (3) red, swollen, and cracked lips, (4) erythroderma (swelling and rudeness) of the hands and feet, and (5) lymphadenitis. Identification and treatment of KD is difficult due to lack of definitive diagnostic markers beyond the clinical criteria noted. Some patients, particularly young infants, fail to meet all of the clinical criteria (Incomplete Kawasaki Disease) but are still at risk of developing coronary artery disease. IKD is defined as a high fever with fewer than 4 criteria, and additional coronary abnormality. The most serious complication of KD might lead to coronary artery lesions (CAL), including myocardial infarction, coronary artery fistula formation, coronary artery dilation, or coronary artery aneurysm. Because diagnosis is challenging, there is commonly a delay in diagnosing IKD. This results in further delay of intravenous immunoglobulin treatment. Such delay increases the probability of developing coronary artery abnormality.

Previous studies have shown a higher incidence of incomplete presentations of KD and coronary involvement in infants older than 6-12 months old, but information about KD in infants younger than 6 months is relatively limited. The purpose of this study is to investigate and compare the clinical and laboratory characteristics, including the echocardiogram of KD between infants younger than 6 months and those older than 6 months.
Methods:

Medical records of all infants diagnosed with KD at less than 6 months of age at Department of Pediatrics, Taipei Veterans General Hospital and National Yang-Ming University, Taipei, Taiwan, were retrospectively reviewed. An equal number of records of children with KD diagnosed at older than 6 months at the same institution was randomly selected for comparison. All records were from children hospitalized during 2003 to 2013. Data collection included the following: mean duration from disease onset to diagnosis, ratio of Incomplete to full-criteria Kawasaki Disease, clinical and laboratory characteristics upon admission, and presence of coronary artery dilatation, irregular surface and/or coronary artery perivascular brightness on echocardiography. All patients were treated with intravenous immunoglobulin (IVIG) and aspirin as per the standard of care. Statistical analysis was performed by independent t-test and chi-square test, as appropriate. The study was approved by the institutional review boards of both the University of Rochester and the National Yan-Ming University; as this was a retrospective study of de-identified medical records, informed consent was not required.

Results:

A total of twenty four infants less than 6 months with KD was found, and an equal number of charts were selected for older children. Twenty-four of the patients were male; eleven in the group under the age of six months and thirteen in the group above the age of six months.

The mean duration from the onset of disease to diagnosis was slightly longer in infants younger than six months than that of older infants/children: 9.3±8.11 days vs. 6.8±1.92 days, P=0.19. By the 10th day of illness, there was no significant difference between the age groups in the proportion of children achieving full diagnostic criteria. There were no significant differences in major clinical manifestations between the two groups.

Review of laboratory data did indicate significant differences in platelet count and alanine aminotransferase levels by age. The platelet count (x1000/mm³) in patients under the age of six months (5.2E5±1.4E5) is significantly higher than patients above the age of six months (3.6E5±1.3E5) (P=0.01). The alanine aminotransferase (units/L) in patients under the age of six months (35.83±29.05) is significantly lower than patients above the age of six months (64.47±43.73) (P=0.028). The difference in total WBC count by age was not significant; however, all children showed elevated WBC compared to age-adjusted normal ranges (Age<6months= 1.8E4±7.3E3; Age ≥ 6months= 1.6E4±5.5E2). No differences in hemoglobin, CRP, cholesterol, TG, LDL/HDL, and albumin concentrations among the 2 age groups were found (P>0.05).

For acute Kawasaki Disease, no significant differences in echocardiographic findings and coronary artery abnormalities were found between the two age groups (P>0.05).

Conclusion:

This retrospective analysis of Kawasaki Disease in the infants less than 6 months of age found no significant differences in clinical or baseline echocardiographic findings compared with infants/children greater than 6 months of age, although it time to diagnosis was generally longer in younger infants. However, platelet counts appeared to be greater, and ALT level concentrations lesser, in those <6 months of age. A larger patient series might show whether these findings could be applied to improve the early diagnosis of Kawasaki Disease in younger infants and thus prevent cardiac complications.

References:


The Effects of the Liberian Civil War on Liberian Communities and their Youth

Introduction: Liberia is a low income West African nation bordered to the west by Sierra Leone, to the east by Cote D’Ivoire, and to the north by Guinea. From 1989 to 2003, there was a civil war in Liberia which left in its wake more than 250,000 Liberians dead and about a third of the country’s population displaced. The fourteen-year civil war resulted in the decimation of educational, healthcare, and communication infrastructure. The consequences of Liberia’s civil war extend, however, beyond its effects on the country’s economic development. Liberians, and notably the youth of Liberia, have been psychologically traumatized by the war. The level of psychological trauma is reflected in the prevalence of post-traumatic stress disorder (PTSD) and depression within the country. Research indicates a prevalence rate of 44% for PTSD and 40% for depression. The war in Liberia has deeply affected all those who call Liberia home. Quoting the current president of Liberia, President Ellen Johnson Sirleaf, the crisis in Liberia “has equally victimized and energized every tribe and group.” Presently, it is known that Liberia faces challenges reintegrating displaced persons back into Liberian communities and noteworthy is the challenge of reintegrating youth combatants, a section of Liberia’s youth. This challenge of reintegration as well as the general effects of the Liberian civil war provide preliminary detail of the effects of the civil war on Liberian youth.

Objective: The objective of this study is to explore the impact of the 1989-2003 civil war on Liberian communities as well as explore ways in which these changes have affected Liberian youth. We sought to qualitatively assess the specific changes in community brought on by the Liberian Civil War as well as assess the effects of these changes on the mental health and general wellbeing of Liberian youth.

Methods: The analyses presented are based on the results of a cross-sectional survey conducted from 30th March 2009 to 30th April 2009 in Liberia. The research project was conducted by the Chester M. Pierce, MD Division of Global Psychiatry at the Massachusetts General Hospital in conjunction with the Liberian Ministry of Health and Social Welfare. Responding to the prompt, “We are interested in your thoughts
and general ideas about the mental health of young Liberians between the ages of 5 and 22” participants in this study identified ways in which the Liberian civil war had changed communities within Liberia and described the impact of these changes on the mental health of Liberian youth. There were 171 key informants from Liberia’s 15 counties and 95% percent of the informants were Liberian. Informants were affiliated with health, educational, and religious NGOs as well as government and judiciary sectors. Transcripts of participants’ responses to questions posed were coded for themes relating to Liberian youth and communities.

Results: It was evident from the narratives of the respondents that the war had very varied broad effects on communities in Liberia. Present day Liberian communities were characterized by a lack of institutional support. Aside from this, there appeared to be shifts in previously engrained belief systems. This was exemplified by an increasingly contentious relationship between the youth and older adults in communities. There was also a loss of positive role models within the communities, a loss of cultural identity, and a disengagement of the youth from these communities. In their narratives, participants identified three main factors (precipitated by the war) that resulted in the above described changes in Liberian communities. These factors were the fragmentation of families, the destruction of institutions and infrastructure, and the psychological trauma brought on by the experience of living through the Liberian Civil war. These changes in Liberian communities, which have essentially left the youth without community support, coupled with psychological trauma brought on by the war, have had profound effects on Liberia’s youth. Participants described increased substance abuse amongst the youth, as well as widespread physical and sexual violence. Liberian youth increasingly disregarded adult authority and participants also noted increased levels of adultification. Overall, it was very evident that the Liberian Civil War had broadly impacted Liberian communities and their youth.

Conclusion: The civil war in Liberia, by all accounts, has and continues to significantly impact the lives of Liberians. It is evident that these effects on Liberia’s communities continue to adversely affect the mental and general wellbeing of Liberian youth, adding to the effects of psychological trauma brought on by their experience of the Liberian Civil War. The youth of Liberia are the future of Liberia. It is therefore crucial, in the process of nation rebuilding, to address underlying factors in Liberia’s communities that continue to negatively affect the wellbeing of Liberian youth. It is also essential that community-based programs aimed at targeting high-risk behaviors exhibited by Liberia’s youth are implemented.

References


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A historical review of the chemical induction of seizures and its relevance to the question – seizure or current?

Introduction:
Electroconvulsive therapy (ECT) was developed as a treatment for severe psychoses in Italy by Ugo Cerletti and Lucio Bini in 1938, and it is still widely used today. However, there was also a rich history of convulsive therapy before ECT became the treatment of choice. Metrazol was an injectable convulsant drug that was in wide use in the years immediately preceding the advent of ECT, and flurothyl (Indoklon) was an inhalant convulsive drug that emerged in the late 1950s. Both drugs produced seizures that were as effective in the treatment of psychotic patients as ECT, and in a study done in 1960 the EEG changes during seizures induced by all three methods were found to be equivalent. However, Metrazol and flurothyl were both discarded in favor of ECT. Today, the mechanism of action of ECT remains unclear, and there is debate as to whether ECT is effective because of the seizures produced or the electric current itself. A look back at the older chemical induction methods provides valuable insight to this question.

Objective:
To determine the history of chemical means of inducing seizures; why these methods fell out of favor; and their relevance to the current debate of whether the effect of ECT lies behind the seizure itself or the electric current used to elicit the seizure.

Method:
A literature review of different means of inducing seizures

Results:
The first experiments in humans to elicit seizures for the purpose of treating severe psychosis were conducted in 1934 using camphor dissolved in oil. Patients who consistently had seizures with this drug showed dramatic improvement, and it was hypothesized at this point that the seizure itself, not the chemical used, was responsible for improvement. Metrazol was an injectable drug that was found to be much more effective in reliably producing seizures, and this became the treatment of choice. The main complaint with this drug was a sense of intense fear that developed between the injection and onset of the seizure. Also, injections had to be given rapidly to give the greatest likelihood of producing a seizure, and this could lead to sclerosis of veins. When ECT arrived in 1938, it easily replaced Metrazol because seizure onset was immediate with the use of electrical stimuli, eliminating fearful reactions in patients, and the use of electricity was technically much simpler than intravenous injection. We lack randomized control trials comparing Metrazol and ECT, but in studies employing both methods they were regarded as equivalent in terms of therapeutic efficacy.
Flurothyl is an inhalant drug that has both anesthetic and convulsive properties. It was discovered in 1957 and in the 1960s was investigated by several clinicians as a possible alternative to ECT. It was shown to be extremely safe, and it had an advantage over Metrazol of a self-limiting dosing system – when a convulsive threshold of the drug was achieved, seizure onset was accompanied by a brief period of apnea. This prevented overdose and possible late convulsions. Randomized control trials found flurothyl convulsive therapy to be as effective as ECT, and by some accounts it produced less postictal confusion and memory loss. However, flurothyl was abandoned for use in psychiatric patients after the early 1970s. This was partly because it was more expensive than ECT and it was viewed as more cumbersome technically than ECT. The flurothyl gas also left treatment rooms with an ether-like odor. This was often disconcerting to treatment personnel after watching patients convulse after a few breaths of the gas, although such low concentrations in ambient air were never shown to cause any ill effects.

Conclusion:

Fears of electric shock keep many patients from accepting ECT, and because the seizure itself is the critical component of convulsive therapy, a look back at older chemical methods of producing seizures is warranted. Several technical issues would remain if Metrazol was to come back into use today, but flurothyl may be a more promising option. Because anesthesiologists are required to be present for ECT treatments, the use of an inhalant drug would not pose any additional difficulties for administration of treatments. Also, the principal objection to ECT is that it causes memory loss, and while more clinical trials would be needed to definitively conclude that flurothyl causes less memory loss than ECT, based on reports from older studies this may be the case. Finally, flurothyl may be viewed by patients as a more benign treatment option than electric shock, and may make convulsive therapy possible in patients who would have otherwise refused it.

References:


The Art and Science of Clinical Ethical Consultation

Introduction: Clinical ethics consultation became a widely spread service in U.S. hospitals in the late seventies as a response to several major events that occurred including the legal case of Karen Ann Quinlan and the President’s Commission report. The primary mission of this service has always been to review and consult in cases that raised ethical issues for health care team members, patients, and their visitors. Medical students and physicians are trained answer seekers. But clinical ethics consultations are complex, emotionally charged, and variable. The different needs, biases, and understandings of the parties involved in individual cases can lead to diverse outcomes. Numerous health care team members are participating in the clinical ethics consultation process and they each come from different training backgrounds. Only 5% of the people doing ethics consultation in the U.S. have done a fellowship or graduate program in bioethics and a mere 41% have formal, direct supervision by an experienced member of their respective consultation service. The American Society for Bioethics and Humanities describes the current “state of affairs” for clinical ethics consultation as being absent practitioners trained and educated in ethics consultation. This is made more problematic by the fact that there is a “lack of educational and training programs specifically relevant to ethics consultation.”

Objective: With the aid of Dr. Rich and Dr. Shaw the goal of this project was to take advantage of the ASBH task force’s recommendation and explore via a directed self-education program the clinical consult process at the UC Davis academic medical center. The approach would rely on two pieces: a review of the literature that discusses the elements of a good bioethics consultation and a participatory experience with the UCDMC ethics consult service. The combination of both academic and clinical experience gave me the opportunity to put the knowledge I had acquired from the literature into action by analyzing and reviewing cases with the team.

Methods: The participatory observation of the ethics consultation service provided the greatest source of learning and skill development since I was permitted to observe consultant-patient interactions, ask questions of the primary care teams involved, discuss ethical issues with the ethics team members of the week, and assist them in writing up the final report. The academic element of researching through the available literature offered me insight into how the service at UCDMC differed from other places and what seemed to work for them and what did not. It also enabled me to formulate more advanced ethical questions in cases.
Results: As a result of my experience at UCDMC, I learned the value and purpose of having an ethics consult service at healthcare institutions first hand. They help care teams navigate challenging patient care situations, engender critical thinking about ethical issues that arise from caring for a diverse patient population, and facilitate the policy creating arm of their institution by providing well-thought out policy changes that address current issues in clinic. During my experience I was able to work with a variety of professionals involved in the ethics service and see the advantages and disadvantages of having a large committee composed of individuals with a vast range of experience in ethics consultation, diverse personal backgrounds, and different professional experiences. Having such a wide base of experience available to the group discussion helps explore the complex ethical issues encountered in a western society founded on pluralist values. However, it also spotlighted the issues currently challenging the professional practice of ethics consultation: the need for a common conceptual approach to cases, the different ability in people to identify their own biases, and the persistent need to make a common ethical language available to consultants.

Conclusion: The project helped me become familiar with the process of going through an ethics consultation and taught me the basic requirements for doing an excellent clinical ethics consultation. It is clear that there are two main challenges ethics consultation services face in the immediate future: the question of how to meaningfully educate their consultants and how to utilize the growing availability of e-records in health care institutions to guide their development as a service and justify their existence in a health care world that is becoming more and more cost-justifying by way of analytics rather than patient care. The ability to develop accessible and specific ethics consultation education and training programs requires an extensive amount of work and it is likely that this work cannot be done in as comprehensive a manner as is required when many of the services at large academic medical centers are composed of professionals who volunteer there time. Ultimately, the best method of training may require a program that utilizes both academic study and apprenticeship to experienced members of clinical ethics services.

References:


American Society for Bioethics and Humanities Clinical Ethics Task Force, Improving Competencies in Clinical Ethics Consultation, 2.
“What’s going on at home?”: The Role of the Medical History and Physical in Domestic Violence Interventions among Immigrant Populations

Introduction:
"Violence against women … is now widely recognized as a serious human rights abuse, and increasingly also as an important public health problem that concerns all sectors of society” (WHO 2005). Victims of domestic violence are physically, mentally, and emotionally strained. Despite its drastic costs to individuals and systems, the culturally censored nature of the discussion of domestic violence allows abuse to go unnoticed and unexplored by communities and institutions. WHO believes that “the health sector has unique potential to deal with violence against women, particularly through reproductive health services, which most women will access at some point in their lives” [1].

The identification of the health care sector as a point of access does not imply that health providers are adequately trained or competent in domestic violence interventions. The role of the health provider in such interventions is desired, but not defined. This role ambiguity contributes to confining health care to a much smaller point of access.

For immigrant populations this access is limited even further because of their marginal status, lack of language skills, and cultural taboos. Unfortunately, it is in these same populations that there is a great risk of domestic violence. Health providers are challenged to effectively intervene in the context of different cultural and life experiences.

Objective:
This study examines the health providers’ perceptions of the role of the health sector in domestic violence interventions among immigrant populations. The project aimed to understand the following:
● challenges that arise when addressing domestic violence in an immigrant community
● health providers’ perceived barriers that patients face when disclosing domestic violence
● opportunities which allow for expansion and optimization of health provider roles in identification and prevention of domestic violence

Methods:
Semi-structured in-depth interviews were conducted with 18 health care professionals from various arenas. Eight were part of a focus group conducted within the Family Medicine department of the University of Chicago. The interviews were all either conducted in person and audio recorded or by telephone. An interview guide was created beforehand to frame the discussions, but not to dictate their directions.

Interviews were analyzed qualitatively and coded for themes. This identification of themes was done periodically so that I was able to use further interviews to expand on views that came up frequently. This study received Institutional Review Board approval.

Results:
Themes of patient barriers, health provider challenges, and opportunities for change emerged from the interviews. Through these categories the health providers’ perception of the role of the health sector in domestic violence interventions among immigrants and the needs to increase effectiveness was clarified.

Patient Barriers:
The health providers offered their perceptions of the barriers that prevented a patient from disclosing a violent relationship. The main barriers identified were language/culture, inability to recognize violence as a problem, a fear of judgment or stigma, and the burden of prevention falling solely on the victim. Some physicians believed that a shared cultural or linguistic background established better rapport between patient and physician. Others found that this facilitator might also become a barrier for the patient if he/she believes his/her health provider would share information with their community.

Health Provider Challenges:
Health providers identified a lack of time, a lack of training, and a discomfort of knowing next steps after a patient discloses as the main challenges that they face when considering if they should screen a patient for domestic violence. Specifically within immigrant populations they noted the difficulties that come with language and cultural barriers. Additionally, because immigrant health care access is often limited by insurability many immigrants utilize the free health clinics available. One physician noted that these free clinics do not allow for a physician to build a long-term relationship with a patient. He emphasized this relationship is important to developing the safe environment in which patients can disclose domestic violence. Another physician noted that the over-all health system that includes social workers is over-burdened and has trouble responding to cases.

Opportunities/Solutions: Providers suggested various unique opportunities that allow them to participate in domestic violence interventions. Some of which include that patient encounters provide for easy access points in which providers can recognize unexplained symptoms. To some
health providers it seems easier for victims to access physicians instead of their own personal social workers.

**Role:**
Health providers determined their main responsibilities to be recognizing a problem, connecting patients to resources, and explaining the health implications of domestic violence.

**Needs:**
Through recognizing the barriers that prevent screening and the opportunities that allow it, physicians were also able to articulate needs to increase the frequency and effectiveness of interventions. Many reiterated the need for a training on effective and sensitive screening in immigrant populations, knowledge of local survivor and perpetrator resources and services, and an understanding of patient expectations. One physician suggested an improvement in graduate medical school education that emphasized communication and cultural competency skills. He noted that many students fail to realize the relevance of tools of communication when presented with other medical tools of higher technology.

**Reference:**
Racial disparities in psychiatric care at the Rochester State Hospital

**Introduction:** The impact of race in healthcare delivery is an important issue in the current practice of medicine in the United States. In order to address this disparity effectively, the role of race today must be considered in the broader context of a history of doctor-patient interactions spanning our collective cultural memory. Examination of primary historical sources, especially patient records, offers unmatched insight into these interactions. Critical analysis of such documents within the framework of contemporaneous historical events, cultural beliefs, and medical knowledge will contribute to our understanding of the role of race, in both the past and present, as a determinant of health – and, therefore, how the issue can successfully be addressed today.

**Objective:** The purpose of this study is to explore the differences between black and white patients residing at the Rochester State Hospital (RSH) during the 1940 US Census. The study aims to explore if there were differences in quantitative characteristics between the black and white patient populations at the time of the 1940 US Census.

**Background:** Western New York was a microcosm for demographic and medical institutional change in the first half of the twentieth century. As black Americans moved away from the rural South to escape violence, segregation, and economic stagnancy, many found their way to the burgeoning industrial city of Rochester. The so-called “Great Migration” came on the heels of a prior “Great Wave” of international immigration, which had brought tens of millions of Europeans to American cities. Urbanization noticeably impacted psychiatry in New York. The State Hospital system was established to deal with the growing number of people seeking psychiatric care; before the advent of anti-psychotics in the 1950s and the arrival of Medicare and Medicaid in 1963, such care generally meant institutionalization. RSH alone cared for over 3000 patients in 1940, including 67 documented as “Colored”. Earlier work has shown that immigrants were grossly overrepresented among those hospitalized at RSH from 1890-1919. Today, data suggest that black patients are more likely to end up in state hospitals than white patients (1). Additionally, black patients are more likely to receive diagnoses of schizophrenia than white patients (2,3). Some scholars argue that this difference originates in the Civil Rights era in conjunction with the stereotype of the “angry black man” (4). We hypothesize that, relative to white patients, the frequency of schizophrenia-related diagnoses will be greater among the black patients at RSH in 1940, and the black patients will be admitted at younger ages than white patients.

**Methods:** The case population was drawn from the 1940 US Census, and included all of the “Colored” persons identified as “inmates” of the “Rochester State Hospital” or “1600 South Avenue, Rochester
Sixty-seven “Colored” individuals were identified, with seven individuals excluded due to illegible names. Sixty individuals were then identified in the RSH case files, which reside at the Rochester Psychiatric Center. Fifty-nine controls were identified by obtaining the next white patient admitted to RSH after each case, as recorded in the Admissions Logs of the Rochester State Hospital, which reside at the University of Rochester Medical Center’s Edward G. Miner Library. Data recorded from each case and control included: race, sex, age at admission, place of birth, time in New York, marital status, diagnosis, committer, length of stay, and psychiatric treatments received.

Results: For age at admission, the race groups were statistically significantly different. The mean age at admission for white patients was 52, and the mean for black patients was 41 (Student’s t-test, p=0.001). When controlling for sex, the overall age difference disappeared for females ($\chi^2$, p=0.119) but remained significant for males ($\chi^2$, p=0.037). When analyzed by age groups, younger patients were more likely to be black and older patients were more likely to be white ($\chi^2$, p=0.004). Black patients were more likely than white patients to be diagnosed with thought disorders (Fisher test, p=0.009). When organic disorders were considered, the two groups were not different (Fisher contingency test, p=0.107). However, when all medical diagnoses were included (organic+alcoholism), black patients were less likely than white patients to have their psychiatric symptoms be ascribed to a medical cause (Fisher contingency test, p=0.030). Additionally, length of stay was significantly longer for black patients compared to white patients (Student’s t-test, p<0.001). The mean number of days was 7541 for black patients, versus 3882 for white patients. For all metrics of close social structure, including marital status, being committed by a relative, and likelihood of parole, there was no difference between black and white patients. Regarding birthplace of patients (NY State, US outside of NY state, and Foreign-born), there were significant differences among the black and white patient populations ($\chi^2$, p<0.001). White patients were largely born outside of the US, whereas black patients were mostly born in mid-Southern US states.

Conclusion: The data suggest that there were many differences in psychiatric care between black and white patients at RSH in the mid-20th century. Black patients tended to be admitted at younger ages than white patients; when controlling for sex, this difference disappeared for women but remained for men. Black patients also tended to be diagnosed disproportionately with thought disorders, whereas white patients tended to carry medical diagnoses. This suggests that the origins for today’s high rates of schizophrenia diagnoses among black Americans may have its origins even earlier than the Civil Rights era. Furthermore, black patients had lengths of stay that were almost twice as long as white patients. One interpretation of these data is that the black patients had some exposure – genetic, physiologic, or environmental – that made them more susceptible than the white patients to developing thought disorders, and their social structures caused them to be institutionalized earlier and longer. However, attributing such racial differences to genetics and physiology is somewhat implausible, if not impossible to test: genetic ancestry and historic – even modern – racial categories do not necessarily correlate. Furthermore, the environmental and social structural differences across the black and white patient groups are not significantly different – both groups are largely comprised of immigrants to New York, and had similar metrics for social structure. An alternative interpretation is that the black and white patients were not intrinsically different, but sociocultural biases in the diagnostic and treatment approach contributed to their different experiences in the state hospital system; it is worth noting that all of the professional staff at RSH during this time period were white. Understanding the historic origins of racial disparities in psychiatric care will be important in addressing the current disparities in the mental health system.

Further Directions: To determine whether the differences observed between black and white patients at RSH in the mid-20th century were due to inherent patient characteristics or diagnostic biases, more
research needs to be done. This study could involve a group of psychiatrists reviewing the patients’ intake mental status exams (MSE), blinded to the initial diagnosis and the race of the patient. While it would not account for biases in the recorded MSE, it would be an important step towards appreciating the influence of diagnostic biases in the observed racial disparities.

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Citations:

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A highly successful strategy to find Sanger validating mutations in exome sequencing of single cases within nuclear families

NextGen Sequencing for gene discovery is a rapidly maturing tool for genetic clinical use. However, the overall success rate is still unknown for general clinical use. As part of the UDP program, we have been tracking how successful the overall process is for different types of cases, with the goal of defining the current rate that NextGen techniques diagnose rare or novel disorders. During the first 3 years we have sequenced 200 exomes in over 40 families along with high density SNP arrays. Our initial analysis for Mendelian, large copy number variants and mosaicism variant discovery has been published and that analysis “solved” about 30% of the cases.

For this project, the UDP studied 31 nuclear family cases using SNP chip and exon sequencing of small pedigrees and initially found Mendelian candidates based on homozygous or compound heterozygous recessive models in 15 cases. The raw NextGen data identified a very large number of sporadic variants (>20K) in our families such that Sanger validation was impractical. To overcome this problem, we developed tools for excluding variants arising from known or presumed artifacts of misalignment. One measure of an accurately genotyped base pair position is the number and percentage of times it was confidently genotyped as homozygous reference in a large population of normal individuals, under the presumption of complete penetrance and accurate phenotyping. For this purpose, we used exome sequences of 160 intensely phenotyped UDP individuals and 581 healthy individuals available to us through the NIH Intramural Sequencing Center. Because we had both parents for all our UDP family cases, we looked at the dependent variations from the vantage of having all the independent chromosomes that were derived from UDP cases. In at least 50% of the entire data set, we found a correlation between sites that were well covered and confidently genotyped, with a substantial likelihood of being Sanger validated as a true de novo mutation. The number varied from 4 to 60 candidates per case. This extreme novel filter produced a list of 84 candidate variants that appeared to be deleterious and possibly causal for 12 cases. Of these 84, 34 (42%) validated as true de novo variants after Sanger Sequencing of both parents and all siblings in each family. After combining dominant and recessive Sanger validated candidates from exome sequencing of nuclear families, we report that 26/31 (84%) families have at least one Sanger validated candidate that was a disease-causing sequence variant. In conclusion, the combination of SNP chip and exome sequencing appears to successfully generate candidate causal genes in a high proportion of single family unknown diseases, but is vastly aided by the availability of nuclear family member DNA and a well characterized control population.
A Murine Model of Shoulder Ostroarthritis using an Unrepaired Surgically Induced Massive Rotator Cuff Tear

**Introduction:** Shoulder osteoarthritis is a common and disabling disease for which few nonsurgical options exist. A cause of this arthritis is from improperly healed rotator cuff tears, leading to shoulder instability. The increased manipulability a mouse model can give over other animal models makes it ideal, but previously a mouse model of shoulder osteoarthritis did not exist. We planned to use an injury model replicating an unhealed rotator cuff tear to generate osteoarthritis.

**Objective:** To generate and characterize the progression of shoulder arthritis in a mouse model. This model would then used to study arthritic progression in the setting of diabetes and obesity.

**Methods:** To generate the osteoarthritis model and characterize the full progression of the disease, mice were injured then harvested at various time points from 4 to 50 weeks. The massive rotator cuff tear was generated by approaching the glenohumeral joint through an incision in the deltoid muscle and severing the distal insertions of the supraspinatus, infraspinatus, and subscapularis muscles. This was performed on the right limb of each animal. At the harvest time points, the arthritic progression was assessed histologically and by micro CT.

Once this model was characterized, it was then applied to an established model of diabetes using mice fed either a high fat or lean diet, and the rates of progression were compared.

**Results:** Micro CT showed thinning/ablation of subchondral bone in the humeral head, trabecular bone changes, humeral head shape changes, glenoid erosion, and acromial ossifications indicative of arthritis in the shoulder. Histology showed similar findings, as well as loss of proteoglycan, cartilage thinning, and chondrocyte maturation at the articular surfaces, and acromial chondrogenesis. Preliminary data on the diabetic mouse study is showing trends in the acceleration of this progression in the mouse fed a high fat diet compared to a lean diet.

**Conclusion:** We were able to generate a mouse model of shoulder arthritis and characterize the arthritic progression over many weeks. This will allow further targeted research that was unavailable with previous animal models.
The Neuroprotective Role of Erythropoietin (EPO) in Chronic Nerve Compression

**Background:** Chronic nerve compression (CNC) is a very common and potentially debilitating condition. The hallmark of CNC is progressive focal mechanically induced demyelination with a resultant decreased in the nerve conduction velocity (NCV). Currently, treatments are directed at surgical decompression but no treatments serve to promote remyelination. Erythropoietin (EPO) is a drug that has been extensively studied in the central nervous system due to its direct and indirect neuroprotective effects. In this study, we evaluate EPO in the setting of a murine model of compression injury.

**Methods:** Murine models of chronic compression were created using a biologically-inert silastic tubing placed on the mouse sciatic nerve at 6 weeks of age. Progression of compressive neuropathy was tracked by electrodiagnostic examination of the NCV and the compound muscle action potential (CMAP). Mice were given weekly clinical doses of either saline or EPO (n=5) for 10 weeks and assessed at weeks 2, 6, 8, and 10. After 10 weeks of compression when compressive neuropathy was evident, they then underwent surgical decompression. Mice received weekly doses of saline or EPO in blinded fashion. Nerves were harvested at varying time points throughout the compression and decompression experiment and stained for NF, EPO-R, P0, and Ki67.

**Results:** There were no significant differences in the progression of compressive neuropathy between the saline and EPO-treated groups. However in the decompression experiment, at week 1 post surgery, the EPO-treated groups showed marked recovery of the NCV as compared with the saline-treated group. Furthermore, of the EPO-treated group, the group that received EPO throughout the duration of compression recovered at a slower rate as compared to the group who received saline throughout the duration of compression.

**Conclusion:** Unlike in acute crush injury, EPO does not improve myelin maintenance during active compressive neuropathy. However, EPO does improve myelin recovery after decompression suggesting its role in potentiating Schwann cell remyelination of demyelinated nerves. Furthermore, EPO may desensitize the chronically compressed nerve possibly via down regulation of its receptor at the site of injury. Ongoing research is aimed at quantifying the expression of particular proteins involved in nerve recovery to further elucidate EPO’s mechanism in the peripheral nerves.
Reference:
Hyperuricemia is associated with HTN and progression of chronic kidney disease in children

**Objective:** The Chronic Kidney Disease in Children (CKiD) data set was used to evaluate relationships between uric acid [UA] and important factors in pediatric kidney disease on a cross-sectional and longitudinal basis.

**Background:** There is limited data on the effect of [UA] in pediatric disease. A small body of evidence indicates that hyperuricemia is associated with essential hypertension in adolescents [1]. The effects of [UA] on HTN and progression of pediatric CKD have not been clarified.

**Methods:** Participants (N=617 cross-sectional; N=432 longitudinal) were stratified by age/gender into two groups based on [UA] distribution (Group 1: all girls and boys < 13 yrs; Group 2: boys ≥ 13 yrs). Cross-sectional analysis was completed using multi-variate linear regression between [UA] and HTN status (BP>95th% for age-sex-height; BP≤95th% with meds; or ≤95th% without meds) while accounting for initial GFR and obesity (BMI>95th% for age-sex-height). The longitudinal analysis used a multi-variate, time-to-event model to predict 30% decline in GFR according to 1) [UA] level (Group 1: low [≤5.6 mg/dL], med [>5.6 to ≤7], high [>7]; Group 2: low [≤ 7 mg/dL], med [7 to ≤9], high [>9]); 2) HTN status (as defined above); 3) initial GFR; and 4) CKD etiology (glomerular vs non-glomerular).

**Results:** Cross-sectional analysis showed that Group 1 participants with BP>95th% or ≤95th% on meds had [UA] values that were significantly higher than those with BP ≤95th% without meds after accounting for GFR and obesity (0.35 mg/dL; 95% CI: -0.04-0.73 and 0.50 mg/dL; 95% CI: 0.21-0.78; respectively). Group 2 participants with BP≤95th% on meds had UA that were significantly higher than those with BP<95th% without meds after accounting for GFR and obesity (0.60 mg/dL; 95% CI: -0.06-1.26). This relationship did not hold in Group 2 participants with BP>95th%. Obese patients in Groups 1 and 2 had higher UA than those not obese (Group 1: 0.64 mg/dL; 95% CI 0.29-0.98 and Group 2: 0.85 mg/dL; 95% CI 0.10-1.60). Longitudinal analysis showed that for Group 1 participants, high UA was associated with sooner 30% decline in GFR compared to the low UA (high UA RH=2.16; 95% CI: 0.95-4.9). Additionally, BP>95th% was associated with sooner 30% decline in GFR compared to individuals with BP≤95th% without meds (RH=4.37; 95% CI: 2.04-9.38). Results did not vary with glomerular vs non-gglomerular etiology. In Group 2, UA, BP, and disease etiology did not reliably predict 30% decline in GFR.

**Conclusion:** In all girls and boys <13 yrs, UA is independently associated with HTN. In this group, UA also independently predicts 30% decline in GFR. In boys ≥13 yrs, these relationships are not reproducible and require further study. Also, obesity is positively associated with UA in kids with CKD.

**References:**
Identification of Low-Risk Adult LQTS Patients with Long-term Mortality Rates Similar to Unaffected Relatives

ABSTRACT:

Objective. The aim of this study was to identify a low-risk adult congenital long QT syndrome (LQTS) population.

Background. To date, most risk stratification studies in LQTS have focused on identification of high-risk subjects. Current data on the long-term clinical course of low-risk adult LQTS patients are limited.

Methods. Patients in this study were from the Rochester-based LQTS Registry. We hypothesized that long-term survival of LQT1-2 patients with QTc <500ms and no cardiac symptoms before age 20 (n=523) would be similar to that of their unaffected genotype-negative family members (n=1134). Kaplan-Meier survival analysis and multivariate Cox proportional hazards regression models were used to evaluate the incidence and risk of all-cause mortality in the study population.

Results. The low-risk LQTS study group comprised 27% (523/1919) of genetically confirmed LQTS Registry patients alive at age 20. The cumulative probability of all-cause mortality between age 20 and 65 was similar in the low-risk LQTS group and the genotype-negative control group (4.3% and 4.4%, respectively at age 65; p=0.49 for overall difference). Multivariate analysis showed no significant difference in the risk of all-cause mortality between the two groups (HR = 0.89; 95% CI 0.33-2.43, p=0.82). Consistent results were revealed in subgroup analyses in female and male LQTS patients and in patients with genetically identified LQT1 and LQT2 mutations.

Conclusion. We identified low-risk, adult LQTS patients with a 45-year survival similar to unaffected family members. These low-risk LQTS patients may be considered for age-related life insurance.
INTRODUCTION

While tendon injury is common, there has been minimal progress in developing medical therapies to improve healing or to decrease the long-term consequences of the repair process. Among the most serious consequences is the development of scar tissue that results in adhesions. Adhesions are particularly problematic in intra-synovial tendon healing since they reduce tendon gliding efficiency and motion. Anabolic therapies that would increase the rate of healing and permit earlier return to full function and/or reduce adhesion formation would be a major advance.

PTH 1-34, a biologically active fragment of parathyroid hormone, is approved for clinical use as an anabolic agent to increase bone formation in patients with osteoporosis. Preclinical studies demonstrate that PTH enhances fracture healing and works as an anabolic agent by activating stem cell populations in the injury and repair environment. Tendon repair is analogous to fracture healing in its dependence on proliferation and differentiation mesenchymal stem cells, matrix formation, and tissue remodeling. The current study was conducted to determine whether PTH has anabolic effects on intra-synovial tendon healing. We tested the hypothesis that PTH enhances tendon-to-tendon healing using both a mouse model of primary flexor digitorum longus (FDL) tendon repair of a fully transected tendon (1) and the collagen gel contraction assay in which cultured tenocytes remodel their pericellular extracellular matrix (2).

METHODS

**Mouse model of tendon healing:** All animals were cared for in accordance with an animal use and care protocol approved by the University Committee on Animal Research (UCAR). The FDL tendon was transected and immediately repaired using a modified Kessler technique in 6-8 week old male mice (1). The tendon was also released at the myotendinous junction to prevent early transmission of active forces against the tendon repair. Mice typically regain active flexion between 21 and 28 days in this model. Ninety seven mice underwent repair alone and ninety seven mice received daily subcutaneous injections of 40 μg/kg of PTH 1-34 (Sigma-Aldrich, St. Louis, MO) beginning on the date of surgery. Limbs were harvested on post-operative days 3, 7, 14, 21 and 28 days for histological analysis (N=4 repairs per time point), immunohistochemistry (IHC) (N=4 repairs per time point) and RNA extraction for real-time RT-PCR (N=5 repairs per time point). Additionally, limbs were harvested at 0, 14, 21, and 28 days post-surgery for biomechanical strength testing (N=8 repairs per time point).

**In vitro model of tendon healing:** FDL tendons were isolated from 7-month old male mice. Tendon cells expanded in cell culture were mixed with a collagen I solution at a density of 7x10⁵ cells/ml). The cell-seeded collagen was cast into custom-made silicone constructs, and fresh media (MEM α supplemented with 10% FBS and 1% Pen Strep) with or without 100 nM PTH 1-34 (Sigma-Aldrich, St. Louis, MO) was
added to the wells. Gel area contraction was measured for a total sample size of 6 per treatment per time point.

Real-time RT-PCR and biomechanical and contraction data were analyzed using a two-way analysis of variance (ANOVA) with Bonferroni’s multiple comparisons at the α = 0.05 significance level.

RESULTS

Histology: On post-operative day 3, PTH treated mice displayed extensive recruitment of inflammatory cells to the injury site while minimal cellularity was observed in their vehicle treated counterparts. On day 7, an external callus of cells from the epitenon had bridged the tendon ends in the PTH treated mice, while less fibroblastic granulation tissue had filled in the repair site in the vehicle treated mice and external callus was not yet present. At 14 and 21 days post-repair, the external callus had grown larger and was beginning to remodel and replace the adjacent tendon ends in the PTH treated mice. By 28 days, the PTH treated mice displayed progressive tendon remodeling with dense collagen fiber organization parallel to the tendon axis. Vehicle treated mice at 14, 21 and 28 days post-repair had smaller callus sizes, more native tendon, and less collagen fiber organization compared to PTH treated mice.

Gene and protein expression: Real-time PCR analysis showed a 2-fold increase in col1a1 gene expression in PTH treated mice at 14 and 21 days post-repair (Fig. 1A; p<0.05). Col3a1 and fn1 gene expression were 1.5- and 2-fold greater in PTH treated mice at 21 days post-repair, respectively (Fig. 1B and C; p<0.05). PTHR1 gene expression was 2- and 2.5-fold greater in PTH treated mice at 14 (p<0.05) and 21 days (p<0.001) post-repair (Fig. 1D). IHC confirmed the findings, showing that staining of type I and III collagen and PTH1 receptor protein was greater in PTH treated mice compared to vehicle treated mice at all times.

Biomechanical testing: Non-destructive metatarsophalangeal (MTP) joint flexion testing showed that the MTP joint range of motion (ROM) was 1.5- to 2-fold lower for PTH compared to WT mice throughout the duration of the experiment (Fig. 2A; p<0.001). Similarly, the gliding coefficient, a measure of resistance to joint ROM, was 2- to 3.5-fold higher in PTH mice (Fig. 2B; p<0.05). Maximum tensile strength testing showed significantly greater tensile strength for PTH mice at 14 days post-repair (Fig. 2C; p<0.01).

Gel contraction: Contraction analysis showed that gels treated with PTH 1-34 contracted to an average of 61% of their initial area after 48 hours, whereas those treated with control media contracted to only 86% of their original area (Fig. 2D; p<0.001).

DISCUSSION

PTH is an important anabolic agent for the treatment of osteoporosis and is being investigated as an agent to enhance injury and repair processes. These experiments demonstrate that PTH has an anabolic effect on murine intra-synovial tendon healing. Histology demonstrated earlier and more robust accumulation of reparative tissue. This was associated with an increased expression of genes involved in tissue repair, including type I and III collagen and fibronectin. IHC showed similar increased expression of the collagens. Interestingly, we observed that treatment with PTH increased gene and protein expression of PTHR1, the cell surface receptor for PTH. This suggests that activation of the PTH signaling pathway in soft tissue repair further increases receptor mediated cell and tissue responses.

As tendon function involves motion in response to tensile forces, biomechanical testing is a direct measure of tendon healing. We performed a biomechanical test of digit motion in situ in harvested limbs to measure digit ROM and determine the adhesion coefficient. Although PTH increased the strength of tendon repair, it increased adhesions and resulted in a decrease in the ROM. This finding was supported by in vitro analysis that showed increased gel contraction in PTH-treated cultured tenocytes.
Altogether our findings demonstrate that PTH exerts an anabolic response on tendon healing and increases the deposition of repair tissue and enhances the mechanical strength of repair. However, this is associated with an increase in the formation of adhesions. The data suggest that PTH may be an effective therapy to enhance healing. Because of the effect on adhesions, PTH might be a more useful therapy for the repair of extra-synovial tendons with limited gliding function, such as the rotator cuff and patellar tendon.

REFERENCES

Figure 1. ABH stained sections of WT and PTH FDL repair tendons

Figure 2. Polarized light analysis of picrosirius red stained sections of WT and PTH FDL repair tendons
Figure 3. Gene expression analysis of (A) col1a1, (B) col3a1, (C) col5a1, (D) fn1, and (E) PTHR1 in WT and PTH FDL tendon repairs

Figure 4A. Col3 immunohistochemical sections of WT and PTH FDL repair tendons
Figure 4B. Col1 immunohistochemical sections of WT and PTH FDL repair tendons

Wildtype

Day 3  Day 7  Day 14  Day 21  Day 28

PTH

Day 3  Day 7  Day 14  Day 21  Day 28

Figure 4C. PTHR1 immunohistochemical sections of WT and PTH FDL repair tendons

Wildtype

Day 3  Day 7  Day 14  Day 21  Day 28

PTH

Day 3  Day 7  Day 14  Day 21  Day 28
Figure 5. MTP joint flexion ROM, gliding coefficient, and maximum tensile force in WT and PTH FDL tendon repairs
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