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Basic Science and Clinical Research



Bronwyn H. Bryant, MS2

Preceptor: Ellen Vitetta, M.D.

Professor and Director

Department of Cancer Immunobiology Center

University of Texas, Southwestern

Evaluation of a Cell Penetrating Antibody Vector Specific for CD19+ B Cell Lymphomas

Abstract: Cell penetrating peptides (CPPs), such as the 12-amino acid membrane translocating sequence (MTS), provide a way to deliver bioactive molecules inside a wide range of cell types. However, there is a need to endow CPPs with cell- targeting properties to treat diseases such as cancer where the target is intracellular. Monoclonal antibodies (MAbs) are proteins with high binding affinity and specificity for their targets and several have been approved for use in humans. We have conjugated MTS to the small-chain fragment of HD37, a MAb directed against B cell surface receptor, CD19, which is present on early B-cells and virtually all B-cell lymphomas. We have shown that this fusion protein, scFv37-MTS, preferentially binds to CD19+ vs CD19- cells, and binds with a higher affinity than scFv37 alone or HD37 alone. We have also shown that scFv37-MTS is internalized in CD19+ cells. Targeting CPP to CD19+ cells could provide therapy specific to any B cell- derived leukemia or lymphoma.

Objectives: To express and purify scFv37-MTS and scFv37 antibody fragments to study the binding affinity, internalization and intracellular localization of scFv37-MTS compared to scFv37 and HD37 in CD19+ and CD19- lymphoma cell lines.

Methods: *Intracellular expression and purification of NusA-scFv37 and NusA-scFv37-MTS:* scFv37 and scFv37-MTS DNA sequences were spliced into a pET-43a vector for intracellular expression of NusA-tagged antibody fragments. Splicing was confirmed by sequencing the plasmid. We confirmed that the protein is expressed in the soluble cell fraction. Fusion tagged proteins were purified on Ni-NTA agarose columns.

Removal of NusA tag: The NusA tag was removed using thrombin digestion to yield scFv27 and scFv37-MTS. We determined the optimal concentration of thrombin for the digestion. Following digestion, scFv37 was reduced and was further purified on anti-HD37 Idiotypic (Id) column to yield correctly fold scFv37.

ELISA: A standard curve of HD37, scFv37 and RFB4 (negative control) were tested against anti-HD37 Id and anti-RFB4 Id.

Binding Assay: ¹²⁵I-labeled HD37, scFv37, and scFv37-MTS constructs were tested for their binding to B-cell lymphoma cell lines Daudi (CD19+), DHL-4 (CD19+), and Jurkat (CD19-). Iodinated antibody and fragments were incubated at concentrations of 0.25, 0.5, 1.0, 2.0, and 4.0 µg/10⁷ cells/mL for 1 hour, after which the cells were collected and the radioactivity of the cells versus the amount of protein added was plotted. Binding coefficient, K_a, was calculated.

Internalization Assay: ¹²⁵I-labeled HD37, scFv37, and scFv37-MTS were incubated with DHL-4 cells for 0h and 2.5h. The cells were then processed to measure the radioactivity in the supernatant, membranes and cytosol. The percent of antibody or fragment internalized into the cytoplasm fraction was calculated and analyzed for significance using paired T-tests (p<0.05).

Results: *Expression and purification of NusA-scFv37 and NusA-scFv37-MTS:* Expression and purification by Ni-NTA agarose column of NusA-scFv37 and NusA-scFv37-MTS yielded impure

protein. Thrombin digest was performed and final purifications of scFv37 or scFv37-MTS by Ni-NTA agarose column showed contaminations with a band consistent at the same molecular weight as NusA. Non-reducing SDS-page gels showed large protein aggregates.

We performed an ELISA to test if purification with anti-HD37 Id would be a valid method for purification. The anti-HD37 Id reacted strongly to HD37, and weakly to scFv37. It did not react to negative control RFB4. HD37 and scFv did not react with anti-RFB4, while RFB4 reacted strongly.

The fragment scFv37 was reduced post thrombin digest and passed through anti-HD37 Id affinity column and yielded 95% pure protein.

Binding Assay: In Daudi and DHL-4 cells, the scFv37 protein gave saturation binding at about $2\mu\text{g}/10^7$ cells/mL, while the scFv37-MTS protein did not show saturation at up to $8\mu\text{g}/10^7$ cells/mL. The K_a for scFv37-MTS and scFv37 in Daudi cells was $1.0 \times 10^{-11}\text{M}$ and $8.9 \times 10^{-11}\text{M}$, respectively, and $0.8 \times 10^{-11}\text{M}$ and $7.0 \times 10^{-11}\text{M}$ in DHL-4 cells. The K_a for HD37 in DHL-4 cells was $2.8 \times 10^{-10}\text{M}$. Binding affinity for Jurkat cells was too low to calculate.

Internalization Assay: In DHL-4 cells, 24.7% of HD37, 13.2% of scFv37, and 8.6% of scFv37-MTs was internalized. All values were statistically significant.

Conclusions: NusA tag and scFv fragments contain cysteines, and disulfide bond formation in the scFv is imperative for correct protein folding. Purification difficulties were likely a result of misfolding of each antibody fragment with disulfide bonds forming between cysteines in scFv37 and NusA. This was probably responsible for the formation of large protein aggregates observed on SDS gels. Reduction of the scFv37 post-thrombin digest allowed for correct folding of the scFv37 and successful purification on the anti-HD37 Id column, selecting for correctly folded scFv37.

The binding assay demonstrated that scFv37 selectively binds to CD19+ cells. The MTS sequences conferred much greater binding of scFv37-MTS, 8-9 fold that of scFv37. This may be due to the bivalency of the scFv and MTS domains, to increased affinity conferred by membrane penetratin, or could be because the protein is being taken up into the cell, making more CD19 receptors available for binding again. HD37 showed the highest affinity for CD19+ DHL-4 cells, likely due to the bivalency of the full MAb.

Internalization assays were performed to determine what percentage of fragment of MAb were internalized compared to the amount that remained bound to the surface. HD37 showed 24.7% internalization in DHL-4 cells, which is consistent with most MAbs. The internalization with scFv37 and scFv37-MTS were considerably less. This is likely due to the monovalency of the antibody fragments. It is surprising that scFv37-MTS showed lower internalization than scFv37. This experiment needs to be repeated to verify the results. Additionally, a localization experiment must be performed to show if scFv37-MTS is localized throughout the cytoplasm, as expected when using the MTS domain. The percent internalization is less important if we can demonstrate that scFv-MTS is selectively internalized and distributed throughout the cytoplasm of CD19+ cells. The therapeutic use of such a receptor-specific internalized protein offers a strategy for targeting cytosolic proteins in many types of cancer cells.

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Basic Science and Clinical Research



Amanda Carpenter, MS2
Annalisa Post, MS2

Preceptor:
Loralei Thornburg, M.D.
Assistant Professor of Obstetrics and Gynecology
Department of Maternal Fetal Medicine
University of Rochester Medical Center

Nuchal Translucency Measurements in the Obese Gravida

Background: First trimester screening uses a combination of serum markers and nuchal translucency (NT) measurements to assess risk of fetal aneuploidy. Accurate NT measurements are critical to the accuracy of the first trimester screen. Since maternal obesity affects ultrasound resolution, it may also affect the sonographer's ability to get an accurate NT measurement.

Objective: To evaluate the time required and failure rate for completion of nuchal translucency (NT) measurements as maternal body mass index (BMI) increases.

Method: A single site, retrospective review was performed for ultrasounds from January 2004 to December 2007 on singleton pregnancies from 11-14 weeks gestation undergoing NT measurement. Subjects were stratified by pre-pregnancy BMI into normal (NL), BMI 18.5-24.9, overweight (OW), BMI 25-29.9, and obese: Class I (I) BMI 30-34.9, Class II (II) BMI 35-39.9, or Class III (III) BMI >40. The failure rate, the time required for measurement, and the total study time in minutes were evaluated by BMI class for the first attempt and for all attempts at NT measurement.

Results: A total of 2508 women underwent attempted NT screening with complete data available on 1678 women with 1707 scans. Failure rate for NT screen varied significantly by BMI, $p < 0.001$. At the first attempt, mean time for NT measurement (NL: 14 ± 14 OW: 13 ± 12 I: 15.3 ± 17 II: 18.8 ± 16 III: 17.7 ± 20 $p < 0.002$) as well as total study time (NL: 20.7 ± 16 OW: 19 ± 13 I: 23.0 ± 18 II: 26.6 ± 18 III: 24.7 ± 23 $p < 0.0001$) varied significantly by BMI. For all attempts, mean time for NT measurement (NL: 14 ± 14 OW: 13 ± 13 I: 15.6 ± 17 II: 18.8 ± 16 III: 17.3 ± 19 $p < 0.002$) and total study time (NL: 20.7 ± 16 OW: 19.6 ± 14 I: 23.3 ± 19 II: 26.6 ± 18 III: 24.8 ± 22 $p < 0.0001$) also varied significantly by BMI.

Conclusion: As maternal BMI increases, time to obtain NT measurements and failure rates increase. Though times for Class III patients appear less than Class II, this likely reflects discontinuation of the attempt rather than more rapid acquisition. Patients with BMI over 30 should be counseled regarding need for additional time and failure rates for first trimester screening before ultrasound examination.

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Michelle Coriddi, MS2

Preceptors:

Lane Bekar, Ph.D.

Maiken Nedergaard, M.D., DMSc.

Center for Translational Neuromedicine

University of Rochester Medical Center

Effects of the Locus Coeruleus on Expression of Growth and Inflammatory Factors in the Sensory Cortex and Thalamus in a Model of Chronic Neuropathic Pain.

Abstract: Symptoms of chronic neuropathic pain, such as hyperalgesia, allodynia, and spontaneous pain, have been associated with hypersensitization and cortical reorganization. As hypersensitization in the spinal cord following injury is a result of glial activation, it has been postulated that cortical hypersensitization also results from increased astrocytic and microglial release of pro-inflammatory cytokines and growth factors. Injury-induced cortical reorganization has been shown to be dependent upon noradrenergic signaling and may have an effect on astrocytic and microglial function. Pain is known to increase activity in the locus coeruleus (LC)^[1], the sole source of norepinephrine (NE) in the thalamus and cortex. NE has been shown to induce expression and release of brain derived neurotrophic factor (BDNF) from astrocytes^[2,3] as well as induce ATP release^[4]. The fact that studies in the spinal cord show ATP increases microglial BDNF expression and release leading to hypersensitization^[5] suggests that NE in the cortex may drive a similar cascade of events. In the present study, we hypothesize that chemical ablation of the LC with the specific LC-neurotoxin, DSP-4, affects injury induced production of growth and inflammatory factors in both thalamus and hindlimb sensory cortex following sciatic nerve transection.

This study evaluates the expression of thalamic and cortical BDNF, NGF, GDNF, IL-1 β , and TNF- α five days following sciatic nerve transection (SNT). Eighteen seven week old C57/BL6 mice were divided into four groups: 1) Saline Sham (3 animals) 2) DSP-4 Sham (3) 3) Saline SNT (6) and 4) DSP-4 SNT (6). Mice received an intraperitoneal (IP) injection of DSP-4 or saline 4 days and immediately prior to surgery. All mice were sacrificed five days following surgery. Tissue samples were collected from ipsi- and contralateral hindlimb sensory cortex and thalamus from all eighteen mice. Reverse transcription and real-time PCR were then used to quantify mRNA levels of the listed compounds.

Following SNT, mice pre-treated with DSP4 showed a significant decrease in BDNF expression in the contralateral hindlimb sensory cortex consistent with our hypothesis that LC-NE provides a trophic drive to the cortex following peripheral nerve injury. Mice treated with DSP4 showed a significant reduction in cortical BDNF and TNF- α implicating baseline NE as a drive for trophic factor expression. Surprisingly, no changes were observed in the thalamus. Other growth and inflammatory factors did not show significant changes between treatment groups. However, trends suggest that NE suppresses IL-1 β and TNF- α and promotes GDNF and NGF expression consistent with NE having both anti-inflammatory and trophic properties, respectively. Larger group sizes may yield additional significance (sham groups contain only 3 animals).

Increasing the sample size should confirm BDNF findings, and potentially also unmask significant changes in GDNF, NGF, IL-1 β , and TNF- α expression following a chronic pain stimulus. Future studies will also study expression levels in the anterior cingulate cortex as this region plays a significant role in pain perception, is heavily innervated by projections from the LC and is known to

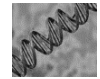
undergo hypersensitization following peripheral injury^[6]. It is our goal that future studies better elucidate the role of the LC in the molecular mechanisms underlying chronic neuropathic pain.

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Basic Science and Clinical Research



Danielle de Campo, MS2

Preceptor:

Julie L. Fudge, M.D.

Associate Professor of Psychiatry Neurobiology and Anatomy

Department of Neurobiology and Anatomy

University of Rochester Medical Center

Hippocampal Projections Terminate Over Immature Neurons in the Amygdala: Anatomic Substrate for Long-Term Structural Change After Emotional Memory?

Abstract: The amygdala is a regulator of emotional processing and is implicated in the pathology of mood disorders. Structural change has been associated with stress in animals, and depression and anxiety disorders in humans. In primates, one possible mechanism mediating amygdala structural changes is through the effects of stress and emotional experiences on the plasticity of immature neurons. Immature neurons in the adult human and non-human primate amygdala are highly localized to specific subregions, suggesting a circuit-specific distribution.

Objectives: One purpose of this study was to verify the location of immature neurons using doublecortin (DCX), a marker for committed neuroblasts in the central nervous system. The second goal of this project was to determine what circuits most influence immature neurons that express doublecortin in order to understand afferent influences on these immature cells.

Methods: Five adult macaques previously injected with neuronal tracers localized to the hippocampus were used in this study. Tissue sections through the amygdala were immunostained for DCX-IR and their distribution charted with respect to specific nuclear regions. Subsequently, the distribution of anterogradely labeled fibers in the amygdala, resulting from hippocampal injections was visualized using immunocytochemistry or autoradiography. Only injections placed into the subiculum or CA1 resulted in labeled fibers in the amygdala. Therefore, the distribution of labeled fibers in the amygdala was charted in these two cases, using sections adjacent to those labeled for DCX protein.

Results: 1. DCX-labeled cells were found in the paralamina nucleus, ventral periamygdaloid cortex and parvocellular basal nucleus of the amygdala. 2. Hippocampal afferents originating in the CA1/subiculum region resulted in heavy distributions of labeled fibers in the paralamina nucleus, ventral periamygdaloid cortex, amygdalohippocampal area and the ventral accessory basal nucleus demonstrating the heaviest distributions. 3. Hippocampal afferents from the CA1/subiculum region and DCX neurons demonstrated a tight overlap in the paralamina nucleus.

Conclusions:

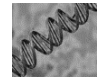
- DCX labeled neurons and CA1/subiculum hippocampal afferents are differentially located in the primate amygdala
- Tight overlap of hippocampal fibers and DCX neurons in the paralamina region suggest a potential region in which inputs from hippocampus may play an important role in the modulation of immature neurons in amygdala.

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Basic Science and Clinical Research



T.R. Eckler, MS2

Preceptors:

Jeff Bazarian, M.D.

Associate Professor of Emergency Medicine

Brian Blyth, M.D.

Assistant Professor of Emergency Medicine

Center for Neural Development and Disease

University of Rochester Medical Center

Development and Analysis of a Murine TBI Model

Abstract: Traumatic Brain Injury, or TBI, is considered a silent epidemic by the CDC because very few people actually grasp its magnitude. It is estimated that the cost of TBI ranges anywhere from \$50 to 150 billion dollars, but regardless it is the leading cause of death of individuals below the age of 45.¹ TBI causes motor and cognitive deficits and may leave patients who suffer a TBI predisposed to neurodegenerative diseases. One patient population in particular demands our immediate attention in making advances towards treating and healing this injury. Blast related Traumatic Brain Injury, or Blast TBI, is the characteristic injury of the current war in Iraq, and given that the number of soldiers surviving their injuries has increased dramatically as well as the time needed to get them back to the US has fallen dramatically, this issue is a very pressing concern. The differences between the injury suffered by individuals with a blast TBI as opposed to a blunt trauma TBI are unknown at this time. Blast TBI patients have more symptoms than blunt trauma TBI patients yet the blast TBI patients lack the positive head CT present in blunt trauma TBI patients. Given that it has previously been shown that head CT is not an effective tool for diagnosis of head CT for blunt trauma TBI², and that soldiers returning from Iraq cannot undergo MRI due to frequent contamination of the wounds by ferromagnetic bodies, the need for a better understanding of this mechanism to develop better diagnostic tests to give military and civilian clinicians a better assessment of the injury is paramount¹. Critical in understanding the mechanism of TBI is the blood brain barrier, which is composed of capillary walls made of endothelial cells, a basement membrane, and the perivascular endfeet of astrocytic glia. Tight junctions between the endothelial cells prevent paracellular transport, thus compounds are forced to take a transcellular pathway through the endothelial cells and its specific receptors, a more controlled environment.³ This thin separation between the brain and the blood and the mechanism by which it breaks down plays a key role in how TBI occurs. When the brain suffers trauma, for example, it is known that bradykinin, a mediator of inflammation, is produced and stimulates production and release of interleukin-6 (IL-6) from astrocytes, which leads to the opening of the blood brain barrier.³ Understanding these chemical interactions and developing diagnostic tools that can measure specific levels of key intermediates is a promising forefront in the treatment and diagnosis of TBI in either model. In this experiment, we hope to compare these two types of traumatic brain injuries in a murine model, and to assess level of injury to the blood brain barrier as well as the chemistry present in each model due to the injury. We hope to develop a mechanism that will enable us to simultaneously visualize blood brain barrier structures, axonal integrity, and correlate these findings with serum biomarkers of injury at clinically significant timepoints.

Objectives: 1. Develop a model to visualize the structure of the blood brain barrier in a mouse by infusion of fluorescent albumin.
2. Incorporate an immunohistochemical technique to visualize astrocyte endfeet structure around the neurovasculature and axonal integrity following injury.
3. Collect serum samples from the mice at time points to correlate ultrastructural damage with serum biomarkers of injury.
4. Compare different mechanisms of TBI including closed head injury, controlled cortical impact, and blast injuries with sham surgery and control results.

Methods:

Injury Protocols:

1. **Controlled Cortical Impact Protocol** - After reaching a surgical plane of anesthesia and cleansing of the surgical area, mice will be placed in a David Kopf stereotactic apparatus. Body temperature will be controlled by means of a Harvard homoeothermic blanket system at 37°C and a rectal thermometer. A ≈ 1 cm longitudinal incision of the soft tissues of the skull will be performed to expose bregma. The craniotomy will be centered 3 mm posterior and 2.5 mm lateral to bregma on the left side. Using a Foredom drill and a surgical trephine, a hole approximately 5 mm in diameter is drilled exposing the dura mater. The dura is visualized at 20x magnification using a Nikon surgical microscope. The animal and stereotactic device are raised using a laboratory jack (1 μ m resolution) until the dura mater comes into contact with the fully extended piston of the controlled cortical impact (CCI) device. The piston is raised and the device adjusted to produce a depression of the cerebral cortex of 0.5 mm when the piston is fired. The piston will be fired at 6.0 m/sec. The dwell time (the time of cortical depression) is typically 50-70 msec. Both the speed of the piston and the depth of depression will be recorded. Animals will be monitored for changes in the nature and depth of respiration. Apnea has been reported as a possible side effect of this model when the piston is positioned over midline structures. We have not noticed this effect in previous studies when striking the lateral aspect of the cortex. Animals will then be removed from the device. The craniotomy will be closed by placing gel foam over the craniotomy, and the skin will be closed using a non-absorbable material (5-0 Ethibond) using simple interrupted sutures. Animals will be placed on a Harvard homoeothermic blanket system at 37°C until recovered from anesthesia.
2. **Closed Head Impact Protocol** - After reaching a surgical plane of anesthesia and cleansing of the surgical area, mice will be placed on a 25 mm thick foam pad. Body temperature will be controlled by means of a Harvard homoeothermic blanket system at 37°C and a rectal thermometer. A ≈ 1 cm longitudinal incision of the soft tissues of the skull will be performed to expose bregma and lambda sutures. The impact will be centered 3 mm posterior and 2.5 mm lateral to bregma on the left side. The animal and stereotactic device are raised using a laboratory jack (1 μ m resolution) until the skull comes intact with the fully extended piston of the impact device (AmScien Instruments, Richmond, VA). The piston is raised and the device adjusted to produce a depression of the skull of 1.0-2.0 mm when the piston is fired. The piston will be fired at 4-8 m/sec. The dwell time (the time of cortical depression) is typically 50-70 msec. Both the speed of the piston and the depth of depression will be recorded. The force of each strike is recorded using a PCB Piezotronics force transducer (Depew, NY). Animals will be monitored for changes in the nature and depth of respiration. Apnea has been reported as a possible side-effect of this model when the piston is positioned over midline structures. We have not noticed this effect in previous studies when striking the dorsolateral aspect of the cortex. Animals will then be removed from the device. The skin will be closed using a non-absorbable material (6-0 Ethibond) using simple interrupted sutures. Animals will be placed on a 37°C heating pad (Gaymar) until recovered from anesthesia.

Following Recovery, mice at two time points (2 hours or 7 days) are anesthetized (ketamine and xylazine as before). They are then administered FITC-Albumin to mark the neurovasculature by one of the following procedures:

Left Ventricle Injection: The abdomen is opened, diaphragm penetrated, and the thoracic cavity is opened. 100 μ L of heparin is injected into the heart prior to extraction of blood from the left ventricle. An experimental amount of FITC-Albumin (5mg/mL stock) is injected into the left ventricle.

Femoral Vein Injection: The Mouse is placed in the supine position, and an incision of 1 cm is made over the inguinal region. Soft tissue is separated by blunt dissection until the femoral sheath is identified. The femoral vein is carefully dissected away from the artery and nerve. An experimental amount of FITC Albumin (5mg/mL stock) is injected into the femoral vein using a 30-gauge needle. Pressure is applied following this until bleeding stops. The incision is not closed, as this is not a survival surgery.

The mouse brain is then preserved by one of the following protocols:

1. Perfusion with 4% PFA pH 7.4 until no response is noted and stiffness is present. Following decapitation, the brain is extracted and placed in a 4% PFA solution overnight at 4°C. On the following day, the brain is transferred to a cryoprotective 30% sucrose solution and remains there until it sinks to the bottom of the tube at which point the water content has been reduced enough to prevent the rupture of cells during the freezing process.
2. Immediate removal of the brain in under 2 minutes, followed by insertion and incubation in 20 mL 4% PFA for three days, changing the PFA each day. This is followed by three days of cryoprotection in 30% sucrose solution and remains there until it sinks to the bottom of the tube at which point the water content has been reduced enough to prevent the rupture of cells during the freezing process.

Results:

1. Fluorescent Albumin Blood-Brain Barrier Model – We achieved significant success in replicating the work of previous experiments(4,5,6) and developing a unique protocol for generating visuals of BBB integrity and function in the C57b mouse model. Surgical procedure, mechanism of injection of FITC Albumin, brain removal and preservation, and sectioning techniques were all adjusted and improved over the course of this research.
2. Immunohistochemical marking of Aquaporin IV, GFAP, and APP was undertaken and completed according to prior studies (7) with significant success in the Aquaporin, limited in the GFAP, and minimal in the APP. APP staining is not expected to be significant until head injury occurs though, and GFAP is a marker for activated astrocytes, which would also be more prevalent in brains following head injury.
3. Serum samples were obtained and frozen for later marking of serum markers of BBB damage from each mouse during the development of the model.
4. Injury models – due to delays in the visualization model optimization, equipment access and coordination of lab efforts, we are about to get underway this week on the injury samples for the controlled cortical impact specimens.

Conclusions: This experiment continues to provide promise to be a valuable source of information about the nature of the blood brain barrier visually and functionally following a TBI with regard to vascular function and extravasation, activated cells and structural abnormalities in the area, as well as correlated serum protein markers of such damage. The opportunity to compare control mice with injuries of a controlled cortical nature, closed head nature, and even perhaps a blast model down the road will lend significant and serious advances to the understanding of this ever-more common injury today.

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Basic Science and Clinical Research



Aaron Farney, MS2

Preceptor:

Jeremy T. Cushman, M.D., M.S., EMT-P
Monroe County EMS Medical Director, Senior Instructor
Division of Prehospital Medicine
Department of Emergency Medicine
University of Rochester Medical Center

Other Authors:

A. Zach Hettinger, M.D.
EMS Fellow
Division of Prehospital Medicine
Department of Emergency Medicine
University of Rochester Medical Center
Manish N. Shah, M.D., M.P.H.
EMS Medical Director, Monroe-Livingston Region
Chief, Division of Prehospital Medicine, Associate Professor
Departments of Emergency Medicine, Community & Preventive Medicine, Geriatrics
University of Rochester Medical Center

Does close physician oversight improve the quality of a RSI program?

JT Cushman, AN Farney, AZ Hettinger, MN Shah

Introduction: Close concurrent and retrospective physician oversight is felt to be a key component of prehospital RSI programs, in addition to ongoing training and quality assurance. Although intuitive, little data support this theory. The objective of this study was to evaluate the impact of adding concurrent physician oversight to a prehospital RSI program.

Methods: A retrospective chart review was performed on all RSI patients between January 2004, and July 2008. No changes in the medical protocol or RSI equipment occurred; however on January 1, 2007, a comprehensive medical oversight program began consistent with NAEMSP recommendations. This included a select number of providers and physicians who provided quarterly skills review, immediate debriefing after any RSI, and review of all cases in which a patient was evaluated for RSI. Data was divided into pre-intervention and post-intervention periods. Variables examined included: demographics, vital signs, procedures performed, medications used, complications, and physician determination of the documented prehospital need for RSI based upon distance from hospital, oxygen saturation, and airway stability.

Results: 109 RSI's were performed before the intervention, and 54 after. Patient demographics, airway difficulty, medications used, and pre- and post-RSI vital signs were the same in both periods. BLS airway management (95% vs 100% respectively, $p=0.02$), CPAP use (5% vs 19% $p=0.01$), and intubation attempts without RSI (8% vs 39% $p<0.001$) increased post-intervention. More midazolam (35% vs. 65%, $p<0.001$) and morphine (4% vs. 28%, $p<0.001$), and less vecuronium (50% vs 22% $p<0.001$) was used post-intervention. There was no difference in intubation success rates or number of intubation attempts. The time on scene (17.3 vs 23.3 min $p=0.02$) and the

transport time (14.3 vs 20.8 p=0.002) increased post-intervention. The frequency of insufficient documented evidence of prehospital RSI need decreased significantly (38% vs 13% p<0.001) post-intervention.

Conclusions: In this system, close concurrent and retrospective physician oversight has variable effects on the provision of RSI. Such oversight appears to not have affected the success rate of RSI, however it may have affected the pre- and post- intubation management of these patients, as well as more accurate patient selection for the procedure itself.

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***Note:**

This abstract has been accepted to the NAEMSP Annual Meeting and will be published in *Prehospital Emergency Care*.



Basic Science and Clinical Research



Thomas Fugate, MS2

Preceptor:

Arthur Moss, M.D.

Department of Cardiology

University of Rochester Medical Center

Long QT Syndrome in African Americans

Objective: We evaluated the risk factors and clinical course of Long QT syndrome (LQTS) in African-American patients.

Methods: The study involved 3,497 patients from the LQTS registry, 41 African Americans and 3456 Caucasians with a QTc \geq .450 ms. Data recorded on the LQTS patients included information about the medical history and clinical course including the occurrence of syncope (defined as the transient loss of consciousness that was sudden in onset and offset), aborted cardiac arrest (requiring external defibrillation during resuscitation), or LQTS- related sudden cardiac death (unexpected sudden death exclusive of a known cause) from birth through age 40 years. The statistical analyses involved Kaplan-Meier time to event graphs and Cox regression models for multivariable risk factor evaluation.

Results: The QTc was 3ms longer and cardiac events and appropriate LQTS therapy were more frequent in African-American than Caucasians. The Cox model revealed similar event rates in African-American and Caucasians (HR=0.93, P=0.76) after adjustment for relevant covariates (See Table)

Table: Hazard Ratios for Syncope, Aborted Cardiac Arrest, or LQTS Death

Factor	Hazard Ratio	95% CI	P-value
African-American:	0.93	0.57-1.50	0.76
Caucasian			
QTc \geq 500ms	2.10	1.87-2.37	<0.0001
Male 0-13 years	1.28	1.08-1.50	<0.01
Female 14-40 years	2.32	1.88-2.85	<0.0001
β -blocker use*	0.55	0.44-0.70	0.70

*Time-dependent β -blocker use.

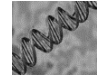
Conclusion: In LQTS patients, the risk for cardiac events in African-Americans was similar to that in Caucasians.

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Basic Science and Clinical Research



Sarel Gaur, MS2

Preceptor:

Ganesh Palapattu, M.D.

Assistant Professor

Department of Urology

University of Rochester Medical Center

Effects of Androgen Deprivation on CD44 Expression in LnCAP Cells

Introduction: Androgen ablation is the primary treatment for metastatic prostate cancer. The prostate is an androgen dependent organ, therefore medical or surgical androgen ablation should cause death or growth arrest of the vast majority of prostate cells. Most patients achieve some level of disease free survival following androgen ablation, however, cancer can recur. The reason for this recurrence is unknown; however we postulate that it may be due to the enrichment of prostate cancer cells that express the putative cancer stem cell marker CD44. To investigate this hypothesis, we studied the effects of androgen ablation on CD44 expression in prostate cancer cells *in vitro*.

Objectives: *Primary:* Examine changes in CD44 cell surface binding in LnCAP cells cultured in androgen depleted medium using Imagestream flow cytometric analysis.

Secondary: To investigate morphological changes in LnCAP cells grown in androgen depleted medium using traditional light microscopy.

Methods: *Cell Culture:* Human prostate adenocarcinoma LNCaP cells (American Type Culture Collection, Manassas, Virginia) were grown in either regular medium (Phenol-Red positive RPMI 1640 medium supplemented with 5% FBS, 1% glutamine, and 0.5% gentamicin) or androgen deprived (AD) medium (Phenol-red free RPMI 1640 medium supplemented with 5% charcoal/dextran –treated, heat inactivated FBS, 1% glutamine, and 0.5% gentamicin). After 2 weeks of growth in selected medium, cells were harvested for experiments.

Microscopy: Before harvesting, microscopic images of AD and control cells were taken at 40x, 100x, and 400x.

Staining: After a wash in cell buffer, cells were stained with CD44 antibody affixed to PE Cy5.5 fluorochrome for 30 min in FACS buffer at a concentration of 1/50 dilution. Cells were then washed and fixed in 1.0% formaldehyde and prepped for Imagestream analysis.

Imagestream: Cells were acquired on the Imagestream imaging cytometer (Amnis, Seattle, Washington). At least 3,000 images were collected for each sample. Cells were imaged with side scatter in channel 1, DAPI in channel 2, PE-Cy5.5 in channel 6, and bright field image in channel 5. After raw data collection, images were compensated in order to eliminate spectral crosstalk between channels and then analyzed using IDEAS application for Imagestream. The cells were gated on cellular size and shape to eliminate apoptotic cells then plotted on the basis of channel intensity on X axis versus size on the Y axis. Secondary statistics of gated regions were also computed.

Results: *Primary:* The channel intensity relating to CD44 binding in AD-LnCAP was no different from the channel intensity in untreated LnCAPs.

Secondary: Photomicrograph images of AD and control cells taken at 14 days post treatment demonstrated some distinct phenotypic differences in response to androgen ablation.

Conclusions: CD44+ cell population does not change in LnCAP cells cultured in androgen deprived media for 2 weeks duration. Two weeks of androgen deprivation, while enough to produce morphological changes in cell phenotype, may not be sufficient to modulate expression profiles of cell surface markers such as CD44.

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Basic Science and Clinical Research



Benjamin Gigliotti, MS2

Preceptor:

Assistant Professor

Department of Medicine, Endocrine/Metabolism Division

University of Rochester Medical Center

Laura Calvi, M.D.

Stromal Cells Supportive of Human Hematopoietic Stem Cells Exhibit Osteoblastic Characteristics

Abstract: Hematopoietic stem cells (HSC) are rare pluripotent cells that give rise to all blood cell types. Our lab has shown that osteoblastic cells form a microenvironmental niche through which murine HSC activity is modulated, and that intermittent Parathyroid Hormone (PTH) treatment effects an osteoblast-mediated increase in HSCs¹. More work is being done to fully characterize the mechanism of this effect². Thus far, the effect of PTH on human HSCs has not been studied despite the potential for therapeutic manipulation and expansion. To study human HSCs *in vitro*, a long term co-culture system with the M2-10B4 murine stromal cell line is utilized³. Determination of osteoblastic character of this cell line would support the notion that human HSCs rely on similar niche signals, and allow us to examine whether PTH causes a similar osteoblast-dependent increase.

Objectives: To determine osteoblastic character of a murine stromal cell line proven to support human HSCs *in vitro*. This will aid the development of a short term co-culture model to study the efficacy of PTH in inducing osteoblastic-mediated expansion of human HSCs.

Methods: M2-10B4 cells were grown and maintained in 1xRPMI 1640 media containing 10% fetal bovine serum in a water-saturated atmosphere of 5% CO₂ at 37°C. Media was changed 3x a week, and cells were passaged every 5-6 days at 100% confluence³. M2-10B4 cells were seeded at 5x10⁵ cells/well in 6-well culture plates for all experiments. To assess osteoblastic differentiation potential, media was supplemented with 50 µg/mL ascorbic acid and 50 mM β-glycerophosphate as previously described⁴. At 7, 14, 21, and 28 days cells were either harvested for RNA or stained for alkaline phosphatase and mineralized nodules, following established lab protocols. For PTH versus vehicle experiments, cells were grown for 7 days under mineralizing conditions, and PTH or vehicle were added to three subsequent mineralizing media changes over seven days. rPTH(1-34)(10⁻⁴ M) was dissolved in 1% acetic acid and added for a final concentration of 10⁻⁷ M per well. This experiment was conducted in the heavily supplemented H5100 myelocult media instead of the RPMI maintenance media to maintain consistency with established protocols for long term co-culture support of hematopoietic stem cells³.

Results: Examination of the stained cell culture plates at 7, 14, 21, and 28 days with M2-10B4 cells in mineralizing media reveals several features consistent with osteoblastic differentiation. During the 28 day time course, cells exhibited a morphological transition from a spindle-shaped fibroblastic appearance to a cuboidal shape which is more typical of osteoblasts. Functionally, the cells produced an osteoid appearing matrix that thickened and matured throughout the time course. Alkaline phosphatase activity increased to a maximum around 14 days, and silver nitrate

staining showed marked increases in mineralization throughout the 28 days, peaking with bone nodule formation at the last timepoint. These results are consistent with well-established data from primary calvarial osteoblasts and bone marrow stromal cells grown in mineralizing media.

The PTH versus vehicle experiment revealed a substantial induction of alkaline phosphatase staining in vehicle-treated wells, with little to no stain in PTH-treated wells. This is consistent with previous observations that the presence of continuous PTH during cell cycling blocks differentiation of rat osteoblasts⁵. Additionally, the response supports the presence of a functional PTH receptor in the cell line. This is typical of osteoblast lineage cells, and a necessary condition for successful utilization of cells in a PTH treated co-culture model with HSCs.

Results for real time RT-PCR analysis for transcription factors and cell surface proteins typical of osteoblasts are pending.

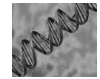
Conclusions: The M2-10B4 murine stromal cell line exhibits osteoblastic characteristics, and will be a suitable candidate for a short term co-culture system to study PTH effects on human HSCs.

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Basic Science and Clinical Research



Joseph Hatem, MS2

Preceptor:

Jill Halterman, M.D., M.P.H.

Associate Professor

Department of General Pediatrics

University of Rochester Medical Center

Behavior and Family Environment in Children with Asthma

Background: Children with asthma are more likely to experience emotional and behavioral difficulties than similar children without asthma. Many factors such as underlying severity of the illness, environmental factors, and child/family characteristics may play a role in determining the behavioral adjustment of a child. Family environment has been shown to be a key determinant for child behavior in children with a chronic illness.

Objective: To describe the relationship between different measures of family environment and 1) parent-reported child behavior and 2) asthma symptoms/management.

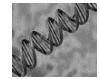
Methods: We conducted a cross-sectional study of urban children (4-11yrs.) in Rochester, NY participating in the School-Based Asthma Therapy Program (9/07-6/08). Eligibility required PCP diagnosis of persistent asthma symptoms in the past year, based on national guidelines. At the end of the school year, parents completed a telephone survey including asthma symptom severity, family environment, and child behavior. Family environment was assessed using 3 subscales from the Family Environment Scale (FES) for cohesion, expressiveness, and conflict. Child Behavior was assessed using the Behavior Problem Index (BPI). Student t-tests and multivariate linear and logistic regression analyses were used to test the relationship between family environment and key outcomes.

Results: We interviewed 167 of 185 parents (90%). 156 families were included in the final analysis. Overall, 12.8% scored low on cohesion, 46.8% scored low on expressiveness, and 26.9% scored high on conflict. The overall behavior score was 10.44 (SD: 7.42), with 32.1% falling above the cutoff of 14, an indicator of clinically significant behavior problems. All three measured components of family environment showed a significant association with total behavior and many behavior subscales. After controlling for covariates, conflict and expressiveness remained independently associated with multiple child behavior outcomes. Asthma symptoms and management were not associated with measures of family environment.

Conclusions: We found that measures of family environment are significantly associated with child behavior for inner-city children with asthma. Children in families with high conflict were nearly 2½ times more likely to have significant behavior problems than children from families with low conflict. Further studies should focus on understanding how family environment and other factors interact to determine key outcomes for children with a chronic illness.



Basic Science and Clinical Research



Brad Hyatt, MS2

Preceptor:

Robert D. Frisina, M.D.

Otolaryngology Department Associate Chair

Department of Otolaryngology, Biomedical Engineering, Neurobiology and Anatomy

University of Rochester Medical Center

Intracochlear Drug Delivery in the Mouse: Correlation of Simulated Concentration Gradients with Shifts in Measured Auditory Response

Abstract: Intracochlear drug delivery in the mouse is challenging due to the extremely small size and volume of the inner ear. Physiological measures can access the impact of delivered compounds on peripheral auditory function, but infusate distribution characteristics must be inferred. Computer simulations offer opportunities to calculate cochlear concentration gradients for different delivery approaches and are an excellent complement to in vivo studies. Fluid modeling software is available to simulate a variety of delivery protocols representing infusions, perfusions, and extracochlear round window drug applications. Diffusion, volume flow, interscala transport, and clearance mechanisms are modeled allowing determination of drug concentration with position in the cochlea. When coupled with a cochlear tonotopic map, simulated concentration profiles can be correlated with shifts in measured auditory responses as a function of sound frequency.

Two different drug delivery approaches are considered in the present investigation involving mice: scala tympani infusion through a basal turn cochleostomy, and this approach coupled with a fluidic exit hole in the posterior semicircular canal. Distortion product otoacoustic emission thresholds were measured from 8-44 kHz before and during delivery of artificial perilymph and sodium salicylate. Shifts in threshold were compared to simulated concentration gradients to highlight the relationship between drug concentration and frequency-dependent changes in auditory function. Model parameters were adjusted to match the profile of these characteristics and to provide insight into mechanisms impacting drug distribution in the cochlea. Strengths and limitations of currently available cochlear infusion models are discussed and critiqued for improvements.

Objectives: 1) To compare measured changes in hearing following a cochlear infusion with results predicted through a computer simulation, and 2) To establish the validity of the simulation for future experiments.

Methods: The program FluidSim 1.6i created by Dr. Alec Salt, was used for all simulations. Input parameters were taken from the literature¹, matched to our experimental infusion², or estimated using animal analogues and expert opinion³. Results were entered into Microsoft Excel and compared graphically with experimental data.

¹ Reference 1

¹ Reference 1

² Ref 2

³ Ref 3

Results: While the simulation predicts a more constant gradient with a perfusion than an infusion, experimental results of perfusions do not follow the constant concentration predicted by the simulation as well as the infusion experimental data follow the gradient distribution predicted by the simulation software for an infusion.

Conclusions: Perfusion does establish a more constant distribution than infusion, and the simulation is a good first approximation of what to expect in an actual cochlear administration. While the simulation is not perfect, it is a useful tool, especially considering the difficult nature of experimenting by directly delivery to the mouse cochlea.

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Basic Science and Clinical Research



Walker Julliard, MS2

Preceptor:

Aristidis Veves, M.D.

Professor of Surgery

Department of Surgery

Beth Israel Deaconess Medical Center

Diabetes and Its Effects on Vascular Health and Wound Healing

Abstract: Diabetic foot ulceration (DFU) is a serious and common complication of diabetes, resulting in greater than 75,000 lower limb amputations yearly. Recent work suggests that the microcirculation disease in diabetes may play a pivotal role in development and failure of these ulcers to heal. Also, endothelial progenitor cells (EPCs) have been implicated in many other systems as important players in endothelial and vascular health, and it is therefore our intention to determine if a possible difference in EPCs could account for this failure to heal.

Objectives: To determine if the concentration of EPCs (1) differs in value in a diabetic state versus healthy controls and (2) if this difference could be associated with a decreased microvascular health and ultimately the ability to heal DFU.

Methods: Patients were enrolled that were either diabetes free (controls), or had type one diabetes mellitus (DM I). DM patients were then divided into groups of high risk to develop ulcers and low risk, and plasma levels of EPCs were measured using flow cytometry. Through follow-up, we then monitored those patients that had developed foot ulceration and were able to see which patients healed from their ulcers and which did not. We also used laser spectroscopy and hyperspectral imaging to evaluate microcirculation.

Results: As this is a long, prospective study (5-7 years) the data is still pending.

Conclusions: Although we do not have any results yet, the study methods have been optimized and literature searches in the field have suggested promise for our pending results.

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Basic Science and Clinical Research



Sirish Kumar Kondabolu, MS2

Preceptors:

Srinivas Pentyala, Ph.D.

Director of Translational Research & Associate Professor in Anesthesiology

Department of Anesthesiology

Michael Hadjiargyrou, Ph.D.

Associate Vice President for Research

Associate Professor of Biomedical Engineering and Orthopaedics

Departments of Biomedical Engineering and Orthopaedics

Stony Brook University Medical Center

The Effect of an Algorithmically Derived Calcitonin Receptor Peptide on the Formation of Bone Matrix *in vitro*.

Abstract: Bone remodeling is a dynamic metabolic process that involves *osteoclast*-mediated bone resorption and *osteoblast*-mediated bone formation. The purpose of bone remodeling is to regulate calcium homeostasis, whereby bone resorption by the osteoclasts releases stored calcium into the systemic circulation, while bone formation by osteoblasts actively fixes circulating calcium in its mineral form. Disrupting this balance between bone resorption and formation can result in various bone pathologies, such as osteoporosis, in which bone mineral density (BMD) is reduced, bone microarchitecture is disrupted, and the amount and variety of non-collagenous proteins in bone is altered. Thus, the goal of treatment for such pathologies would be to boost osteoblast activity and block osteoclast activity to precisely suppress bone resorption below bone formation.

Peptide hormones are released from precursor proteins by the actions of specialized enzymes whose substrate specificities define distinctive sequence patterns in the precursor proteins and in the post-translational processing intermediates. This concept is essential in algorithmically identifying unique peptide sequences in precursor and mature proteins as well as from predicted products that are derived from protein processing mechanisms. From a list of 123 sequences that our algorithm identified from protein databases, a conserved sequence of the calcitonin receptor was found. Calcitonin (CT) is a hormone that inhibits bone resorption through receptor-mediated inhibition of osteoclasts and is used clinically for its anti-resorptive effects. It has been described that the C-terminal peptide of the calcitonin receptor (CTR) is unique for its ability to rapidly mobilize second messengers in cultured cells and it plays a significant role in switching on the G-protein signaling pathway. There is no evidence of an osteoblastic calcitonin receptor and it is argued by experts that it is unlikely that an osteoclast-derived molecule can be involved in the signal for increased bone formation. Initial trials showed increased bone matrix formation in an undifferentiated pre-osteoblastic cell line (MC3T3-E1) *in vitro* when treated with our algorithmically derived calcitonin receptor peptide (CRP). This study intends to show the effects of CRP on bone matrix production in human fetal osteoblast cells *in vitro*.

Objectives: *Primary:* Examine the effects of synthesized CRP from both mouse and human origin on MC3T3-E1 cells and hFOB 1.19 cells *in vitro* through phase-contrast microscopy, spectrophotometry, and Western Immunoblotting using bone matrix-specific antibodies.

Secondary: To elucidate the mechanisms underlying the potential anabolic and resorptive effects of CRP.

Methods: *Cell Culture:* An immortalized human fetal osteoblast cell line (hFOB 1.19; American Type Culture Collection, Manassas, VA) was used for the cell culture study. This cell line is temperature sensitive, where cells proliferated at 34°C and differentiated between 38° and 39°C. Cells were maintained in Dulbecco's modified Eagle's medium (DMEM) without phenol red, 10% fetal bovine serum (Atlanta Biologicals, Lawrenceville, GA), and 3% G418 disulfate solution (Sigma-Aldrich, St. Louis, MO). Cells maintained in T-75 flasks were considered the grower cells, and cells used for experiments were grown in 10-ml Petri dishes. Each dish contained a cover slip for easy mounting on glass slides for microscopy. Cells were fed until they reached 20%–30% confluency. The Cell Culture and Hybridoma Facility at Stony Brook University's Department of Molecular Genetics and Microbiology were responsible for growing these cells for our study.

Cells were treated with 2.3 μ M peptide in increasing 1 μ L: 1mL peptide to cell medium concentrations (2x, 4x, 6x, 8x). Positive controls contained identical concentrations of DMSO and the negative controls did not receive any treatment. In one experiment, non-specific peptides derived from the same algorithm as CRP were also used to treat the cells. These peptides also elicited calcium mobilization response in second messenger assays in PC12 cells as our initial part of screening the peptides. Also, experiments were done to compare mouse-synthesized CRP with human-synthesized CRP. After treatment, the cells were incubated for approximately 48 hrs.

Staining: After incubation, the cells were processed using an Osteogenesis Quantitation kit (Millipore, Billerica, MA). The medium was carefully aspirated from each dish and cells were washed once with 2mL of PBS solution. Next, the cells were fixed with 2 ml of ice cold 70% ethanol and incubated at room temperature for 15 minutes. Then, the ethanol was aspirated and cells were rinsed three times (5-10 minutes each) with an excess of distilled water, using caution to wash cells without disturbing the monolayer. Next, the water was removed and 1mL/well Alizarin Red Stain Solution was added and cells were incubated at room temperature for at least 20 minutes. Finally, the dye was aspirated and washed 4 times with deionized water. 1 mL of deionized water was added to the plates prevent the cells from drying.

Microscopy: The plates were viewed and imaged under both phase contrast and traditional light microscopes at 40x, 100x, and 400x. The Alizarin Red Solution stained differentiated cells containing mineral deposits bright red.

Western Immunoblotting: Certain cell batches were reserved for Western Immunoblotting. They were processed according to the aforementioned protocol, however after incubation, the cell plates were scraped and dissolved in lysis buffer. The samples were then microcentrifuged at high speed (15,000 rpm). The supernatants were removed into separate tubes. The remaining pellets and the supernatants were resuspended in sample buffer. Based on a spectrophotometry analysis using BioRad standards, the amounts of sample to be run on a 12% SDS-PAGE gel were ascertained from a standard curve. The gel was then transferred to a PVDF membrane. The membrane was then blocked with Bovine osteocalcin primary antibody and then secondary goat-anti rabbit antibody. Membranes were then placed in ECL reagent and exposed on Kodak film in a dark room.

Results: A preliminary experiment with the MC3T3-E1 line showed almost a 100-fold increase in bone matrix deposition measured by μ M concentration of calcium from Alizarin Red S staining. The current study, which primarily focused on the effect of CRP on hFOB 1.19 cells showed a dose-dependent type response with increasing concentrations of calcium crystals in CRP-treated cells

compared to both positive and negative controls shown through microscopy. In our experiment testing the effect of non-specific peptides on the production of bone matrix in the human fetal osteoblast cells, it was found that CRP increases matrix whereas the other Non-specific peptides do not increase matrix even though they mobilized calcium in PC12 cells in our initial screening. It was also shown in our one trial comparing mouse-synthesized CRP with human-synthesized CRP that the mouse peptide produced more bone matrix than the human peptide on hFOB 1.19 cells. Western immunoblotting using Bovine osteocalcin as a biomarker for bone matrix formation showed increased expression of low molecular weight band in CRP treated samples as compared to controls, which implies increased secretion of Osteocalcin with CRP treatment.

Conclusions: As shown by the aforementioned techniques, our algorithmically derived calcitonin receptor peptide shows a significant increase in bone matrix secretion by hFOB 1.19 (human fetal osteoblast) cells when compared to negative controls, positive controls, and other non-specific peptides that mobilize calcium. Further experiments, such as animal fracture models need to be conducted to assess the potential anabolic effects of this peptide. Anti-resorptive activity of CRP should also be assessed on osteoclasts *in vitro*. In addition, the exact mechanism of action of this peptide needs to be studied further.

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Basic Science and Clinical Research



David Ta-Chen Lee, MS2

Preceptor:

Gordon K. Lee, M.D.

Director of Microsurgery, Assistant Professor of Surgery (Plastic Surgery)

Program Director, Plastic Surgery Residency

Stanford Plastic & Reconstructive Surgery

The Use of Cold Ischemia Facilitates Microvascular Breast Reconstruction

Introduction: A major drawback to microvascular free flap breast reconstruction is the length of operation, which may be 6 hours or more for unilateral reconstruction and 9 hours or more for bilateral reconstruction. This takes a significant mental and physical toll on the surgical team which can produce fatigue that may compromise patient care and surgical outcome.

Objective: To facilitate the operation we have incorporated a period of cold ischemia of the flaps such that members of the surgical team can alternate a brief respite during the operation. Flap outcomes are assessed and compared to previously published studies to evaluate safety and efficacy.

Methods: We retrospectively reviewed our series of microvascular free flap breast reconstructions performed over a four year period in which cold ischemia of the flaps are induced, and recorded ischemia times, operative times, complications, and outcomes.

Results: Average cold ischemia time for unilateral reconstruction was 1 hour 53 minutes. For bilateral reconstruction, average cold ischemia time was 2 hours 20 minutes for the first flap and 3 hours 42 minutes for the second flap. Average operative times were 6 hours 25 minutes for unilateral and 10 hours 35 minutes for bilateral reconstruction. Average rest time for each surgeon was 35 minutes. Complications included 2 total flap losses (1.9%), 1 partial flap loss (1.0%), 2 hematomas (1.9%), 3 fat necrosis (2.9%), 2 delayed healing (1.9%), and 1 venous thrombosis (1.0%).

Conclusion: Cold ischemia facilitates breast reconstruction by allowing the surgical team to take breaks during the operation. This helps to reduce surgeon fatigue, and is well-tolerated by the flaps as the complication rate and patient outcomes compare favorably to previously published studies. Furthermore, cold ischemia appears to be tissue protective – the probability of complications decreases as cold ischemia time increases. We believe that the routine use of cold ischemia, especially for bilateral cases, is particularly advantageous in microvascular breast reconstruction.

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Leroy Lindsay, MS2

Preceptor:

Ilya Voloshin, M.D.

Department of Orthopedics

University of Rochester Medical Center

Anterior Deltoid Fascia and Muscle Tensile Strength: A Cadaveric Biomechanical Study

Abstract: There is currently no consensus on how much deltoid insertion can be disrupted before clinical failure of the deltoid origin occurs. The hypothesis of the study is that anterior acromioplasty as part of subacromial decompression partially disrupts the footprint of the anterior deltoid origin. The results of this study provide practical anatomic guidelines and landmarks for surgeons performing anterior acromioplasty to prevent detachment of the anterior deltoid.

Objectives: Subacromial impingement is a common problem causing shoulder pain and disability. There is currently no consensus on how much deltoid insertion can be disrupted before clinical failure of the deltoid origin occurs. The hypothesis of the study is that anterior acromioplasty as part of subacromial decompression partially disrupts the fascial footprint of the anterior deltoid origin and weakens the attachment.

Methods: Sixteen fresh frozen cadaveric shoulders were dissected after thawing to room temperature. A 2.0 cm segment of the anterior deltoid origin was isolated on the acromion. The segment bordered the acromioclavicular joint medially and anterolateral corner of the acromion laterally.

The shoulders were mounted on an Instron machine. They were divided into four groups for testing. Group 1 (N=2) served as controls with whole, uncut fascia. Group 2 (N=3) had the inferior fascia cut along the entire undersurface of the anterior acromion. Group 3 (N=9) had the entire inferior fascia cut as well as a 10mm portion of superior fascia.

Group 4 specimens had a deltoid segment 2.5 cm wide. The inferior fascia was undercut as in Groups 2 and 3. The 1 cm superior fascia cut was made in the central portion of the segment and the tendinous septum we identified during dissection remained undisturbed.

Failure was defined as the strength in Newtons of the yield point. Statistical analysis was performed using an unpaired student t-test to analyze for difference in the mean yield point between groups. Observation of the site of complete loss of tissue integrity were also recorded.

Results: The failure for Groups 1 and 2 were through the muscle belly and not the tendon origin of the deltoid. Combined, Groups 1 and 2 (N=5) had a mean load-to-failure of 166.4 N with a SD of 34.97 N. Group 3 failed at the tendon origin on the acromion. Group 3 (N=9) had a mean of 96.22 N, SD 47.75 N. The 95% confidence interval of the difference of means (70.18 N) was 16.82–123.54 N ($p=0.0142$). Group 4 was not included in the analysis due to difference in the location of the cut superior fascial segment and was used for observational analysis. Testing yielded much higher load-to-failure (226 N and 271 N) with failure through the muscle belly and not the acromial attachment despite an equally sized, but differently located superior fascial defect compared to Group 3.

Conclusions: Partial anterior deltoid detachment in a cadaver model can yield complete failure at the acromial attachment in shoulders with defects of 1 cm of the superior fascia of the anterior deltoid. Undercutting the inferior fascia does not yield failure at the origin; instead failure is distributed in the muscle belly itself.

We identified two important structures that must be left intact during acromioplasty. The first is the superior fascia of the anterior deltoid insertion. The second is a tendinous septum that is consistently located 2-2.5cm lateral to the AC joint. The results of this study provide practical anatomic guidelines and landmarks for surgeons performing anterior acromioplasty.

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Basic Science and Clinical Research



Kyle Lybrand, MS2

Preceptor:
Gross, M.D.
Orthopedics
Center

Jonathan
Department of
University of Rochester Medical

Healing Rates in Supracondylar Femur Fractures

Abstract: Supracondylar femur fractures are complex fractures that typically require surgical intervention. These fractures are traditionally seen in a bimodal distribution of patients: low energy fractures in the elderly, who have multiple medical co-morbidities, and high energy fractures in younger populations. Nonunion, or failure of the fracture to heal properly, remains a big concern for these patients. To our knowledge, there are no studies that look at the effects of co-morbidity on the development of nonunion.

This project retrospectively reviewed all patients over age 18 who presented to the Orthopaedic Trauma Service at University of Rochester with a supracondylar femur fracture over the past 8 years. Charts were reviewed for treatment course and medical co-morbidity. Steroid use, diabetes, osteoporosis, smoking, open fractures, and multiple fractures were analyzed against the need for a second procedure to correct nonunion.

Objectives: The effect of co-morbidity on the development of supracondylar femur fracture nonunion was reviewed. Age, history of steroid use, diabetes, osteoporosis, smoking, open fractures, and multiple fractures were specifically examined.

Methods: Charts were reviewed retrospectively for treatment course and co-morbidities for 116 patients with a supracondylar femur fracture. Associated co-morbidities were analyzed against the need for a second procedure to correct nonunion. Data were analyzed using a Wilcoxon rank-sum test for age and Fisher's exact test for other factors.

Results: The overall nonunion rate was 14%. The results showed no significant association between age ($P=0.423$), history of steroid use ($P=0.393$), diabetes ($P=0.423$), osteoporosis ($P=0.327$), or smoking ($P=0.632$) on the need for a second procedure. Open fractures ($P=3.486e-05$) and multiple fractures ($P=0.032$) both showed a significant association to the need for a second procedure. However, the variable of multiple fractures was not significant ($P=0.22$) after a Bonferroni multiple testing adjustment.

Conclusions: All co-morbid factors were not significant with the exception of an open fracture, which was strongly associated with nonunion ($P=3.46e-05$). Based on this significant association, the overall nonunion rate of 14% in this patient population seemed to correlate more with sustaining an open fracture versus the other co-morbidities investigated. These results show that good surgical principle may be more important than co-morbidity in determining uncomplicated union. However, this conclusion is preliminary and we are still deciding how to best interpret these data.



Basic Science and Clinical Research



Mark Marinescu, MS2

Preceptor:

Manish Shah, M.D., Ph.D.

Chief, Division of Prehospital Medicine

Associate Professor of Emergency Medicine, Community and Preventive Medicine, and Geriatrics

Department of Emergency Medicine

University of Rochester School Medical Center

Screening for Depression and Cognitive Impairment in the EMS System: Comparing transportations routes to the ED

Introduction: Depression, anxiety, and cognitive impairment have been shown to have a profound impact on the lives of older adults.^(1,2) Many older adults with these conditions have not been diagnosed by their physicians and have not received interventions.^(3,4,5,6) Some have proposed screening older adults in alternate sites such as the emergency department (ED) or the prehospital emergency medical services (EMS) settings.^(7,8) Little is known about the comparative prevalence of these conditions among patients arriving to the ED via EMS or those arriving via other means.

Objective: To compare the prevalence of anxiety, depression and cognitive impairment among patients who arrive at the ED by EMS or other means.

Methods: We conducted a prospective cohort study of all community dwelling, English speaking, adults aged 60 or older, presenting to the Strong Memorial Hospital ED between May 27, 2008 and August 1, 2008. Data obtained from consenting patients is as follows: chief complaint, past medical history, demographics, and arrival method to the ED. Consenting patients were also evaluated for cognitive impairment, anxiety, and depression using the Six Item Screener, GAD-7, and PHQ-9 screening tools respectively.^(9,10,11) Patients were stratified based on their mode of arrival to the ED, EMS or other means, and the acuity of their symptoms (ESI 1-2 high acuity, ESI 3-5 low acuity).

Results: Of 2055 individuals approached to consent, 1422 (71%) consented. Individual with multiple ED visits during the study period may have been included multiple times. Among these patients 754 (53%) arrived by ambulance, and 656 (46%) met high-acuity criteria. Patients reported a history of anxiety (267, 19%), depression (238, 17%), and cognitive impairment (52, 4%). In the ED, 142 (10%) screened positive for anxiety, 204 (15%) screened positive for depression, and 153 (11%) screened positive for cognitive impairment. Among patients who screened positive for anxiety and depression, similar proportions arrived via EMS or other means (11% vs. 9% and 15% vs. 19% respectively), $p > 0.05$. Significantly, more patients screening positive for cognitive impairment arrived via EMS vs. other means (13% vs. 9%, $p = 0.02$).

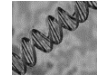
Conclusion: We found that the prevalence of anxiety and depression is comparable among ED patients who arrive via EMS and who arrive via other means. The prevalence of cognitive impairment is significantly greater among patients who arrive via EMS. These findings suggest that although the EMS system may be an appropriate setting to screen for these conditions, solely screening in this setting would fail to identify almost half of those at risk.

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Basic Science and Clinical Research



Benjamin Marsh, MS2

Preceptors:

Martha Johnson Gdowski, Ph.D.

Jason Schwalb, M.D.

Department of Neurobiology and Anatomy

University of Rochester Medical Center

Deep Brain Stimulation of STN: Gating Sensorimotor Information Flow

Abstract: Subthalamic deep brain stimulation (STN-DBS) is a highly effective therapy for alleviating some of the akinetic motor symptoms of Parkinson disease (PD). We sought to test the hypothesis that voluntary movement execution improve during STN-DBS as a consequence of reduced variability in reaction time. To characterize the kinematic effects of deep brain stimulation of the subthalamic nucleus (STN-DBS) as a treatment for Parkinson disease (PD), we quantified upper limb motion of one subject with the diagnosis of PD during a visually guided button press task performed with and without the ability to plan for movements in advance. To quantify the individual and combined effects of stimulation and medication, the study participant was tested without dopamine replacement therapy with STN-DBS off, without dopamine replacement therapy with STN-DBS on, and with dopamine replacement therapy with STN-DBS on. Reaction time and movement time were calculated as measures of movement planning and execution, respectively. Kinematic measures of upper limb movement were also quantified (e.g. velocity, acceleration). We found that there are some changes in variability of reaction time, but that most of the improvement in voluntary movement execution seen in STN-DBS is due to shortened movement times and increased velocity. DBS improves sensorimotor integration in behaviors that involve planning, while DBS retards movement execution in unplanned behaviors. It also improves movement acceleration and peak velocity, but increases the time spent in deceleration. This subject showed hand specific differences in the off stim state. Clinical benefits of DBS may be due to a decrease in the tonic unplanned movements and restore planned movement through disinhibition of a braking pathway.

Objectives: Disrupted cross-modality integration (e.g. gait arrest from visual input) is a hallmark of Parkinson's Disease (PD) [1-6]. In PD increased activity of the subthalamic nucleus (STN) is thought to underlie the akinetic motor symptoms [7, 8]. Previous studies suggest that deep brain stimulation (DBS) acts to inhibit neurons proximal to the electrode head, mimicking an ablation or focal lesion. A potential role of STN may be to inhibit certain voluntary movements, therefore inhibition of STN's inhibitory action (disinhibition) allows a desired movement to be generated [9, 10].

We quantitatively compared movements a single PD patient with DBS (on- and off-stim, on and off meds conditions) with a control individual matched for both age and gender during a button pressing task. The goal of this study was to test the hypothesis that voluntary movement execution improve during STN-DBS as a consequence of reduced variability in reaction time. Such results would improve our understanding of the influences of STN upon sensorimotor integration.

Methods: Subjects with DBS implants were recruited from patients treated at the University of Rochester Neurology and Neurosurgery clinics. Using a 3-D motion system (Vicon Motion

Systems), we quantified task-related index finger velocity for intra-subject comparison in on/off DBS states with age matched controls. The following measures were calculated: reaction time (delay between movement cue presentation and movement onset), time to peak velocity (time between movement onset and peak velocity (greatest velocity achieved during the second phase of movement), and peak to instruction target (time from peak velocity to instruction target press, and movement time (MT: delay between button release to subsequent button press). For this study, only the distal index finger marker was used as its motion is an end product of these combined movements, and the best indicator of behavior.

Results: We assessed changes in variability of reaction time as a possible source of improvements in voluntary movement execution as a result of STN-DBS using the coefficient of variance. In the left hand there is a slight increase in variability in both planned and unplanned tasks, with greatest variability in the more distant instruction targets. The right hand shows improvement across all targets, especially in the closest target. STN-DBS also affects reaction time, time to peak, peak to instruction target time and peak velocity. Much of the improvement in voluntary movement execution is attributed to changes in movement times and velocity. In a comparison of reaction time the PD subject is affected by planning while the control shows no changes in reaction time with planning. Treatment differentially impacts movement planning whereby RT improves with advance target information and is impaired without such information.

In a comparison of time to peak during planned and unplanned tasks stimulation improved the acceleration phase of movement execution independent of advance target information. The improvements seen in the execution of visually guided button pressing tasks is, at least in part, due to a faster acceleration phase of movement.

Comparing peak velocity in planned and unplanned tasks it was found that stimulation not only increases the acceleration phase of movement execution but also increases the peak velocity reached in a hand specific fashion, shortening movement times. This effect does not have a differential association with advanced target information.

We also compared the length of time from peak velocity to the pressing of the instruction target. In this subject, performance is hindered during the deceleration phase of movement execution in the treatment condition.

Conclusions: DBS improves sensorimotor integration in behaviors that involve planning, while DBS retards movement execution in unplanned behaviors.

It also improves movement acceleration and peak velocity, but increases the time spent in deceleration. This lengthening may result since greater peak velocities may increase the need for online error correction or adjustments because a less efficient path to target is implemented. Further investigation of the kinetics of this phase of movement is warranted.

Even though the PD subject did not demonstrate handedness in disease severity (as assessed by UPDRS scoring) and underwent bilateral DBS stimulation, this subject showed hand specific differences in the off stim state. This could indicate that behavioral tests such those that we used could be used to assess disease severity with greater precision than current clinical tests.

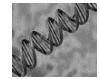
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Basic Science and Clinical Research



Patrick Milord, MS2

Preceptor:

William B. Macaulay, M.D.

FOCUS Transfusion Trigger Trial

Center for Hip and Knee Replacement, Department of Orthopaedic Surgery

Columbia University College of Physicians & Surgeons

FOCUS Transfusion Trigger Trial

Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair

Abstract: Historically, in regards to US medical interventions, blood transfusions remain to be among the most common. Yet despite suggested hospital protocols, there are currently no detailed set standard indications for post-operative blood transfusions. An increased risk of mortality and negative outcomes is associated with anemia, especially for those in higher risk populations (cardiovascular disease/risk). Consequently, in patients with such impaired compensatory physiological mechanisms, the specific hemoglobin threshold for transfusion is still subject to debate.

Objectives: This study was designed to determine whether patients with a history of cardiovascular disease or cardiovascular risk factors, after undergoing surgical hip fracture repair, have better long term functional outcomes from either higher or lower transfusion triggers.

Methods: The FOCUS Trial is a 2,000 patient, multicenter clinical trial based in UMDNJ-RWJ, funded by the National Heart, Lung, and Blood Institute. It has currently closed enrollment, and is in the data analysis phase.

Hip fracture patients with a history of cardiovascular disease or cardiovascular risk factors were screened and consented; if post-operative hemoglobin concentration fell below 10 g/dL within 3 days of surgery, patients were subsequently randomized to one of two study arms. The trigger arm required blood transfusions to maintain the patient at a baseline [Hb] > 10 g/dL; the symptomatic arm indicated transfusions only if the patient developed symptoms of anemia (or [Hb] < 8 g/dL). Hemoglobin levels were continually measured.

The primary outcome measured was the patient's ability to walk across the room or 10 feet without human assistance at 60 days post-discharge. Secondary outcome measures were the development of an acute coronary syndrome (as indicated by EKG + corresponding blood samples), or death within 30 days of discharge.

Results: During the eight week period of June 2008 - July 2008, a total of fourteen patients were screened, consented, and registered. A total of six patients were completely enrolled and randomized; all other patients either refused enrollment, had unavailable data, or did not meet appropriate post-operative hemoglobin levels. Of those selected randomized, four patients were randomized to the transfusion trigger arm of > 10 g/dL, and two patients were randomized to the symptomatic arm. Data collection of these selected patients shows the mean [Hb] at randomization for the trigger arm (8.95 ± 0.74 g/dL, $p > 0.05$) was greater than that of the symptomatic arm ($8.85 \pm .05$ g/dL, $p > 0.05$). With regards to the amount of transfusions received, the patients of the trigger arm received a mean 1.75 ± 0.433 transfusions, while those patients designated only to symptomatic treatment received a mean 1.00 ± 1.00 transfusions. Analysis of [Hb] before discharge

showed that regardless of trial group, there was an overall increase in [Hb] as compared to hemoglobin concentration on hospital admission; in the symptomatic group, there was a mean hemoglobin increase of 0.35 ± 0.85 g/dL, and an increase of 0.875 ± 0.570 g/dL present in the 10g/dL transfusion trigger group.

Conclusions: Patients with cardiovascular disease and risk factors are especially susceptible to anemia and subsequent pathology. The threshold hemoglobin concentration required for transfusion has not been universally defined; this limited data shows that higher transfusion triggers are associated with greater number of transfusions, and an overall greater increase in hemoglobin concentration from admission to hospital discharge. Primary and secondary functional outcomes were not obtained, as that information was acquired by blinded individuals at the data collection headquarters. In order to have any appreciable statistical significance, a larger sample size and corresponding power is needed. Thus, data from the full multicenter trial (approximately 2,000 patients) will be needed to make any substantial conclusions. It is of note, however, that regardless of treatment group, elderly hip fracture patients whom consent to clinical research truly are special individuals.

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Basic Science and Clinical Research



Jamie Mullally, MS2

Preceptor:

Arthur Moss, M.D.

Professor of Medicine

Department of Cardiology

University of Rochester Medical Center

Long QT Syndrome: Clinical and Prognostic Significance of Cardiac Events in the First Year of Life

Objectives: The clinical and prognostic significance of long QT syndrome (LQTS)-related cardiac events occurring during the first year of life has not been studied previously. The goals of the present study are to assess the clinical risk factors for experiencing LQTS-related cardiac events in the first year of life and to evaluate the subsequent clinical course of LQTS patients in the next 10 years of life among those who did and did not experience a cardiac event before age 1.

Methods: The study population of 3,323 patients (pts) with $QTc \geq 450$ ms enrolled in the International LQTS Registry was categorized into 3 groups during their 1st year of life: 1) 20 pts with sudden cardiac death (SCD); 2) 50 pts with a nonfatal LQTS-related cardiac event (NFCE) (34 with syncope and 16 with aborted cardiac arrest (ACA)); and 3) 3,253 asymptomatic pts. Among pts who survived the 1st year, risk factors for life-threatening cardiac events during age 1 to 10 years were evaluated by Kaplan-Meier and Cox model methods.

Results: Of the 20 infants with SCD in the 1st year of life, 8 had an ECG (6/8 with $QTc \geq 500$ ms), 4 experienced a prior cardiac event, and 4 were on beta-blockers at the time of death. Infants with ACA in the 1st year of life had a significantly higher risk of experiencing ACA or SCD during the next 10 years than those with syncope (Fig). A NFCE in the 1st year of life had a hazard ratio of 4.28 ($p < 0.001$) for ACA or SCD during age 1-10 years after adjustment for gender, QTc , and time-dependent syncope during follow-up; beta-blockers were associated with a moderate reduction in ACA/SCD in high-risk patients with recent syncope during follow-up ($HR=0.47$, $p=0.10$).

Conclusions: LQTS pts who experience ACA during the first year of life are at very high-risk for subsequent life-threatening cardiac events during their next 10 years of life.

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Basic Science and Clinical Research



Derek Ng, MS2

Preceptor:

Samantha Hendren, M.D.

Assistant Professor of Surgery

Department of Surgery

University of Rochester Medical Center

Anal Dysplasia Screening and Treatment

Introduction: It is now well-recognized that the anal canal epithelium may undergo dysplastic change in response to human papillomavirus (HPV) infection, similar to the female cervix. This anal dysplasia may be the precursor lesion to invasive squamous cell carcinoma of the anal canal (SCCA). High-risk individuals such as HIV-positive men who have sex with men have a high prevalence of anal dysplasia, and national statistics have shown a dramatic increase in cases of SCCA in this population.

In response to this trend, HIV and colorectal specialists across North America have begun to screen high-risk patients for anal dysplasia and treat high-grade dysplasia in an effort to prevent SCCA, analogous to the screening and surveillance programs for cervical dysplasia. However, these programs are in their infancy, and there is a great deal of controversy about the effectiveness and cost-effectiveness of this strategy. At the core of the controversy are the following questions:

1. What is the natural history of anal dysplasia?
2. Does dysplasia treatment actually prevent progression to SCCA?
3. What are the costs and morbidities of the screening program, from the perspectives of the patient and the health system?

Previous research since the advent of highly active treatment for HIV (HAART-era) has shown that a screening program [with anal pap test, anal colposcopy, biopsies, and treatment with infrared coagulation (IRC)] in the outpatient setting is feasible. There is a suggestion that rates of progression may be decreased in small, uncontrolled studies. The anal pap test has shown a variable sensitivity and specificity, ranging from 69-93% and from 32-59%, respectively.

Objectives:

- Collect and analyze data from patients screened and treated for anal dysplasia from Strong Memorial Hospital Dysplasia Clinic
- Using collected data, measure the test characteristics of the anal pap test in the clinic's population
- Measure the rate of progression from low-grade to high-grade dysplasia, and from dysplasia to SCCA in the clinic's population over time, stratified by clinical risk factors.

Methods: Clinical and laboratory data were collected from all patients at the Strong Memorial Hospital Dysplasia Clinic who underwent both an anal Pap test and an anal histological biopsy within 6 months of the Pap test. The patient population for this study includes males and females, HIV-positive and HIV-negative patients. Each lesion identified and biopsied was followed for progression or regression over time and documented for exact location.

The sensitivity, specificity, positive predictive value and negative predictive value of the anal pap test in predicting biopsy-proven high-grade dysplasia or SCCA will be calculated and stratified by patient characteristics (HIV status).

Results: Due to unforeseen challenges, the data collection phase of the study is ongoing. Thus, results have not yet been obtained. The study hypotheses include:

- High-risk patients referred for anal dysplasia screening will have a high rate of biopsy-proven dysplasia
- Office treatment for high-grade dysplasia with IRC will result in a low risk of progression to SCCA
- Screening and treatment for anal dysplasia in a specialized clinic will lead to low rates of morbidity and sexual dysfunction

Conclusions: The primary hypothesis driving this study is that treatment of moderate and high grade dysplasia with infrared coagulation will cause “down-grading” of the condition to low-grade dysplasia or no dysplasia, and prevent the progression to invasive squamous cell cancer. Secondary hypotheses are (1) that the anal Pap test is an accurate predictor of the finding of high-grade dysplasia on biopsy, and (2) that advanced states of immunosuppression (as evidenced by low CD4 count or high viral load in HIV) predict treatment failures.

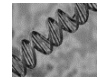
Additional information about the accuracy of screening tests, the natural history of anal dysplasia, and the morbidity of the procedure from the patient’s perspective are clearly needed, as practitioners across North America struggle with the question of whether to institute anal dysplasia screening programs in their communities.

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Basic Science and Clinical Research



Lisa Niswander, MS2

Preceptor:

Dr. David Korones, M.D.

Pediatric Hematology/Oncology Division

Golisano Children's Hospital

University of Rochester Medical Center

End-of-life Care for Children Enrolled on CompassionNet, a Community-Based Pediatric Palliative Care Program

Abstract: While the majority of childhood deaths are due to unintentional injury or accident, over 20% of childhood deaths are attributable to complex chronic conditions, which encompass a broad spectrum of disorders including cancer, cardiac anomalies, neurodegenerative, and genetic disorders.¹ Importantly, these children suffer greatly as they approach the end of life, and some of this suffering is not recognized or addressed by their healthcare teams.² Regarding the quality of care, families report dissatisfaction with communication, pain management, support for siblings, and inconsistent bereavement support.³ Pediatric palliative care (PPC) strives to relieve the physical, emotional, social, and spiritual suffering of children and their families.

Traditionally, most children with complex chronic conditions die in the hospital; however, in the last decade increasingly more children are returning home to die.¹ Despite the success of inpatient hospital-based pediatric palliative care programs, hospital end-of-life care alone is not sufficient to accommodate the growing number of children dying at home. Accordingly, there is an initiative to develop community-based pediatric palliative care programs to facilitate care for children who spend increasing time at home. To date, there are few published data on community-based care of dying children. To promote the development and growth of this field, we sought to describe the end-of-life of children enrolled on CompassionNet, a community-based pediatric palliative care program in Rochester, NY run by Lifetime Care Home Health and Hospice, and Excellus BlueCross BlueShield-Rochester Region.

Objectives: To describe end-of-life care during the last 6 months of life for children on a community-based PPC program.

Methods: A retrospective review of children < 21 years old who died while enrolled on a community-based PPC program (CompassionNet) from 12/2004 through 5/2008. Data were extracted on the last 6 months of life from hospital records (University of Rochester) and records of CompassionNet and its home-nursing team.

Results: Thirty-six children died on CompassionNet; diagnoses included cancer 20 (56%), genetic/neurologic disorders 7 (19%), cardiac anomalies 6 (17%), and other 3 (8%). In the last 6 months of life, there were a median of 2 emergency room visits (range 0-12) and 2 unplanned hospitalizations (range 0-6). Home visits by CompassionNet (case manager, physician, nurse) ranged from 1 to 121 (median 24). Thirty-two families (89%) received financial support; 14 children (39%) and 17 parents (47%) received massage therapy. A "goals of care" discussion was

documented for 29 children (81%), occurring a median of 16 days before death (range 0-118). Sixteen children died at home (44%); 20 died in the hospital (56%). Of the 16 families with a documented preference for location of death, 14 children died in this location (88%). Twenty-four of the 33 (73%) documented deaths were described as peaceful and/or in the parents' arms. Thirty-two families (89%) had bereavement support through CompassionNet.

Conclusions: The children who died on this PPC program received numerous supports in the home that may not be available in the hospital setting. Community-based teams are invaluable in easing the medical, social, emotional, and financial burdens of dying children and their families.

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Basic Science and Clinical Research



Stephen Ou, MS2

Preceptors:

Lloyd Rucker, M.D.

Vice Chair, Education, IM Program Director

William Gustin, M.D.

Assistant Clinical Professor of Medicine

UC Irvine Department of Medicine

UC Irvine Medical Center

Teaching at the Bedside and Its Impact on Patient Care

Abstract: A number of studies have demonstrated the value of formal bedside teaching and its effects on students. Yet, few studies have sought to demonstrate the effects of bedside teaching on patient's perception of their care. This novel study seeks to determine patients' perception of their care following participation in a Doctoring Skills Rotation (DSR) curriculum in a university-based teaching hospital. Compared to their normal physician team, patients in a university-based hospital participating in a Doctoring Skills Rotation (DSR) curriculum perceived their teaching team as spending more time at the bedside and sufficient time teaching medical students about their illnesses. This perception tended to persist and transfer to their normal physician team following the exercise, demonstrating the benefits that bedside teaching has on patients' satisfaction with their care.

Objectives: To test the hypothesis that bedside teaching through a novel Doctoring Skills Rotation (DSR) curriculum will result in an increase in patients' satisfaction with their care, knowledge about their illnesses, and willingness to be cared for in a university-based teaching hospital.

Methods: A total of 27 adult, English-speaking patients on an inpatient medical or surgical service were evaluated with surveys designed to assess the perception of their care in a university-based teaching hospital in Orange, CA before and after participating in a DSR curriculum. Following an initial survey evaluating patient baseline values, patients participated in a teaching exercise in which medical students interviewed and presented patients to a teaching physician followed by a discussion of the patients' illnesses. Patients were then surveyed to determine their perception of the DSR curriculum and when discharged, their perception of their care while in the hospital. Combined, these surveys sought to evaluate the impact of the DSR curriculum by measuring a number of values relevant to their care on a 5-point Likert-scale, including 1) satisfaction with current care, 2) understanding of his/her current medical plan, 3) satisfaction with the daily teaching at bedside by the primary care teams, 4) perception of time the medical team spends at bedside, 5) participation in teaching and care plan, and 6) overall satisfaction with their hospital experience. General information was also collected such as gender, chief complaint and length-of-stay during the study intervention to address basic demographics, participation bias, and to assess randomization. Furthermore, a total of 30 additional patients who did not participate in the DSR curriculum were also surveyed as a control group. Patients were consented prior to participation in the study.

Results: Patients' surveys were compared with a paired t-test (90% power; $p = 0.05$) to determine intergroup statistical significance and a student t-test to determine intragroup statistical significance. When comparing patient values before and after undergoing the teaching exercise, the DSR team were found to be easier to understand ($p = 0.03$) and tended to involve patients more when teaching students ($p = 0.01$) in comparison to patients' normal primary care teams. The DSR team was also perceived to spend both more time at the bedside ($p = 0.00002$) and sufficient time teaching students about their illnesses ($p = 0.02$). When comparing patients' baseline values to their values following discharge from the hospital, patients reported their normal physician team involving them more in the teaching of students and residents ($p = 0.04$). Finally, when comparing DSR participating patients with control patients, DSR patients reported both more time spent by their normal physician team at the bedside ($p = 0.01$) and sufficient time spent teaching students about their illnesses ($p = 0.02$).

Conclusions: Compared to their normal physician team, patients in a university-based hospital participating in a Doctoring Skills Rotation (DSR) curriculum perceived their teaching team as spending more time at the bedside and sufficient time teaching medical students about their illnesses. This perception tended to persist and transfer to their normal physician team following the exercise, demonstrating the benefits that bedside teaching has on patients' satisfaction with their care.

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Basic Science and Clinical Research



Gregory Ouellet, MS2

Preceptor:

Arthur J. Moss, M.D.

Professor of Medicine

Department of Cardiology

University of Rochester Medical Center

Long QT Syndrome (LQTS): Influence of Diabetes on Outcome in Patients Over 40 Years of Age

Abstract: Long QT Syndrome (LQTS) is an infrequently occurring genetic disorder that results in delayed cardiac repolarization and a prolonged QT interval on the electrocardiogram (ECG). Patients with LQTS are at increased risk for arrhythmogenic syncope due to ventricular tachycardia (torsades de pointes) and sudden cardiac death (1). The genetic aspects of LQTS reflect locus and allelic heterogeneity, and various mutations in several different genes have been shown to cause LQTS. However, the vast majority of patients have a mutation in one of three genes (KCNQ1, HERG, and SCN5A), and the related syndromes are referred to as LQT1, LQT2, and LQT3, respectively (2).

While most prior LQTS studies have focused on pediatric and young adult patients with this disorder, (3) a few recent studies have highlighted the association of LQTS with common co-morbidities in older adults (>40 years of age). (4) However, no study has focused on the risk conferred by diabetes mellitus in LQTS patients despite the fact that QTc prolongation occurs in diabetic patients and contributes to increased risk in patients with this metabolic disorder. (5,6)

Objective: The objective of this study was to investigate if diabetes mellitus (DM) is associated with an increased risk for cardiac events in older patients with Long QT Syndrome.

Methods: The study population consisted of 2,747 patients enrolled in the U.S. portion of the International LQTS Registry who survived beyond 40 years of age. Diagnosis of DM was based on the age at which oral diabetic medication or insulin was initiated. End points were; 1) first cardiac event [CE] (syncope aborted cardiac arrest, or all-cause mortality), and 2) all-cause mortality. Follow-up extended from age 41 to 75 years. Analyses involved graphic Mantel-Byar probability of mortality before and after DM and the Cox model.

Results: During follow-up, 302 patients experienced a first CE, and 215 patients died. The risk factors (hazard ratios and p-values) for first CE were syncope before age 41 (HR=3.53, $p<0.001$), female (HR=1.48, $p=0.01$), $QTc\geq 0.50s$ (HR=2.50, $p<0.001$), and a protective beta-blocker effect (HR=0.70, $p=0.05$); diabetes did not enter the CE risk model (HR=0.90, $p=0.80$). The development of DM was associated with an increased risk mortality risk (Fig). The risk factors for mortality were male (HR=1.62, $p<0.001$), $QTc\geq 0.50s$ (HR=1.49, $p<0.03$), and DM (HR=2.34, $p<0.001$); beta-blockers did not contribute to a reduction in mortality (HR=1.20, $p=0.32$). There was no significant or meaningful interaction of DM with $QTc\geq 0.50s$.

Conclusion: DM and prolonged QTc contributed independent mortality risks in the LQTS Registry population, and there was no significant interaction effect of diabetes on LQTS.

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Basic Science and Clinical Research



Nirav B. Patel, MS2

Preceptors:

Jeremy T. Cushman, M.D., M.S., EMT-P

Paramedic Program Medical Director

Monroe Community College

Manish N. Shah, M.D., M.P.H.

Department of Emergency Medicine

University of Rochester Medical Center

A Comparison of the Ohio and American College of Surgeons Guidelines in Identifying Trauma Center Need for Older Adults

Objectives: No studies have identified the accuracy of trauma triage guidelines for the older adult population. The objective of this study was to determine the sensitivity and specificity of the Ohio Geriatric Trauma Triage Guidelines (Ohio) compared to the American College of Surgeons Trauma Triage Guidelines (ACS) in identifying trauma center need.

Methods: EMS providers in charge of care for all injured adult patients transported to the only regional trauma center were interviewed between March 2007 and May 2008. Included were patients injured as a result of a motor vehicle crash, motorcycle crash, fall, or pedestrian or bicyclist struck by a motor vehicle. The interview included patient demographics, medications, past medical history, initial vital signs, apparent anatomic injury, and details of the mechanism of injury. All enrolled patients were followed until emergency department or hospital discharge. A combined outcome of death, admission, or operative procedure was used to define trauma center need. The Ohio and ACS guidelines were applied to all patients aged 70 years and greater. The sensitivity and specificity of each guideline for identifying trauma center need was determined.

Results: Five hundred sixty-four patients greater than 69 years of age were available for analysis. One hundred ninety-nine (35%) patients met the Ohio criteria which had a 29% (95% CI 21-38%) sensitivity and 63% (58-68%) specificity in identifying trauma center need. When including the Ohio "special consideration" criteria of co-morbid conditions suggesting transport to a trauma center, the criteria identified 319 (57%) patients which resulted in a 52% (43-61%) sensitivity and 42% (38-47%) specificity. The ACS guidelines identified 126 (22%) patients and had a 21% (14-29%) sensitivity and a 77% (73-81%) specificity in identifying trauma center need. When including the ACS "special considerations" of dialysis, anticoagulation, and bleeding disorders, the criteria identified 138 (25%) patients which resulted in a 25% (18-34%) sensitivity and a 76% (71-80%) specificity.

Conclusions: The Ohio Geriatric Trauma Triage Guidelines and the ACS guidelines have poor sensitivity and specificity to identify older adults in need of trauma center care. New criteria must be developed to ensure quality care for the geriatric trauma patient.

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Basic Science and Clinical Research



Jeromy Patterson, MS2

Preceptor:

Martha Gdowski, Ph.D.

Department of Neurobiology and Anatomy

University of Rochester Medical Center

Effects of Aging on Voluntary Movement Observed Through Instrumental Paradigm

Abstract: Parkinson's disease (PD) is a disease of the elderly characterized by progressive loss of motor and cognitive functions¹. Clinical signs include tremor, hypokinesia, akinesia, rigidity, loss of postural reflexes and difficulty with higher order cognitive tasks. Favored therapies include oral dopamine replacement therapy and the surgical insertion of a stimulating electrode into the subthalamic nucleus (STN-DBS). Although used successfully for over a decade², the mechanism of action for STN-DBS therapy remains poorly understood. To dissociate changes in movement planning and execution related to PD and/or its treatments, we must first characterize voluntary movement changes that accompany normal aging.

To do so, an instrumental paradigm which measured forearm movements in a set of sensorimotor tasks involving a panel of buttons was used. It was found that the elderly have quantifiable decreases in peak velocity than the young, longer reaction and movement times than the young and that most of the increase in movement time occurred in deceleration from peak velocity as opposed to being from acceleration to peak velocity.


Objectives: To characterize the changes in voluntary movement occurring from age. This has two purposes. First, it better understanding of the natural process of aging. Second, changes in voluntary motor function that occur with age need to be determined so they can be differentiated from changes in voluntary motor function that occur with disease states containing a motor component, such as Parkinson's Disease.

Methods: Subjects sat in a light and sound attenuated room for the performance of two button pressing tasks guided by visual and auditory cues. Audible tones triggered movement onset and provided feedback about successful completion of each trial. Two tasks (Planned vs. Unplanned) used for this study differed in whether subjects have knowledge of the target to which they would move prior to the movement onset cue. A representative trial from each task is shown in figure 1. To acquire data about the position of the arm in space throughout the task, reflective markers were placed relative to anatomical landmarks on the sternum, shoulder, elbow, wrist, and index finger. Vicon Motion Systems cameras continuously recorded all marker positions throughout data collection while a National Instruments System coordinated and time stamped the occurrence of all task events.

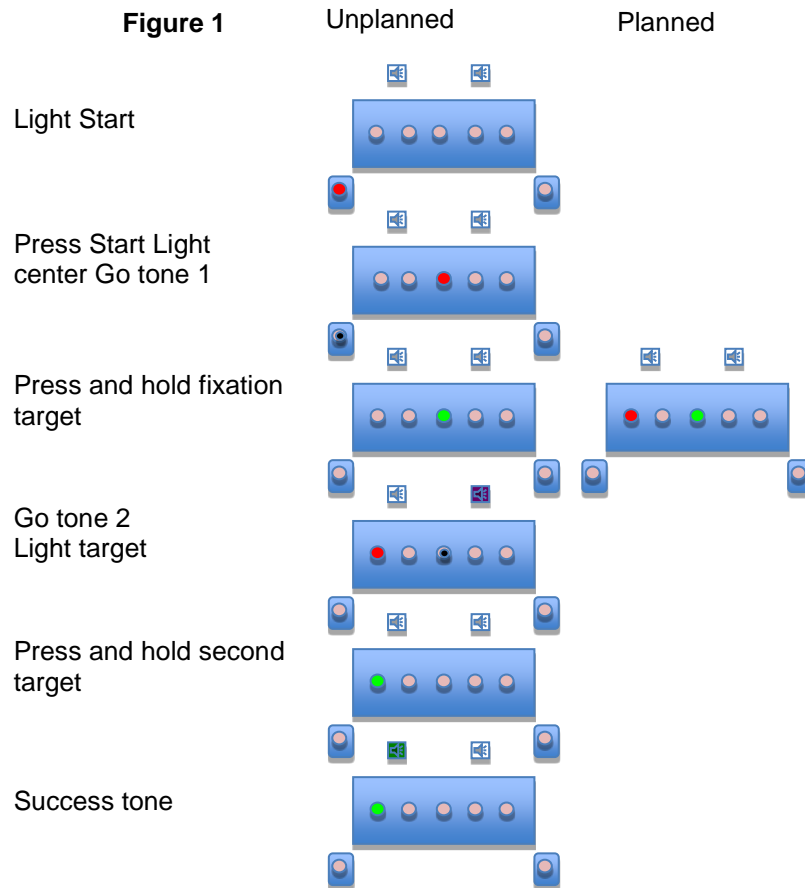
Figure 1: Red represents target illumination cueing the subject to move to that target.

Green represents that the target is has been reached.

 = no auditory cues are given

 = auditory cue to move has been given

 = auditory reward tone has been given upon completion of task



Results: It was found that peak velocities decrease with age ($p=0.001$), that times to reach peak velocities increase with age ($p=0.001$), that the elderly have higher reaction times and time spent from onset of movement to peak velocity than the young age group ($p=0.005$ and $p=0.001$), that the elderly have longer movement times ($p=0.00005$) and longer times from peak velocity to reaching their target ($p=0.001$). Additionally it was observed that the increased movement times of the elderly was mostly from time spent decelerating (i.e. from peak velocity to reaching their target) than from time spent accelerating (i.e. time from onset of movement to peak velocity).

Conclusions: Easily observed qualitative deficits in voluntary motor function with age have both cognitive and motor components when quantified. This is demonstrated in the higher reaction times and movement times of the elderly as compared to the young age group, similar to findings

made by Rossit³ and Romero⁴. Movement time had two components, time from onset of movement to peak velocity and time from peak velocity to the target, or acceleration time and deceleration time, respectively.

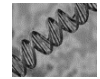
It was also found, as in other studies such those done by Romero and Rossit, that peak velocity decreased with age. In contrast to the study by Romero, it was found that time to peak velocity was higher for the elderly than the young. Nonetheless, similar to Morgan⁵, it was observed that most of the increased movement time seen in the elderly came from time spent in deceleration.

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Basic Science and Clinical Research



Joseph Point Du Jour, MS2

Preceptor:

Silvia Sörensen, Ph.D.

Assistant Professor of Psychiatry

Department of Psychiatry

University of Rochester Medical Center

The Effect of a Preventive Problem Solving Intervention on Social Problem Solving in Elderly Patients with Macular Degeneration.

Abstract: Age-related macular degeneration (AMD) is the leading cause of severe visual impairment in developed countries, affecting approximately every fifth older person between 65 and 74 years of age and nearly every third person beyond the age of 75. Because of significant losses in ability to perform activities of daily living, the impact of AMD quality of life of the elderly can be very severe. Because of its rampant pathological destruction, AMD has led its patients to suffer significant emotional distress and profoundly reduced quality of life.

Due to many challenges that AMD patients face, some have used interventions aimed at teaching problem solving skills to enhance the quality of life of those individuals. These approaches are generally based on the social problem solving theory. Social problem solving (SPS) is a behavioral-psychosocial theory that has proven to be an important element in the development of both mental and physical health problems emerging from poor adaptation to stressful life events. SPS theory has been translated into problem solving therapy in various research fields. Problem solving training (PST) is a collection of strategies directed at helping individuals to comprehend the nature of problems in the “real world” and shifts their attempts at changing the nature of the problematic situation itself. These consist of negative problem solving orientation, positive problem solving orientation, rational problem orientation, avoidance style, and impulsivity/carelessness style. This project aims at measuring the impact of the problem solving training in the lives of patients with macular degeneration.

Twenty AMD patients, 33% male and 67 % female, aged 69-94 participated in an intervention to improve preparation for future care. The entire preventive problem solving intervention includes four Vision Education classes delivered at the Association for the Blind and Visually Impaired (ABVI). The participants also had in-home sessions with certified problem solving therapist, which include four sessions of formal Problem Solving Training and four sessions of Preparation for Future Care training.

A paired t-test analysis was performed to determine the effectiveness of the training by comparing the participants' scores at pre-intervention with respect to post-intervention. The results indicated a statistically significant increase from PPO pre-intervention compared to PPO post-intervention. Further analysis showed a significant decrease both from NPO pre-intervention to NPO post-intervention and from ICS pre-intervention to ICS post-intervention.

The data clearly indicate that AMD patients are more likely to learn new positive problem skills while rejecting problem solving methods that lead to negative outcomes. Furthermore, the

diminished use of impulsiveness/carelessness style that was observed in the study shows the potential health benefit of using the PST intervention in helping AMD patients deal with everyday problems. It was thus concluded from this preliminary data gathered from the study that the problem solving therapy can help adults apply their problem solving skills at various life challenges, which subsequently leads to greater well-being in AMD patients.

Objectives: This project aims at employing the problem solving therapy in managing “everyday-problems” in patients with macular degeneration. Though this project has some similarities to the work Rovner et al [2006] has done, yet there are many differences worth mentioning. While Rovner et al focused on the efficacy of problem-solving treatment in preventing major depression AMD patients, our work is testing the efficacy of problem solving therapy in helping AMD patients prepare for future care. In addition, while their work emphasizes the effects of depression on patients’ problem-solving skills, this project intends to not only teach the participants the problem-solving skills, but also to integrate and implement those skills in resolving future problems.

Methods: The Social Problem Solving Inventory –Revised (SPSI-R) [D’Zurilla et al., 2002] short form is 25-item multi-dimensional measure of social problem solving ability that was expanded from the original social problem solving inventory based on the results of various analytical studies [D’Zurilla et al, 2003; D’Zurilla & Nezu, 1990]. It comprises five major scales that measure five different social problem solving dimensions. They are positive problem orientation (PPO), negative problem orientation (NPO), rational problem solving style (RPS), impulsiveness/carelessness style (ICS), and avoidance style (AS). Participants are asked to respond to a statement on a five-point likert-type scale from “0” (not at all true of me) to “4” (extremely true of me).

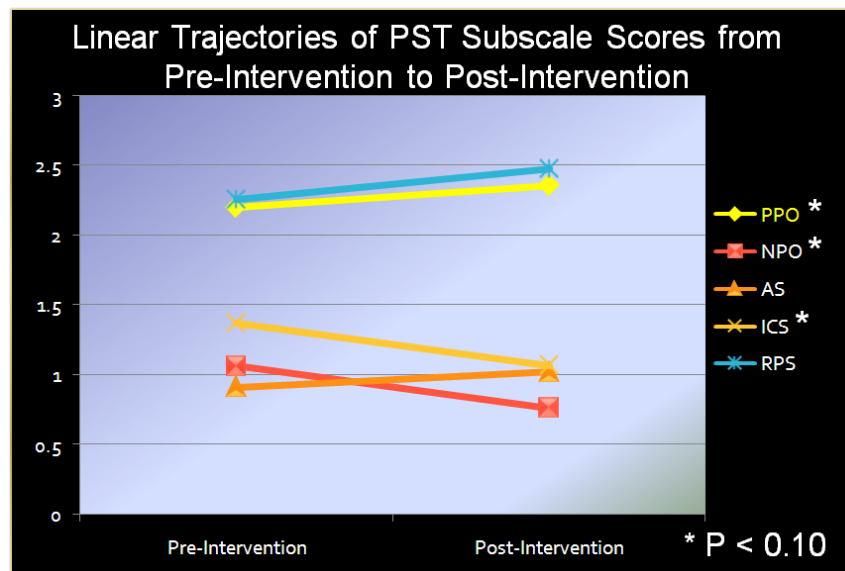
Whereas problem orientation is comprised of a set of generalized thoughts and feelings regarding problems in life and the individual’s ability to solve them, problem-solving style refers to specific cognitive-behavioral actions aimed at coping with stressful problems [D’Zurilla & Nezu, 2007]. Positive problem orientation defines a person who perceives problems as opportunities to learn and benefit from the outcome. In addition, this person has a firm belief in his/her ability to solve the problem effectively. An item from the positive problem orientation scale reads, “When I have a problem, I try to see it as a challenge or opportunity to benefit in some positive way from having a problem.” On the contrary, negative problem orientation defines an individual who views problems as a major threat to their well-being, which hinders their ability to solve the problem. An item from the negative problem orientation reads, “I feel threatened and afraid when I have an important problem to solve.” Rational problem solving style identifies an individual who carefully gather facts about a problem, analyzes the outcomes, sets potential problem-solving goals and generate various alternative solutions. An item from the rational problem solving scale reads, “Before I try to solve a problem, I set a specific goal so that I know exactly what I want to accomplish.” Impulsivity/carelessness style is the practice of hurried and incomplete attempts at solving problems. An item from the impulsivity/carelessness scale reads, “When making decisions, I do not evaluate all my options carefully enough.” Avoidance style represents one who procrastinates and depends on others to solve problems. An item from the avoidance scale reads, “I wait to see if a problem will resolve itself first, before trying to solve it myself.”

This project is part of a 20-people pilot study that plans to increase preparation for future care in age-related macular degeneration. The sample includes 33% male and 67 % female aged 69-94. In that sample, 46% were married, 33% widowed, 8.3% single, 13% divorced. The educational level of this population varied significantly where 4% had less than High School education, 42% had High School or GED, and 54% more than High School. The participants had visual acuity ranges from

20:40 to 20:400 and 33% of them were considered to be legally blind. The training sessions for the problem solving therapy were carried out as shown in the figure below.

The entire preventive problem solving intervention includes four Vision Education classes delivered at the Association for the Blind and Visually Impaired (ABVI), along with transportation assistance. Topics discussed during those sessions include: a) What is Age-related Macular Degeneration, b) Emotional Adjustment to AMD, c) Orientation and Mobility, d) Adaptations in the Home. The participants also had in-home sessions with certified problem solving therapist, which include four sessions of formal Problem Solving Training and four sessions of Preparation for Future Care training, which are applications of problem solving skills to future concerns.

Results: A paired t-test analysis was performed to determine the effectiveness of the training by comparing the participants' scores at pre-intervention with respect to post-intervention. Three of the five pre-intervention SPSI-R scales were found to be significantly different with respect to post-intervention at a 0.10 alpha level. The results indicated an increase from PPO pre-intervention (mean = 2.200, SD = 0.349) compared to PPO post-intervention (mean = 2.356, SD = 0.414, cohen's d = 0.405). Further analysis showed a decrease both from NPO pre-intervention (mean = 1.0889, SD = 0.876) to NPO post-intervention (mean = 0.7944, SD = 0.648, cohen's d = -0.38) and from ICS pre-intervention (mean = 1.3646, SD = 0.738) to ICS post-intervention (mean = 1.0972, SD = 0.685, cohen's d = -0.39). A summary of the results is shown in the figure below.



Conclusions: The data clearly indicate that AMD patients are more likely to learn new positive problem skills while rejecting problem solving methods that lead to negative outcomes. Furthermore, the diminished use of impulsiveness/carelessness style that was observed in the study shows the potential health benefit of using the PST intervention in helping AMD patients deal with everyday problems. It was thus concluded from this preliminary data gathered from the study that the problem solving therapy can help adults apply their problem solving skills at various life challenges, which subsequently leads to greater well-being in AMD patients. As a pilot study, the results of this study should be viewed with care. The sample size clearly suggests that further testing is necessary to support these claims. Furthermore, it is difficult to project to what extent these results can apply to other illnesses as the pathological and the environmental factors that surround each disease are different and unique. Studies have shown that AMD patients are more motivated to change and more responsible to training than other group, which may bias the outcomes of this study.

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Basic Science and Clinical Research



Izad-Yar Daniel Rasheed, MS2

Preceptor:

Jean M. Bidlack, Ph.D.

Professor

Department of Physiology & Pharmacology

University of Rochester Medical Center

Levetiracetam's Ion and Drug Profile Suggests Binding to the AMPA Glutamate Receptor Family

Introduction: Levetiracetam ((S)-alpha-ethyl-2-oxo-pyrrolidine acetamide; LEV; ucb L059; Keppra) is an antiepileptic drug with an unknown mechanism of action. Previous research from UCB Pharma showed that [³H]LEV bound to rat brain membranes with a K_d value of 780 ± 115 nM under unoptimized binding conditions.¹ A photoaffinity derivative of LEV showed binding ($K_d = 52 \pm 14$ nM) to SV2A², a 90 kDa synaptic vesicle protein involved in glucose-evoked granule recruitment.³ However, SV2A's role in epilepsy, if any, remains unknown. The ubiquitous CNS expression of SV2A in all synaptic vesicles is inconsistent with the discrete binding regions seen with [³H]LEV.⁴

Objectives: Radioligand binding experiments were performed to optimize the binding of [³H]LEV to brain membranes and to determine the mechanism of action that is responsible for LEV's antiepileptic effects.

Methods: To optimize binding conditions, various ions, drugs, and buffers were incubated with brain membranes and 10 nM [³H]LEV (18 Ci/mmol; GE Healthcare). After incubation for varying times and temperatures, the membranes were filtered through Whatman #32 glass fiber filters, which were washed three times with 3 ml of cold 50 mM Tris-HCl, pH 7.5. The filters were counted in Scintsafe scintillation fluid and the disintegrations per min were obtained. Assay conditions were optimized for membrane source (rat whole brain), protein content (300 µg), time (4 hr), temperature (4°C), pH (7.5), and buffer (50 mM Tris-HCl). Once optimized, the effects of various anions, cations, and drugs on [³H]LEV binding were determined.

Results: Anions (Cl^- , Br^- , I^- , NO_3^- , SO_4^{2-} , MeSO_3^- , ClO_4^- , CN^- , SCN^- , CH_3COO^-) at 100 mM concentrations increased [³H]LEV binding ($E_{\text{max}} = 214\text{--}384\%$ relative to control) inversely proportionally to their molecular weight. Monovalent cations (Na^+ , K^+ , Cs^+ , Li^+) showed modest concentration-dependent binding increases ($E_{\text{max}} = 4\text{--}20\%$). Some divalent cations (Ba^{2+} , Ca^{2+} , Mg^{2+} , Mn^{2+}) increased binding ($E_{\text{max}} = 20\text{--}41\%$) whereas the majority (Cd^{2+} , Co^{2+} , Cu^{2+} , Hg^{2+} , Ni^{2+} , Pb^{2+} , Zn^{2+}) inhibited [³H]LEV binding ($I_{\text{max}} = 50\text{--}100\%$), both in concentration-dependent manners. Previous literature shows this ion profile to be consistent with what is known about the AMPA glutamate receptor (AMPA) family. In contrast, all of the five allosteric modulators of AMPAR desensitization (BCP-1, CX 546, cyclothiazide, diazoxide, IDRA21) inhibited [³H]LEV binding ($I_{\text{max}} 30\text{--}100\%$). Numerous other drugs known to act at other CNS receptors were tested and produced negligible effects on [³H]LEV binding.

Conclusions: Our results suggest that LEV's high-affinity binding site may be the AMPAR family, and that LEV likely acts as an allosteric modulator of AMPAR desensitization. Aniracetam, structurally similar to LEV, was previously reported to bind GluR2.⁵ Furthermore, AMPAR molecular weights –

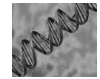
~100 kDa – is within the range of possible targets for LEV as reported by Lynch *et al.*² and elsewhere⁴ (93 ± 8 kDa). AMPA agonists and antagonists had no effect on [³H]LEV binding. Further experimentation is required to determine which subunit(s) and isoform(s) of the AMPAR family LEV binds to. AMPARs provide a more rational explanation of LEV's antiepileptic effects than SV2A does.

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Basic Science and Clinical Research



Brett Talbot, MS2

Preceptors:

Victor Morales, Ph.D.

Research Assistant Professor

Claudia Jasalavich, Ph.D.

Postdoctoral Fellow

Lawrence Saubermann, M.D.

Associate Professor of Medicine

Gastroenterology Division, Department of Medicine

University of Rochester Medical Center

Patterns of Expression of Interleukin 32 Isoforms in the Normal and Inflamed Intestinal Mucosa.

Abstract: Interleukin 32 (IL-32) was first described in 2005(3). Since that time it has been implicated in several immune inflammatory diseases such as inflammatory bowel disease (IBD)(4), rheumatoid arthritis (RA)(2) and chronic obstructive pulmonary disease (COPD)(1). IL-32 triggers the expression of inflammatory cytokines such as $\text{TNF}\alpha$, IL-8, IL-1 β and IL-6 by normal human macrophages or monocytic cell lines. IL-32 is also found at higher concentrations in the mucosal tissues of IBD patients, especially those with Crohn's disease. The IL-32 gene in humans produces 7 different proteins (isoforms) through alternative splicing. There are indications that the individual isoforms may have unique roles in different cell types. This preliminary study examined the expression patterns of IL-32 isoforms α , β , ϵ , γ and D. It additionally observed the expression patterns of two inflammatory (IL-6 and IL-17A) and two, not so well known, dual-role cytokines (IL-22 and IL-25) in the colonic mucosa of 14 volunteers.

Objectives: The role of IL-32 in IBD is currently unresolved, yet may be a potential target for diagnostic and/or therapeutic intervention. Although the etiology of IBD remains unknown, our current knowledge indicates that IBD is a group of complex diseases that develop from an excessive immune reaction to normal gut microflora. The complexity of the disease is revealed by the variety of cytokine patterns that can be observed in inflamed intestinal mucosa. As new players in the immune response are discovered, we must reevaluate our understanding of the mechanisms by which immune homeostasis is maintained.

Methods: Human intestinal tissue biopsies were obtained from 14 informed volunteers during routine colonoscopy for screening or disease surveillance. Total RNA was extracted from each sample and cDNA was synthesized. The mRNA levels of five isoforms of IL-32 (α , β , ϵ , γ and D), IL-6, IL-17A, IL-22, and IL-25 were estimated using real-time PCR. Data were normalized using two housekeeping genes (Glyceraldehyde-3-phosphate dehydrogenase and RNA polymerase II). Statistical analyses were performed using SAS.

Results: The pattern of IL-32 isoform expression is conserved among volunteers, with no statistical differences in expression pattern between diseased and control samples and inflamed and uninflamed tissues. Relative expression of IL-17A and IL-6 were elevated in diseased patients although not to a statistically significant level; however, no difference was observed between

inflamed and uninfamed tissues from the same person. Conversely the relative expression of IL-25 and IL-22 were increased in controls. There was statistically significant difference between controls and Crohn's disease patients. When stratified by disease state, characteristic patterns of cytokine expression were observed.

Conclusions: Although there were trends observed in the expression patterns of IL-32 isoforms in diseased versus normal volunteers, these were not statistically significant probably due to a limited sample size. There was, however, a general pattern of higher levels of the pro-inflammatory cytokines IL-6 and IL-17A, and lower levels of the dual-role (pro- and anti-inflammatory) cytokines IL-22 and IL-25 in diseased versus normal volunteers. A larger sampling may allow us to distinguish characteristic patterns of cytokine expression among IBD disease states that may constitute a feasible diagnostic tool.

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Basic Science and Clinical Research



Catherine Trimbur, MS2

Preceptor:

Jody Rich, M.D., M.P.H.

Brown University School of Medicine

US Prison Policies on Methadone and Suboxone Opiate Replacement Therapy: Results from a Nationwide Survey

Abstract: The United States has the world's highest incarceration rates. Approximately 10 million individuals are incarcerated each year; in 2007, approximately 2.2 million individuals were incarcerated in the country's prisons and jails.⁴ More than 50% of prisoners have a history of substance abuse⁵, 20% have a history of injection drug use and 24-36% of all heroin addicts, or 200,000 individuals, pass through the criminal justice system each year.⁶ Furthermore, 55% of individuals with a history of drug addiction will relapse back to substance use within one month of release from incarceration.⁷ Substance abuse relapse is associated with increased criminal activity,⁸ risk of HIV and HCV infection,¹⁰ overdose,¹¹ and reincarceration.¹² Offering inmates treatment for opiate dependence prior to release decreases the likelihood of drug relapse, and the negative outcomes associated with return to drug use¹³ ¹⁴. Methadone maintenance therapy (MMT) has been used in the United States for over forty years to treat chronic heroin addiction, to detoxify opiate-dependent drug users.¹⁵ Buprenorphine is an opiate replacement therapy that acts

⁴ U.S. Department of Justice. Bureau of Justice Statistics. Correction Statistics Summary Findings <http://www.ojp.usdoj.gov/bjs/prisons.htm> Accessed July 20, 2008

⁵ Karberg, J and Mumola, C (2004) "Use and Dependence, State and Federal Prisoners." (NCJ-213530) <http://www.ojp.usdoj.gov/bjs/abstract/dudsfp04.htm>. Accessed July 12, 2008.

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as a partial opioid agonist.¹⁶ It has been used widely in France for ORT and has been associated with improved stability in housing and employment, reduced heroin use by self-report and decreased risk of HIV, HBV, and HCV infection in high-risk populations.¹⁷

A 2003 survey that examined the attitudes and practices of medical directors of state and federal prisons regarding methadone treatment finds that less than half of the prison systems in the U.S. use methadone, primarily to treat pregnant inmates or acute detoxification, just 8% of prisons referred inmates with a history of opiate dependence to community-based methadone programs upon release and only 30% of medical directors reported that they believed that methadone benefits opiate-dependent patients.¹⁸ To build upon the previous survey, we surveyed the medical directors of state prisons about prescribing practices, policies and attitudes regarding both methadone and suboxone during incarceration and after release. The aim of this study is to understand how and why medical directors of state and federal prisons are using ORT to treat opiate addicted patients.

Methods: In July 2008, we emailed or faxed a 17-question survey to the Medical Directors of the 50 state departments of corrections, as well as for the Federal Bureau of Prisons and the District of Columbia in July 2008. Surveys were re-emailed and refaxed, and phone calls were made to follow up with non-respondents. Questions addressed the opiate screening practices, methadone and suboxone provision within the prison setting, and administrator attitudes about the usefulness of suboxone and methadone. We concluded the survey with a free response question that encouraged respondents to comment on anything we may not have included in our survey.

Results: Like the similar study conducted in 2003 that examined the attitudes and practices of medical directors of state and federal prisons regarding methadone treatment, we found that both methadone and suboxone are largely underutilized resources in the treatment of opioid dependent prisoners. Methadone continues to be used primarily for acute detoxification or for pregnant women. Suboxone, on the other hand is routinely used in only one state. When prompted for further explanation, medical directors reported favoring drug free detoxification and lack of partnership with methadone or suboxone providers as the primary reasons for the limited use of ORT in the prison setting. Furthermore, when asked about attitudes about the effectiveness of the medications, respondents reported methadone to be very beneficial or beneficial, but the benefit of suboxone to be unknown. Finally, medical directors reported low rates of referrals to assist patients access any type of substance use treatment upon release. The most common barrier reported was lack of relationships with community-based providers.

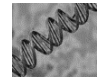
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Basic Science and Clinical Research



Paul Youn, MS2

Preceptor:

Jean-Philippe Couderc, Ph.D.

Assistant Professor

Department of Cardiology, Heart Research Follow-up Unit

University of Rochester Medical Center

Pre-arrhythmic T Wave Profiling for Risk Stratification of Polymorphic Ventricular Tachycardia

Abstract: Four 24-hour Holter ECG recordings of patients with rare polymorphic ventricular arrhythmia, called torsade de pointes were analyzed to evaluate the potential of ECG parameters as predictors onset of TdP. Four ECG parameters, RR, QTc, QTApex, and TpTn, were analyzed for 1 hour duration before the event. All parameters were elevated, showing QT prolongation prior to TdP.

Objective: Torsade de pointes (TdP) is a rare ventricular arrhythmia with a distinct morphology that leads ventricular fibrillation and subsequent sudden cardiac death. Little is known about mechanisms of development of TdP, though it is mostly commonly caused by antiarrhythmic medications. Identification of T wave morphology abnormality on patients with TdP may show a triggering mechanism of an onset of TdP. In addition, the morphology analysis may identify patients with increased risk of ventricular arrhythmia upon use of antiarrhythmic medication, such as sotalol.

Methods: 24-hour Holter ECG recordings of seven patients with TdP were acquired by Dr. Stefen Kaab at Munich Medical International GmbH, Munich, Germany. The ECG signals were first processed by COMPAS and TCA, proprietary software developed by Dr. Jean-Philippe Couderc. The software reports 10 heartbeat average of pertinent ECG and T wave morphology properties, including RR, QT, corrected QT (QTc), QTApex, and TpTn intervals. Three patient data were dropped due to poor quality of ECG recordings. Specific times of TdP event were identified using commercial ECG reading software. RR, QTc, QTApex, and TpTn values were analyzed for the duration of 1 hour before the onset of TdP to identify QT prolongation that may trigger the event.

Results: Among four patients whose 24-hour Holter ECG recordings were analyzed, two had a congenital long-QT syndrome, whereas the other two were put on sotalol. All patients showed evidence of QT prolongation. On average, QTc, QTApex, TpTn values were elevated for 17.5%, 13.75%, 39.5%, respectively. Further analysis on QT prolongation pattern and statistical analysis are pending.

Conclusions: This study demonstrates QT prolongation prior to torsade de pointes. These findings may help improving our understanding on instabilities in T wave that develop into ventricular arrhythmia.

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Basic Science and Clinical Research



Owen Young, MS2

Preceptor:

Ming Qi, Ph.D., FACMG

Adinovo Center for Genetic and Genomic Medicine

Zhejiang University

Methylation pattern of Mismatch Repair Gene MSH2 in Gastric Cancer

Abstract: Gene methylation patterns are part of the epigenetic mechanisms used to control gene expression. In some cases, promoter hypermethylation at CpG islands is the mechanism found in tumor cells to silence expression of tumor suppressor genes without any direct mutations to the gene itself. At least one mismatch repair gene, MLH1, has been shown to have promoter hypermethylation in sporadic gastric cancer.

Objective: To characterize the methylation state of the MSH2 promoter in both differentiated and undifferentiated gastric cancers

Methods: Bisulfite Genomic Sequencing

Results: Research Ongoing

Conclusions: Research Ongoing

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Community Health Research



Thomas Falls, MS2

Annabel Fu, MS2

Preceptor:

Adrienne Morgan, M.S.

Director of Student Outreach Programs

University of Rochester School of Medicine and Dentistry

UR Well Student Outreach at St. Joseph's Neighborhood Center

Background

St. Joseph's Neighborhood Center (SJNC) provides the uninsured and underinsured with appointment-based healthcare, dental and other wellness visits for a nominal fee. Psychiatric and counseling services are provided on a sliding scale, and smoking cessation assistance is provided by UR Well at no cost. Most healthcare visits cost \$5, and new patient physical exams cost \$15. As articulated on St. Joseph's website, <http://www.sjncenter.org/>, "services will never be denied to an inability to pay". Required laboratory work from ACM labs is available to patients at or below cost. By partnering with SJNC, the UR Well clinic is able provide primary care services to patients on Tuesday nights. As 58% of our patient population is employed, these evening appointments are intended to avoid interfering with patients' work schedules. In addition to providing primary care services, the neurology clinic at UR Well Neurology now has its own healthcare team and is in its second year of operation on Tuesday nights. Ophthalmologic care is also a recent addition to Tuesday nights as the new project UR Well Eye Care. Currently diabetic patients from SJNC are being screened for diabetic retinopathy as a part of a more comprehensive diabetic wellness plan including foot care and diabetic education. In order to achieve a better understanding of the needs of the population served by UR Well at SJNC, we partner with students in the Department of Epidemiology and Biostatistics to collect demographic data from patients seen on Tuesday nights.

Population Served

In the first four years of operation, the UR Well Student Outreach Project provided care for approximately 326 patients. Demographic data were extracted from surveys administered to patients at their first visit. Fifty-seven percent were male and more than half were non-white (55%). Among the non-white population, there were 44% African American, 7% Other, 2% Asian and 1% Hispanic. Most are employed (58%), although 79% earned less than \$20,000 in the previous year. Only one-fifth had a college education, and the average age was 39 years, ranging from 0 to 86. Ninety-four percent did not have any kind of insurance.

Diversification of UR Well

During the past year, UR Well began a homeless outreach project and continued to expand the services provided. Collaborations with the YWCA, Genesis House and the Volunteers of America

provided opportunities to offer health and wellness education to a variety of at risk and underserved populations. With the assistance of the Monroe Department of Public Health, we hope to continue mass TB screenings at homeless shelters. In the past year UR Well helped to screen more than 50 individuals, and at least one active case of TB was discovered through the screening process. In another collaboration with the department of public health, we will be offering influenza vaccinations to the homeless population, with the potential to expand to project to include other vaccinations, such as hepatitis B. Finally, UR Well will be partnering with the newly formed walk-in clinic at Asbury church to provide longitudinal care for more individuals in the community that do not have regular access to healthcare.



Community Health Research



Nisha David, MS2
Kathleen Effler, MS2

Preceptors:
Victorie Heart
Laurence Guttmacher, M.D.
Clinical Professor
Department of Psychiatry
University of Rochester Medical Center

The Role of Western Medicine and Traditional Culture in the Alaskan Community Health Aide Program

Objectives: Our aim in this research was to qualitatively assess the feasibility of practicing high quality, culturally competent medical care to rural Alaskans through the use of the CHA/P program. Additionally we hoped to learn about Native Alaskans' conceptions of wellness and the interaction of traditional and western medicine as practiced in these communities. This study explored the cultural beliefs and practices of health and well being in villages throughout Alaska.

Methods: Exploratory, descriptive qualitative study based on structured observation, in-depth interviews, training sessions and conferences. Interviews were conducted with 17 CHA/Ps and 3 midlevel practitioners to answer four key research questions: 1) The current conditions within the clinic and the services provided by the CHA/Ps, 2) Preventive medicine commonly practiced within the villages, 3) The challenges of providing comprehensive care in a remote area, with limited resources and/or assistance and 4) The synthesis and/or conflict between conventional western medicine and these culturally indigenous practices

Results: 1) The majority of clinics contained at least two examination rooms, two CHA/Ps, access to telemedicine, common medications, first aid supplies, basic medical instruments, and basic laboratory equipment. Approximately 80% of all CHA/P visits were acute care patients with the majority presenting with upper respiratory infections. 2) Preventive medicine has become a major focus at the ANTHC with the creation of the Wellness and Prevention Program, directed by Dr. Gary Ferguson. Programs have been created to address tobacco cessation, nutrition, health promotion and disease prevention, youth and media, injury prevention and worksite wellness. These programs will be incorporated into the CHA/P program in order to provide patients with comprehensive care. 3) The numerous challenges faced by the CHA/P program, combine to create difficulties in two major areas: managing chronic health problems and providing preventative medicine. Since most villages can't support physicians/specialists, weather conditions and remoteness of the villages make efficient and affordable transportation for complicated medical conditions inaccessible. Preventive services are similarly difficult to provide as many recommendations involve sensitive lifestyle changes, and CHA/Ps often have dual relationships with their patients. Additionally, with the high workload and the understaffed clinics, CHA/Ps often overlook preventive services in order to perform acute care. 4) The CHA/P program was strictly based on Western medicine. Traditional medicine did not play any role within the CHA/P training,

education or clinical practices. Regardless of the CHA/Ps personal beliefs, traditional medicine was not practiced in the clinic, but it was recognized to play a role in many of the communities.

Conclusions: The CHA/P program has created an effective, affordable and feasible way to provide healthcare to rural Alaskan Native populations. This has been one of the main forces driving the alleviation of health care disparities of Alaskan Natives. With the success of the program comes the challenge to continue to improve the medical care and health conditions within the villages. The next step is to incorporate preventive medicine into CHA/Ps daily services provided. This will require additional personnel and training, and a shift in the roles and responsibilities of the CHA/P.

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see original paper and

The Alaska Health Aide Program, "A tradition of helping ourselves." Philip Nice and Walter Johnson, M.D.. 1998.



International Medicine Research



Jamie Adams, MS2
Emily Berkman, MS2
Jen Cialone, MS2

Preceptors:

Timothy Quill, M.D.

General Medicine, Psychiatry, and Medical Humanities; Director, Palliative Care Program
Department of Palliative Care

University of Rochester Medical Center

Father Jack Davis

Father of Our Lady of Perpetual Health; President of Los Amigos del Padre Juan
Our Lady of Perpetual Health - Chimbote, Peru

Hospicio Santiago Apostol: A Case Study of Hospice Care in Chimbote, Peru

Introduction: Hospicio Santiago Apostol was implemented in 2001 in Chimbote, Peru, a very poor community with limited healthcare access and resources. In 2005, the program was further expanded with the addition of an inpatient facility. The hospice is run by both Peruvian and American parish and healthcare workers. The program provides home-based and inpatient palliative care services, offering both spiritual and medical support to families and patients.

Objectives: Our goal was to conduct a comprehensive analysis and review of the initiation, current status, and future plans of Hospicio Santiago Apostol. This study examined the current workings of the hospice including day-to-day activities, medical care, spiritual guidance, access to the facility, and barriers to care. We explored the themes of death and dying, and the role of religion in palliative care and hospice in Peruvian culture. We also inquired about advice for other communities looking to establish a similar program.

Methods: We conducted 9 in-depth staff interviews (7 female, 2 male) as well as 11 patient and/or family member interviews (6 female, 5 male), with the use of a Spanish translator as needed. Our interview questions focused on the above objectives. In addition, we recorded extensive field notes while observing home visits, in-hospice care, and other community activities. Our interview notes and observations were recorded in journals and reviewed by all three researchers, noting any themes that emerged.

Results: The major barriers faced in implementing the hospice program in Chimbote were resistance from the medical community, lack of resources, and lack of education about hospice care and its principles. For the 50 patients enrolled in the program during our visit, care included, but was not limited to, taking vitals, wound care, bathing, massage therapy, medication, psychologist visits, and spiritual care. Future plans include continued education about hospice and further expansion of the program.

Major themes arising from our research concerning death and dying include the notion that the acceptance of death is a critical component of hospice. As death is considered the most sacred time of life to many, it is important that people are able to speak about this difficult topic more

openly. In Chimbote, this was usually more difficult for the family of the patient and the larger community, than for the patient himself/herself. The hospice program helps prepare the patient and his/her family for death and helps the family in the grieving process. Dying with dignity is highly important to this community.

Religion is used more as a part of hospice treatment and care in Chimbote than in the United States. Religion and spirituality are important aspects of dying and end-of-life care in this community, regardless of denomination, as it helps patients to accept death and gives them a sense of comfort during a difficult time. However, there are no organized religious activities in the hospice program as religion and spirituality are viewed personal choices.

Advice for other communities in establishing a hospice program was to first educate both the medical and general communities about hospice and palliative care, then gather funding and necessary resources and launch a pilot outpatient program before implementing an inpatient facility.

There is an overwhelming appreciation for the hospice program by the patients and their family. The program has allowed them to be more comfortable with death and experience a higher quality of life in their last days. Patients and families felt the program treated them with respect and dignity, as a person and friend, and not just as a patient.

Conclusions: Due to the lack of resources and education in the surrounding community, Hospicio Santiago Apostol has faced several obstacles in its initiating and running the current program. Despite these barriers, the hospice has achieved success in many ways. The program has allowed death to become less of a taboo topic in both the general and medical communities. Patients have received medical care from devoted staff that treats them with respect. Through hospice education and word of mouth in the community, Chimbote doctors are now referring to the program. By increasing education about the program and raising more funds, Hospicio Santiago Apostol hopes to expand and improve the program for the future.

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International Medicine Research



Shannon Andrews, MS2
Caren Bartosz, MS2
Christopher Chang, MS2

Preceptor:
Michael Keefer, M.D.
Director of Developmental Center for AIDS Research
Professor of Medicine
University of Rochester Medical Center

Confusion, Mistrust, and Enthusiasm: A Follow-Up Qualitative Study to the Phambili HIV Vaccine Trial

Abstract: The Phambili HIV vaccine trial, a phase IIb study in South Africa, was prematurely terminated due to evidence of lack of efficacy in a similar trial with the same vaccine in the Americas (the STEP Study). We hypothesized that this outcome as well as other preexisting factors may have led to a negative perception of HIV vaccine trials and confusion in the community. We conducted a qualitative study in Soweto, South Africa, involving focus group discussions with forty total participants, males and females ages 18 to 35. The focus group script consisted of open-ended questions and vignettes designed to elicit the spectrum of communities' opinions and emotions. Data were analyzed by identifying common themes, and an explanatory conceptual model was developed to assess the impact of the trial on prevailing community beliefs. Our explanatory conceptual model incorporates three elements: 1) confusion about the role of vaccines in healthcare, 2) mistrust of the methods of medical research and the intention of researchers, and 3) enthusiasm over medical advances. This apparently paradoxical model can be explained by illegal clinics and "sham doctors" that generate mistrust and confusion, while fear of HIV and passion for global eradication of HIV/AIDS fuel continued enthusiasm. We conclude that the trial failure and any resultant negative publicity did not substantially harm the scientific community's relationship with Soweto residents. We find it unlikely that recruiters will experience increased difficulty obtaining participants for future trials.

Objectives: The objective of this qualitative study was to explore the Soweto community's confusion, concerns, and emotions regarding the Phambili HIV vaccine trial. Our hypothesis involved multiple aspects: There is confusion about vaccine function and distribution; early termination of the Phambili trial generated fear of vaccine-induced HIV infection and frustration with repeated failed trials; the people of Soweto mistrust research due to unfamiliarity with investigators' methods and intentions.

Methods: We conducted a qualitative study in Soweto, South Africa. Past HIV vaccine trials have been conducted there, making it a good target population. A qualitative approach was used because it is better suited to eliciting emotions and concerns. Focus group discussions were held with a total of forty participants, male and female adults ages 18 to 35. This is the same demographic that was used in the Phambili trial. Focus groups are well suited to eliciting community opinions and beliefs.

Our exclusion criterion was participation in Phambili. We wanted to minimize any bias, educational or emotional, caused by participation in the trial. We collaborated with counselors from the Phambili trial for recruitment and translation. The focus group script consisted of unbiased, open-ended questions and vignettes. These were designed to elicit the spectrum of the communities' opinions and emotions. Data were analyzed by identifying common themes, and an explanatory conceptual model was developed. This model can be used to assess the impact of the project failure on prevailing patterns of understanding, beliefs, and reaction.

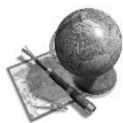
Results: Our research revealed five major themes: 1) a high level of confusion in the Soweto community about vaccines; 2) prevalent feelings of anxiety and mistrust in medicine and research; 3) agreement that the an HIV vaccine would be a "good thing"; 4) lack of knowledge of the Phambili trial prior to the study; 5) a variety of reasons for participating in or avoiding a future HIV vaccine trial.

Conclusions: Our explanatory conceptual model incorporates three elements: 1) there is a high level of confusion in the Soweto community about the purpose of vaccines; 2) people have feelings of anxiety and mistrust in accepting approved vaccines and medical research; 3) participants were in agreement that the development of a HIV vaccine would be a "good thing."

No substantial amount of damage has been done to the relationship between the scientific community and Soweto residents as a result of the trial failure or any negative publicity. We find it unlikely that recruiters will have any increased difficulty obtaining participants for future trials. However, recruiters must contend with the confusion and mistrust surrounding medical research. Fear and ignorance about HIV status, testing, and treatment may also complicate future attempts to recruit for HIV vaccine trials.

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International Medicine Research



Yetunde O. Balogun, MS2

Preceptor:

Nancy Chin, Ph.D., M.P.H.

Department of Community and Preventive Medicine

University of Rochester Medical Center

Reconciliation in post-genocide Rwanda: The Role of the Kigali Memorial Center

Introduction: Genocide is the deliberate and systematic killing of a national, ethnic, cultural or racial group. In 1994, the genocide in Rwanda left one million people dead and more than two million displaced, in 100 days. The survivors and victims of this genocide were left to bear the burden of burying their families, facing the guilt of surviving, as well as fostering reconciliation.

Objective: This research study explores the ways in which the Kigali Memorial Center, constructed in 2004, is used as a tool for reconciliation in Rwanda.

Methods: The study utilized qualitative methods including exhibit analysis, on-site participant-observation, and in-depth interviews of visitors and employees.

Results: To date, about 258 000 human remains, collected from latrines and shallow mass graves around Kigali, have been buried in KMC and more bodies are still been discovered. However, unlike other memorial centers/sites in Rwanda, the KMC displayed minimal human remains and materials. The memorial center instead uses pictures, videos and a text to describe chronologically, the history and events leading to the genocide. Most people interviewed recognize the role that understanding history can play in preventing retaliation and future re-occurrence, and how the memorial center is facilitating this process. Many respondents also agreed that the center not only dignifies the dead, it also helps survivors and perpetrators understand their actions and reconcile their pasts to forge a common future. Finally, the memorial center has an educational initiative that is currently underway for all the youths of Rwanda, to encourage openness and objectivity and to foster unity amongst them.

Conclusions: 1) Though there are still challenges, four years after it was constructed, the Kigali Memorial Center seems to be contributing to the process of reconciliation.

2) Though, the study was only conducted in Rwanda, the elements essential for reconciliation described, can be adopted by countries in other post-war situations.

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International Medicine Research



Ann Barry, MS2
Emily McQuaid, MS2

Preceptor:
Charles Inboriboon, M.D.
Fellow in Emergency and International Medicine
Department of Emergency Medicine
University of Rochester Medical Center

Perceptions and Attitudes Towards Road Traffic Injuries in Ladakh, India

Abstract: Road traffic injuries are a growing cause for public health concern. The World Health Organization estimates that by the year 2020, traffic fatalities will be the sixth leading cause of death in the world, and the second leading cause of disability-adjusted life-years (DALYs) lost in developing countries (1). In particular, if current trends continue and public health policies remain unchanged, India's road death rate is not expected to decline until 2042 (1).

Ladakh is a district in the state of Jammu-Kashmir in the Indian Himalayas. The region has become increasingly developed in recent years and has seen a corresponding increase in the use of motor vehicles. Road traffic accidents are a particular problem in Ladakh due to the rugged geography of the region, which is home to some of the highest motorized passes in the world (up to 17,800 feet of elevation).

The aim of our project was to assess perceptions and attitudes toward road traffic accident prevention among the health care workers as well as the general public in the region of Ladakh. Using a qualitative, interview-based approach, we sought to gain understanding of the experiences of these two groups as well as their personal practices with regards to road safety.

Objectives: To assess attitudes towards road traffic accidents and accident prevention in Ladakh, India.

Methods: We conducted 36 interviews in Leh (capital city of the Ladakh region) and the surrounding rural areas. Our interview subjects included a mix of professional drivers (taxi and truck drivers), medical personnel, people working in the tourism industry, and other members of the general public. Our interviews included questions about personal accident experiences, seatbelt and helmet use, following road safety rules, the causes of accidents, accident prevention, and emergency response to accidents.

Results: Of the 36 interviewees, 23 reported having witnessed or been directly involved in a motor vehicle accident. Prominent themes of the interviews included drunk driving, lack of police enforcement, little use of seatbelts or helmets, lack of driver training, reckless driving, and poor road conditions combined with mountainous terrain.

Conclusions: As the themes suggest, reckless driving, lack of top-down enforcement of road safety rules, and limited driver education are major contributing factors to the rising level of traffic accidents in this region of the world. According to several of our interviewees, police enforcement

is extremely effective when it is implemented, but seems to be extremely erratic. Campaigns to heighten driver awareness of road safety rules are useful as well, although literacy is a barrier to the effectiveness of such campaigns. There was also a strong sentiment among many interviewees that the responsibility of safe driving falls to each individual. Based on these results, it seems that a government-initiated, but community-centered approach would be the most effective in improving rates of accidents in Ladakh.

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International Medicine Research



Isaiah Chase, MS2
Christel Parker, LEAH Fellow
Department of Adolescent Medicine

Preceptors:
Laurence Guttmacher, M.D.
Department of Psychiatry
University of Rochester Medical Center
Prakarn Thomyangkoon, M.D.
Department of Psychiatry
Rajavithi Government Hospital- Bangkok, Thailand

Supportive Structures for Mental Illness in Thailand

Objective: This study examined the relationship between Theravada Buddhism, psychiatric illness and supportive mental health structures in Bangkok, Thailand.

Background: Theravada Buddhism is practiced by nearly 95% of the population in Thailand and is an integral part of Thai cultural identity. Previous research has shown that Buddhist principles and beliefs significantly influence the Thai health care system, including the care of the mentally ill. Mental health perceptions, concerns and practices are understudied in Thailand. World Health Organization has reported that less than 1% of the health research conducted in the country focuses on mental healthcare access, availability and usage. This lack of research may be directly related to the reported shortage of mental health care programs and resources in Thailand. Alternative supportive structures have developed over time in the absence of government and community programs. Identified supportive mental health constructs include the family, Buddhist monks and temples, hospitals and outpatient units. Within the supportive structures described, Buddhist concepts and beliefs may also play an important role in *belief* about mental illness (complexly intertwined with traditional animistic beliefs and practices), and in the *treatment* of mental illness. How Buddhism influences the understanding of psychiatric illness within the context of the indicated supportive structures in Thailand was the central question of this project.

Methods: Interviews were conducted with 10 adults from 4 different subject groups who had, in their own unique way, experience with both mental illness and Buddhism. 7 semi-structured, narrative reports focused on interviews with 3 psychiatrists, 1 pediatrician, and 3 Buddhist monks. The participants were asked open-ended questions from investigators with the support of a Thai-speaking translator. All interviews were tape-recorded for review and in-depth analysis. A 21-item qualitative questionnaire was developed for 3 schizophrenic patient interviews. The patient was invited to participate and the patient's treating psychiatrist determined capacity to consent to participation. The diagnosis of schizophrenia was chosen for the study based on the high occurrence of outpatient clinics treating this disorder in Thailand. Schizophrenia is also the most prominent mental illness treated in the inpatient setting (59%). In analyzing the interviews, significant and noteworthy statements made by participants were extracted and clustered into themes.

Results: The prominent themes analyzed include the following: (1) perceptions about the origins of mental illness, (2) Buddhist concepts of *kwan*, merit-making (*boon*), ghosts (*phi*) and *karma*, (3) what prompts a person/family to seek help and where they go to find it, and (4) the role of Buddhism in supporting/treating/helping those with mental illness. Further results will include a comparison of themes from each subject category to assess for reoccurrence. The resulting comparison will incorporate these findings as well as a review of relevant literature into a narrative description.

Conclusion: The preliminary results of this small study indicate that Theravada Buddhism plays a meaningful role in the support of mental health and illness in Thailand.

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International Medicine Research



Stanley Dunn, MS2

Preceptor:

Cheryl Kodjo, M.D.

Assistant Professor

Department of Pediatric Adolescent Medicine

University of Rochester Medical Center

Conservation vs. Survival- The Creation of Gabon's National Park System

Abstract: President Omar Bongo of Gabon established a national park system in 2002, setting aside just over 10%(10,000 square miles or 26,000 square kilometers) of the nation's land mass for conservation within 13 National Parks. Prior to this decision Gabon had a smattering of national forests and reserves, but no unifying national park system. Conservationists regard Gabon as one of the last pockets of wilderness in Africa. Environmentalists and conservationists from around the world have successfully lobbied for the protection of Gabon's robustly diverse flora and fauna, which is equaled in only a few other places on Earth. The parks will protect pristine rain forests, mangroves, savannas, ancient forests, lagoons, marshes, rivers, and canyons. These landscapes provide vital habitat to everything from sea turtles and whales to forest elephants, rhinos, gorillas, buffalo, and numerous plant and bird species found only in Gabon. The designated land is under threat from a host of pressures: logging, mining, poaching of elephant tusks and of animals for bushmeat, forest clearing for agriculture, and burning of trees for firewood. Even though these are national parks, most of them have villages just outside their borders. This begs the question of how will the parks be managed so that the flora and fauna are protected and so that the local villagers can still feed themselves?

Objectives: This study looks at Gabon's policies regarding the creation of its national park system, and how this affects what nearby villagers may hunt, fish, and plant within the boundaries of the parks. The goal was to ascertain what effects these potential changes have had on the diet and nutrition of the Gabonese people. 20 interviews were conducted of people living on the outskirts of three national parks: the Loango, Moukalaba-Doudou, and Mayumba national parks. A broad spectrum of individuals were interviewed including hunters, fishermen, farmers, nurses, doctors, traditional healers, social workers, and conservationists.

Conclusions: The interviews revealed that enforcement of laws limiting the use of the land within the national parks, while slowly increasing, after 5 years is only occasional. All the hunters and fishermen interviewed still performed their subsistence activities as before. Some had been forced to stop hunting certain protected species such as elephants and gorillas. The farms that had at one time been in the parks were forced to relocate. The health care workers who were interviewed felt that malnutrition was not a problem in their towns or villages. The social workers however did feel that malnutrition was a serious issue in their communities, but they did not correlate it to the national park system.

In conclusion the creation of the national park system has had no noticeable effect on the diet or nutrition of the Gabonese people. This seems to in part be due to the lack of enforcement of park regulations as well as the availability of other lands to use for subsistence activities.



International Medicine Research



Nurain M. Fuseini, MS2

Preceptor:

Jennifer K. Carroll, M.D., M.P.H.

Associate Professor

Department of Family Medicine

University of Rochester Medical Center

Access to Water: A Matter of Health for Burmese Refugees in Northern Thailand

Abstract: “Every week an estimated 42,000 people die from diseases related to low quality drinking water...”¹ Since Burma’s civil war and coup d’ etat, as many as one million Burmese have fled to Thailand.² Many are refugees escaping human rights violations.² In Thailand, many of these refugees have few rights and little access to basic resources such as clean water. Paul Farmer’s concept of structural violence – defined as the harm caused by withholding basic resources to specific populations through intentional social arrangements – is helpful in exploring the circumstances of these refugees.

Objective: The study aim was to identify the social arrangements that affect their access to clean water.

Methods: The researcher conducted a qualitative study outside of Chiang Rai, Thailand involving participant observation while working with Burmese refugees to construct water supply systems. Fifteen in-depth interviews with refugee mothers on child health, factors affecting child diarrheal diseases, water access, and sanitation were also conducted to help identify and analyze common themes that shape water access.

Results: Three major factors impact these refugees’ access to clean water: 1) Their status as unrecognized refugees which denies them the basic rights of Thai citizens; 2) the location where they have been forced to settle; and 3) the resources that these refugees have access to.

Conclusion: These elements prevent refugees from earning adequate wages, owning land, and other necessary resources as unrecognized refugees. This forces them to live in rural areas where access to clean water is scarce and activities to find sustainable sources of water are difficult.

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International Medicine Research



Havalee Henry, MS2

Preceptors:

Cheryl Kodjo, M.D.

Department of Pediatric Adolescent Medicine

Assistant Professor

University of Rochester Medical Center

Charmaine Webb, M.D.

Department of Family Medicine

Medical Associates Hospital

Kingston, Jamaica

Factors Influencing the “Brain Drain” of Jamaican Physicians

Abstract: There is evidence indicating that there is substantial migration of Jamaican physicians to more developed countries, particularly the United States. It has been postulated that this brain drain is a leading factor in the healthcare system’s inability to adequately tackle public health issues such as HIV/AIDS, disparities in healthcare, as well as impeding the implementation of disease-reduction initiatives sponsored by outside agencies. This study sought to determine if Jamaican physicians currently practicing in Jamaica feel that there is a brain drain; as well as some of the factors influencing the doctors’ decision to leave. Interviews were conducted with Jamaican physicians from a variety of specialties. These doctors, currently working in the Jamaican healthcare system, do not believe there is a significant brain drain amongst doctors and that the emigration of doctors is not the major contributing factor to the inadequacies of the healthcare system.

Background and Rationale: It is generally agreed that increasing the educational level of the populace of a developing country should lead to an increase in the income of said populace. It stands to reason then, that mass emigration of highly educated individuals from that country will result in negative economic and social repercussions. There is data to show that many professionals such as educators, scientists, engineers, physicians who depart in large numbers from developing countries currently live and work in the United States, Canada and the UK; a phenomenon commonly referred to as the “brain drain”. An implication of the brain drain is that the investment in education in the developing country may not lead to the expected faster economic growth if a large number of its highly educated people leave the country.

The exodus of highly educated individuals from the poorest has been described as a “silent theft” by the richest countries. Over recent years, Jamaica is reported to have lost as much as 41 % of its doctors in this manner. (3) It can be concluded that the loss of these physicians

- represents a loss to the health care system of the country
- worsens the already depleted healthcare resources
- becomes a major impediment to disease-reduction initiatives
- is costly to the source country in terms of the invested financial resources and loss of human capital
- has ramifications not just for the healthcare sector but also socially and economically. (3,4)

It would not only be an overwhelming task; but also not feasible, to thoroughly investigate the many factors involved in these areas in this brief summer research project. As a doctor in training I automatically gravitated to the health issue. As a Jamaican currently studying medicine outside of Jamaica, this concept of a Diaspora of well-educated Jamaicans is an issue that resonates deeply with me. I also am acutely aware of the need for trained physicians in the Jamaican healthcare system. It would appear that financial gain, the opportunity to obtain advanced training, desire for more educational opportunities for children are important motivating factors contributing to this brain drain. (2,5)

The study sought to explore specifically:

- the reasons for the high level of emigration of physicians from developing countries to practice medicine in developed countries, based on the Jamaican experience
- the potential impacts of the brain drain on the Jamaican healthcare system
- whether doctors practicing in Jamaica felt that there was indeed a brain drain
- if more physicians would remain, if working conditions in Jamaica were more favorable with regard to salary or advanced training
- what are other contributing factors to the emigration of Jamaican doctors.

Methods: Seven Jamaican physicians currently practicing in Jamaica were interviewed along a prescribed line of questions. They represented the following specialties: family medicine, orthopedic surgery, cardiothoracic surgery, anesthesia and intensive care, and were selected from private, public and academic medical institutions. Each interview was conducted on an individual basis.

Results: Five of the seven doctors do not believe a brain drain exists as the University of the West Indies graduates 100 doctors each year. When the proportion of that number, who stay in their home country, is taken into account this number is sufficient to meet the needs of the health care system. In fact, some argued that there is a possibility of a surplus of new doctors. The two doctors who agreed that there is a brain drain stated that it was not in the number of doctors leaving but in the caliber as a large fraction of those leaving intended to specialize in fields that the Jamaican health care system would stand to benefit from. However, Jamaica can not offer a sustainable future to these specialists. They also believed that a disparity existed between urban and rural doctors with there being a scarcity of doctors in rural areas, resulting in an influx of doctors from other countries such as India and Ghana (and who are not trained in the same manner and thus are not accustomed to the healthcare system) to fill this need.

In response to the question of whether doctors would remain in Jamaica if there were more favorable salaries or advancement opportunities, there was a consensus of opinion that a much larger proportion would remain or return. However, but there would undoubtedly still be a significant loss of doctors and the reason for this differed widely amongst the interviewees. Some of the reasons offered were: the increasing social instability and the high rate of crime and violence; the latter being a large driving factor for individuals to leave; there is a staunch "Old Boys Network" that is virtually impenetrable to many new graduates, and unless you have the proper social connections it is extremely difficult to establish a medical career; when some doctors become very specialized the demographics, the Jamaican population simply does not provide enough patients for a practice of that kind to be viable. There is also the lack of access to or the opportunity to conduct biomedical research and so research-oriented doctors seek these opportunities elsewhere.

The interviewees also provided opinions as to what they believed to be the most important contributing factors to the inadequacies of the current healthcare system. They believe the impact of any potential brain drain would be far outweighed by factors such as insufficient physical infrastructure, lack of supportive staff such as RNs and specialist nurses, inefficient management strategies and most importantly insufficient monetary support from the government.

Conclusions: The data collected do not fully support my premise and point to other factors that are having negative effect on the healthcare system in Jamaica. I am therefore lead to believe that generalization based on extrapolating information from literature can at times be inaccurate. For example the figure of 41% of Jamaican doctors being lost to more developed countries may give the impression that there is a huge void in the system and possible solution would be to increase the number of medical school graduates or increase incentive programs to retain more doctors. While these suggestions might have some role in the Jamaican healthcare system, this project indicates that in order to obtain a more realistic picture of the factors contributing to the inefficiency of the Jamaican health care system, it is prudent to also get information from individuals who are directly involved in the system.

Additionally, as a scientist, I am also inclined to believe that sampling error here may have resulted in a somewhat skewed result. I am leaning more toward the latter. The doctors whom I interviewed were all from the two busiest hospitals in Kingston (and Jamaica). Because of their location and the demand placed on these hospitals require that they are comparatively well staffed and well equipped. Critical cases are often flown from other parts of the island to these hospitals. Thus the data obtained is not necessarily representative of the majority of Jamaican hospitals. A larger composite sample may paint a different picture. I also think a lack of supportive and specialist nurses might be a result of heavy emigration of Jamaican nurses to greener pastures.

Recommendations: Based on my assumptions as well as the data collected, I would make the following recommendations:

- A continuation of this study to include personnel from other hospitals over a wider cross section of the country, to verify and determine if data obtained is reflective of hospitals island-wide as well as with a view to improve conditions.
- Officials from the Ministry of Health should endeavor, and make plans, to correct current inadequacies.
- Officials should work in conjunction with WHO, PAHO and regional bodies to improve conditions at the national level as well as streamline health activities in line with regional and global practices.
- The Ministry of Health should make representation at the government level for improve budgetary allotment in order to address the concerns expressed.

Closing Remarks: This research has indicated that the efflux of doctors is likely not the primary problem in Jamaica's healthcare system, and also brought to light other more significant factors. There was even the suggestion that with each new batch of graduates merely adding to the stock of established doctors can not be considered a replacement to any great extent. This actually forces new doctors to leave the country and find employment elsewhere, thus contributing to the appearance of a brain drain.

There are obvious limitations to this study, the first being the very small sample size. It is also possible that the selected physicians are not representative of the all the other physicians, and views

so far expressed may also have been very biased. While I agree that a large loss of educated people is generally negative for the growth and development of a country as a whole, this study indicates that the apparent loss of doctors from the Jamaican healthcare system is perhaps not the most significant factor in the health care system which has room for much improvement.

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International Medicine Research



Ilana Jacobs, MS2

Preceptors:

William Bonne, M.D.

Associate Professor

Department of Infectious Diseases

University of Rochester Medical Center

Patrick Marcellin, M.D.

Department of Hepatology

Hôpital Beaujon, Clichy, France

“J’étais toute seule” (I was all alone): HCV Positive North African immigrants and the French National Health Care system

Introduction: Hepatitis C (HCV) is a devastating disease which, if left untreated, can lead to liver cirrhosis and hepatocellular carcinoma. Prevalence rates vary from 1-2% in industrialized nations to 20% in developing countries, with higher prevalence rates in minority groups. Treatment is difficult for patients to endure because of the vigorous schedule as well as the debilitating side effects. The French nationalized health care system has been lauded as exemplary by other nations because of its quality of care, and 100% coverage of citizens. One aspect of the system that has been called into question is whether marginalized groups receive the same benefits from the system as other citizens. The North African immigrant population has a long, tumultuous history in France, recently falling victim to the conservative backlash against immigration.

Objectives: The purpose of this study is to examine the experiences of North African immigrant patients with Hepatitis C Virus (HCV) at a hepatology clinic in Clichy, France, a suburb of Paris with a large North African Muslim immigrant population. This study investigates this immigrant population’s access to the French national health care system and their experiences with the HCV treatment regimen.

Methods: Researchers performed qualitative interviews with 21 subjects from North Africa, who were recruited following physician consultations. The interview guide contained 18 questions, exploring the subject’s background, and their experiences with HCV and social security. Data was then analyzed for emerging themes and recurrent ideas expressed.

Results: The greatest reason cited for immigrating to France was to find work, with other reasons being to get an education, or for social liberties. When asked about how they contracted HCV, the majority of subjects did not know, while blood transfusion and vaccination with unsterile needles were common responses as well. The most highly reported side effects from treatment were fatigue and depression. The vast majority of patients reported being very satisfied with the French health care system. Most patients did report feeling alone in managing their illness.

Conclusions: Although the vast majority of patients reported satisfaction with the French health care system, most patients also reported not having much support in managing their illness. This discord may be related to lack of familial presence, physical isolation during treatment, treatment of medical disease more than biopsychosocial illness, and taboo of HCV as “dirty.” These factors merit further investigation and may be applicable to other immigrant populations facing disease and treatment in a foreign country.

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International Medicine Research



Michael Nabozny, MS2
Temitope Oshodi, MS2

Preceptor:
Ann Dozier, R.N., Ph.D.
Associate Professor
Department of Community & Preventative Medicine
Division of Social & Behavioral Medicine
University of Rochester Medical Center

Free Maternal and Child Healthcare in Ecuador: How to Realize its Potential

Abstract: Globally, 11 million children die every year with the majority of those deaths occurring in developing countries. In an effort to combat this crisis, the UN in 1990, proposed a two-third reduction in under-5 mortality as the fourth of the 2015 Millennium Development Goals. Correspondingly, Ecuador made great strides to reduce child mortality rates from fifty-seven to twenty-five per thousand live births. In particular, the Law for the Provision of Free Maternal and Child Care was established in 1998 to provide services such as prenatal check-ups, care for normal and at-risk births, and care for healthy and sick newborns. In spite of this improvement, majority of deaths still occur in infants (0-1yr) with a mortality rate of twenty-two per thousand live births. Hence for every 25 children under 5 who die in Ecuador, 22 of them die before the age of one.

This project explored the factors that influence how well mothers are able to access healthcare for their infants. We surveyed 45 women and briefly interviewed some of them. Analysis of the results revealed that 1) The program provided free healthcare for children under five; 2) Vaccination efforts through the program seems organized and effective; 3) Funding for the program seems inadequate i.e. insufficient medications; 4) Lack of finances and distance to healthcare source possibly plays a role in the difficulty accessing healthcare for infants.

We conclude that adequate funding for the program in form of medication and transportation vouchers would increase the ease of accessing healthcare for infants.

Objectives:

- To assess the knowledge and utilization of the Free Maternal and Child Care program.
- To assess other external factors that might contribute to neonatal mortality thereby decreasing the effectiveness of the Free Maternal and Child Care program.

Methods: We surveyed 45 women from Quito (big city), Olón (small fishing village) and Otavalo (indigenous Andean community) who were given a 24-question survey relevant to child and maternal health. Several of the 45 women were briefly interviewed to elicit more information about their answers on the surveys.

Results:

- (1) Vaccination efforts seem organized and effective. Questions eliciting vaccination history showed that all the children born to the mothers surveyed had been vaccinated. Shadowing

opportunities in an Ecuadorian hospital revealed active efforts by the doctor to ensure vaccination compliance. A US Peace Corps volunteer who worked in rural Ecuador confirmed that vaccination vans went to rural areas to vaccinate and provide adequate records for children.

- (2) Free healthcare for children under five. In some areas, the women received free prenatal care as well as free care for their children.
- (3) Funding for the program seems inadequate. There is a lack of needed medications so families had to pay out of pocket. Most of the women surveyed had to pay extra for the visit to the doctor and medications.
- (4) Lack of finances some of the women had difficulty paying for the extra costs involved in accessing health care for their children.
- (5) The average distance to nearest health care source was about 25 minutes; most of the women surveyed depended on public transport and had to pay for it as well potentially making it more difficult to access health care.

Conclusions: There were little differences found between the different locations although more people in the indigenous community did not know about the Free Maternal and Child Health Law compared to the other two locations.

Although great strides have been taken to reduce infant mortality, more effort must be put into making the services more accessible to families especially those who can't afford it. Medication vouchers can be provided to families when medicines are unavailable at the hospital, transportation vouchers would also help in making services more accessible.

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International Medicine Research



Amy Potter, MS2

Preceptors:

Edgar Rodas, M.D. (Cuenca, Ecuador)

Stephen Lurie, M.D., Ph.D.

Assistant Professor

Department of Family Medicine

University of Rochester Medical Center

Potential Internet: A Vertical Assessment of Access and Education in Ecuador

Abstract: The Internet poses the ultimate paradox to a globalizing world. Information on the World Wide Web is available, free, to any user. However, the costs associated with infrastructure, bandwidth, and computer hardware make access to the Internet largely unobtainable. This disparity to access based on socioeconomic status is referred to as the “digital divide,” a term that was first used by newspapers, and then adopted by the Clinton administration in the mid-1990’s.¹ The number of users in the developed world greatly exceeds those in Latin American countries.¹ This gap in tele-accessibility, computer ownership, and connectivity is especially pronounced in the health sector.²

A survey of physicians in Brazil reveals that 52% of 42,744 physicians surveyed use the Internet at a level commiserate to the general U.S. population. However, most of those physicians accessed the Internet at home (85%); 10% did so at the office and only 2-3% at a university or the hospital.² To contrast, 40% of U.S. physicians access at their workplace.²

Health care professionals in South America must contend with a language barrier; 70-80% of all web content is in English (and, 1.5% in Spanish).³ Being a “digital citizen requires familiarity with English.”⁴ The quality of publicly available information is a concern to health professionals around the world; several studies evaluating single medical conditions have suggested deficiencies in the quality of Web-based information.⁴

Recent studies have addressed the digital divide with a wide lens. The heavy Internet users – Brazil and Mexico – have been analyzed separately, but less “connected” countries (i.e., Ecuador) are lumped into a “non-user” bloc. Additionally, existing literature fails to address the Internet use of a key component of Latin America’s health sector: its students. The content and extent of Internet initiatives in health professional school is undetermined but not unimportant; this data reveals critical information about the future of the Digital Divide.

Objectives: The chief objective of this project is to assess how health care professionals and students in Cuenca, Ecuador use the Internet for medically related research. The aims are as follows:

- To establish the frequency of Internet use by health care professionals and students.
- To determine how and where health care professionals and students access the Internet.
- To examine the content viewed, and the language it is viewed in.

Methods: This survey study was designed to assess how health care professionals and students in Cuenca, Ecuador use the Internet for medically related research. Data collection occurred from June 9, 2008 to July 25, 2006. The study's protocol was approved by the Institutional Review Board at the University of Rochester School of Medicine and Dentistry prior to enrollment. Permission to administer the survey was granted by Deans at each institution: Hospital Regional San Vicente (Cuenca, Ecuador); Universidad de Azuay (Cuenca, Ecuador); Universidad de Cuenca (Cuenca, Ecuador). Students were asked to voluntarily participate; of 252 students asked to participate, 249 consented (98.8% response rate). Physicians participating in a rural health care continuing education at the Universidad de Azuay were asked to participate; all voluntarily enrolled. Two separate surveys were distributed: one to physicians, and the other to medical, dental and pharmacy students at the Universidad de Azuay and the Universidad de Cuenca. Excel was used for all statistical calculations.

Results: Of 281 subjects, 277 (98.6%) use the Internet for medically-related inquiries. In the physician cohort, 72% of respondents access at least 2 to 3 times per week. Of 249 health professional students surveyed, 186 accessed at least 2 to 3 times per week (74.6%). Spanish is the predominant language used for Internet searches, though 51.6% of physicians access in English (19% consider themselves proficient English speakers). Interestingly, only 30% of medical, dental and pharmacy students surveyed search in English, even though 47.8% of respondents consider themselves proficient in English. The majority of physicians access at home (61%), work (35%) and Internet cafes (26%) on laptop computers (32% versus desktop computers, 19%; 29% said they use both). Students reported using the Internet at school (University), home and Internet cafes most frequently (50.2%; 51.4%; 46.6%), primarily on desktop computers (63%). The most commonly accessed Internet website for medically related questions was www.google.com (40% physicians; 76.3% students).

Conclusions: This study's findings suggest that the dynamics of the health care Digital Divide is changing in Cuenca, Ecuador. Physicians and health profession students are frequently employing the Internet for medically-related inquiries, though the majority continue to log on at home, school and Internet cafes. Access to the Internet in the health care setting (i.e., hospitals, private offices, clinics) and education regarding the resources therein lag in comparison. Despite the predominance of Internet content in the English language, more English-proficient Ecuadorian users are opting to search in Spanish. This data is localized to a small region in Ecuador, and would benefit from an expanded study population. As Cuenca, Ecuador and Rochester, New York are similarly sized cities, it would be interesting to conduct a parallel study at the University of Rochester. As the gap in access narrows, it will become increasingly important to focus interventions on

Internet education (i.e. how to determine and find the most reputable and powerful sources on the web).

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International Medicine Research



Rachel Anne Steinman, MS2

Preceptors:

Kendra Hennig (in-country)

Nicholas Jospe, M.D.

Department of Medical Education Awards Program

University of Rochester Medical Center

Measuring the Impact of Youth Empowerment and Diabetes Education on Diabetes Quality of Life for Youth with Type 1 Diabetes in Ecuador: A Case Study from AYUDA's *Campo Amigo Ecuador*

Background: AYUDA (American Youth Understanding Diabetes Abroad, Inc.) is a 501(c)(3) non-profit organization, which empowers youth to serve as agents of change in diabetes communities abroad. AYUDA trains teams of international volunteers to work alongside local diabetes youth leaders to empower children and adolescents with diabetes to live happier and healthier lives. AYUDA has established *Campo Amigo Ecuador* (CAE), a national diabetes camp, outside of Quito, Ecuador, with the help of the Fundación Diabetes Juvenil del Ecuador (FDJE). *Campo Amigo* operates under the philosophy that "a lack of education is just as dangerous as a lack of insulin" and thus, works to provide youth empowerment and diabetes education to campers with diabetes (primarily type 1 diabetes).

Objectives: The goal of this study is to assess the impact of AYUDA's *Campo Amigo Ecuador* on the campers' quality of life with diabetes as measured by the short form of the Diabetes Quality of Life for Youth questionnaire (DQOLY-SF).¹⁹

Methods: The short-form of the Diabetes Quality of Life for Youth questionnaire (DQOLY-SF) was translated into Spanish and modified to fit Ecuadorian cultural standards by two native Spanish speakers and AYUDA staff members. AYUDA staff members administered the DQOLY-SF questionnaire to 62 Ecuadorian campers and counselors with type 1 diabetes (1 had type 2 diabetes) of ages 10 years and older. For campers from Quito, the questionnaire was filled out during the registration period prior to the start of camp, and for campers/counselors from outside of Quito, the questionnaire was filled out on the busses to camp. Some campers/counselors were unable to complete the survey prior to the start of camp and completed it during the camp session. For younger campers or for those who had difficulty reading, the survey was read to the camper and the answers marked by the AYUDA staff member.

For the DQOLY-SF analysis, different point values are given for each response to each question (0-4, 0=Never, 1=Very seldom, 2=Sometimes, 3=Often, 4=All of the time). The results for each subscale (Impact of Diabetes-Related Symptoms, Impact of Treatment, Impact of Diabetes on

¹⁹The DQOLY-SF was discussed in the paper, "A short form of the Diabetes Quality of Life for Youth questionnaire: exploratory and confirmatory analysis in a sample of 2,077 young people with type 1 diabetes mellitus" (Diabetologia (2006) 49; 621-628).

Activities, Parent Issues, and Worries about Diabetes) can be analyzed individually by totaling the points earned for each subscale, or the total score can be obtained by summing the point values earned for all of the scales. In order to make the results more intuitive, the scores were inverted so that a higher score corresponds to a higher diabetes quality of life. The highest possible score is 84. The average QOL scores were calculated for groups of campers based upon the number of camps attended, age (10-13, 13-15, 15-19, and 19+), and gender (female vs. male).

Results (Based upon the preliminary data review): The total average diabetes-related quality of life score improved for each additional year of camp attended. There was a 37% improvement in total diabetes-related quality of life (based upon the total DQOL score) from attending 1 camp to attending 5 camps. The largest DQOL improvement from 1 camp to 5 camps was seen in the Parent Issues and Worries about Diabetes subscales. For each additional AYUDA camp attended, there was an average annual increase of 6% in quality of life related to diabetes symptoms, 7% in quality of life related to diabetes treatment, 5% in quality of life related to the impact of diabetes on activities, 26% in quality of life related to parent issues, 13% in quality of life related to worries about diabetes, and 9% in total diabetes-related quality of life.

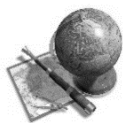
In terms of gender-associated quality of life, females have a 6% lower total DQOL than males. Regarding the Impact of Diabetes Treatment (11% difference between males and females, 1.5 t test score), and the Worries about Diabetes (10% difference between males and females, 1.17 t test score) subscales, females have a particularly low quality of life as compared to males. Within the Worries about Diabetes subscale, females worry more than males about having children (13% QOL difference), fainting or passing out (29% QOL difference), body image (17% QOL difference), and diabetes-related complications (37% QOL difference).

In terms of the age-associated quality of life, the total quality of life was lowest in the 19+ age group and the highest in the 13-15 age group. The 19+ age group had the lowest quality of life as compared to all of the other age groups in the Worries about Diabetes subscale.

Conclusions: Based upon the preliminary data review, attending AYUDA's *Campo Amigo* is associated with improved diabetes-related quality of life in Ecuadorian campers with type 1 diabetes. In fact, the more camps at AYUDA's *Campo Amigo* attended, the greater the improvement in diabetes-related quality of life. In addition, female campers/counselors tend to have a lower quality of life with diabetes than male campers/counselors particularly in the Worries about Diabetes and Impact of Diabetes Treatment subscales. This could potentially be due to concerns about pregnancy and family life, which are of great importance in Ecuadorian society, and body image, which is a related issue. The impact of these concerns and related concerns about employment and independent living may also contribute to the lower quality of life in the 19+ age group. These results indicate the importance of increasing the number of returning campers to *Campo Amigo* and providing additional mentoring and educational programs to female campers and campers 19 years of age and older.

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2. Mette Bauditz and Dr. S.E. Skovlund who provided the DQOLY-SF to AYUDA.
3. Adam Ross, Vice President of AYUDA, who performed all of the data analyses.
4. Maria F. Garcia and Dr. Patricia Blanco who translated the DQOLY-SF into Spanish
5. Dr. Gary M. Ingersoll who provided the Spanish version of the DQOLY.
6. Members of the AYUDA staff who gave the surveys to the campers and counselors.



International Medicine Research



Iyerus M. Tariku, MS2

Preceptors:

Michael Keefer, M.D.

Department of Infectious Disease

University of Rochester Medical Center

Shitaye Alemu, M.D.

University of Gondar College of Medicine & Health Sciences

Assessing Patients' Willingness to Disclose their HIV/AIDS Diagnosis

Abstract: Sub-Saharan Africa has the highest incidence and prevalence of HIV/AIDS in the world with 22 million currently living with the virus⁴. Educational efforts have expanded throughout Sub-Saharan Africa to reduce incidence of HIV and the negative stigma associated with the illness. Unfortunately, knowledge about HIV/AIDS is still poor in Ethiopia³. HIV/AIDS has an immense impact, threatening human welfare, productivity, economy, and many other aspects of societal functions. Above all, an enormous burden lies on those who have become victims of the disease. Unfortunately, patients with HIV/AIDS are still being discriminated against in their communities all around the world. As a result, patients become victims not only of the disease but also by being marginalized in their own community¹. It is crucial that people living with HIV/AIDS have adequate support systems in order to alleviate the burdens of their illness. This study explores disclosure among HIV/AIDS patients seeking care at Gondar University Hospital ART clinic in Gondar, Ethiopia.

Objectives: The study assessed the following:

- 1) The proportions of people that disclosed their positive HIV diagnosis.
- 2) Explored the factors affecting the decision not to disclose positive HIV diagnosis among participants.
- 3) Investigated correlations between the overall quality of life for people who share their HIV status versus those who do not. Quality of life was measured based on participants' ability to seek treatment when needed, availability of transportation for medical care, financial resources, and social and emotional support.

Methods: Men and woman ages 18 and above were eligible to participate in the study. Study subjects were interviewed at Gondar University Hospital ART clinic during a routine care visit. Participants were asked whom they have informed regarding their HIV status and if that has influenced their health care and social life. For participants who did not disclose their HIV status, factors contributing to their decision were explored. From the data obtained, analysis was performed to elucidate major themes and reasons to and to not disclose positive HIV status and its effect on the quality of life for patients.

Results: A total of 50 patients were interviewed. Forty three (86%) of the participants disclosed their status to at least one person. Seven participants (14%) kept their status absolutely confidential, two participants changed their names in order to access treatment but not be identified. Eight (16%) participants disclose their HIV/AIDS status within their community.

18 participants had spouses in which 77.8% disclosed their status to their spouse; the 22.2% who did not disclose were all female. 31 participants had 1 child or more in which 25.8% disclosed their status to their child/children; 39 participants had parents in which 61.5% disclosed their status to their parent(s); 45 participants had sibling(s) in which 71.1% disclosed their status to their sibling(s); 49 participants had non-immediate family members in which 36.7% disclosed their status to their non-immediate family members.

The three main reasons patients disclosed their illness were: to seek emotional support, financial support, and to receive aid during periods of illness. The three main concerns regarding disclosure expressed among the majority of patients were fear of being marginalized, their families' or communities' misconception/misunderstanding of the disease, and not seeing an emotional or financial benefit to disclosure. However, 100% of participants expressed their desire to disclose their status in the absence of negative stigma associated with HIV/AIDS.

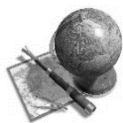
83.7% (n=43) of those that disclosed their status to at least one person received help with one or more of the following: seeking treatment, taking medications, aid during illness, financial support, compared with 14.3 % (n=7) of those that did not disclose. 97.5% of participants who disclosed believed that they had an emotional support compared with 42.9% of those who did not disclose. Among participants who disclosed their status to their neighbors and friends, some experienced discrimination and decreased social life.

Conclusions: The majority of patients living with HIV/AIDS openly share their illness with at least one person. However, most participants emphasized that their quality of life and their willingness to disclose their status solely relied on economic factors and fear of deteriorating social life. Although participants who disclosed their status received more aid with regards to their health and gained emotional support, they revealed that it was not sufficient enough to cope with the disease. For most participants, disclosure was a question of whether they will gain financial support or not. Participants that did not disclose to family member expressed that the family is too poor to help. The second factor affecting disclosure is fear of being marginalized by both their family and community. Many expressed that there is still fear of the disease and misconception about transmission. This reveals that education still needs to expand in Gondar and surrounding rural areas so that disclosure is safe and supportive.

Nonetheless, disclosure to at least one person is a positive factor in patients' well-being. As a result, health care providers should encourage patients to find at least one person or resource to share their status but with careful consideration of potential negative outcome.

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International Medicine Research



Tegan Vay, MS2

Preceptors:

Marilyn Brown, M.D.

Professor of Pediatrics, GI and Nutrition

Department of Pediatrics

University of Rochester Medical Center

Conombo Mady

Director

CSPS (Centre pour Sante et Promotion Sociale) de Mogtedo, District of Zorgho, Burkina Faso

Early Childhood Nutrition in Rural Burkina Faso : A focus on Vitamin A

Objectives: A quarter of the under five population in Burkina Faso suffers from vitamin A deficiency. It follows that a significant portion of the population will be suffering from the vision-related effects of a vitamin A deficiency, including night blindness, complete blindness, and xerophthalmia and that there will be a significant incidence of poor growth and slow recovery from infection. The hypothesis is that these symptoms will be higher in families who lack access to adequate nutrition and further, that knowledge about what foods can provide vitamin A will protect families who might otherwise be at risk. If this is true we will attempt to ascertain the most important barriers to adequate consumption of vitamin A rich foods. In addition, this study will provide information to Peace Corps volunteer Katherine Kalaris and her supervisors at the village clinic as they plan nutritional interventions. They will be able to use the data gathered to assess the magnitude of the problem in their area and to focus educational interventions to address the specific conditions in Mogtedo.

Methods: First a market survey and interviews of clinic nurses were conducted to determine which vitamin A rich foods are locally available and regularly consumed. We then conducted structured interviews of women with children under the age of five who presented to the CSPS for treatment or vaccinations. Women were asked to report their child's total food consumption on the previous day. They were also asked generally about other foods their children commonly consume and specifically about consumption of locally available foods rich in vitamin A. Data were collected on family structure, illnesses, and vision related sequelae of vitamin A deficiency. Finally, women were asked their opinions on the relationship between health and nutrition and why their children did or did not eat certain foods. This data was analyzed to determine barriers to adequate vitamin A consumption among children in the catchment area of the CSPS.

Results: The assessment of the previous day's intake showed that the three most commonly consumed foods were tô and bouille, made from pounded millet, sorghum, or corn, and rice. Intake of six vitamin A rich foods was as follows: liver – 0%, eggs – 0%, morringa – 0%, mango – 6.25%, boulvaka – 25%, and milk – 56%. No one reported any of the visual sequelae of vitamin A deficiency and records of such conditions were not kept in the clinic's monthly reports. 31.25% of the women had lost at least one child to infection or illness but specific causes of death were impossible to obtain. 72% reported cost as the primary reason their children did not eat vitamin A

rich foods. Other commonly reported barriers were availability, taste, and cultural beliefs. Less than 1/3 of women believed that foods could be related to health and of those who did, only two listed vitamin A rich foods among foods believed to be beneficial.

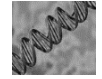
Conclusions: We concluded that very few of the children in Mogtedo are receiving adequate amounts of vitamin A in their diets. The primary barriers to consumption are lack of money and lack of knowledge. While the financial problems are difficult to remedy in the short term, many of the parents find the means to pay for needed health care for their children. If parents were educated about the importance of vitamin A in their children's diets they might be more likely to find ways to incorporate those foods into family meals. Interventions should focus on foods that are available year round and foods that are very inexpensive in their season. Finally, due to lack of screening and reporting we were unable to assess the presence of vitamin A related visual symptoms as a measure of the vitamin A status of the population.

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Year-Out Research



Stephan Barrientos, MS4

Preceptors:

Marjana Tomic-Canic

Harold Brem M.D.

Department of Tissue Engineering Repair and Regeneration Laboratory

Hospital for Special Surgery, New York City

Molecular Markers of Pathogenesis of Chronic Wounds

Objective: Our aim was therefore to determine if histology, β -catenin and c-myc can be used as markers to identify the non-healing tissue within a chronic ulcer. To identify molecular changes that lead to pathogenic alterations in keratinocytes we used biopsy specimens obtained from venous, diabetic foot and pressure ulcers and characterize them by histology (H&E), immunoperoxidase (c-myc) and immunofluorescent staining (β -catenin). Histology of all three types of chronic ulcers before debridement had an epidermis that was hyper-proliferative, hyper-keratotic and parakeratotic. Before debridement keratinocytes in the chronic wound had nuclear presence of β -catenin and increased expression of c-myc throughout the epidermis. After debridement keratinocytes in the chronic wound have an absence of nuclear β -catenin and a reduction in the expression of c-myc in the epidermis. Our finding shed new light on the molecular mechanisms underlying the development of chronic wounds and identify molecules that can be utilized as pathogenic markers.

Objectives: Keratinocytes are major contributing cells to the wound healing process. In normal skin upon wounding keratinocytes first migrate and then proliferate to fill in the wound bed. In the chronic wound keratinocytes have impaired migration, thus contributing to the pathogenesis. One of the techniques employed to treat chronic wounds is debridement with the goal of removing these impaired keratinocytes. Determining the debridement margin is difficult seeing as how there are no objective markers to help identify these cells. There have been several studies using transgenic mouse models that showed β -catenin and c-myc played a role in the chronic ulcer. In particular, a nuclear presence of β -catenin and over expression of c-myc lead to impaired keratinocytes migration. Our aim was therefore to determine if histology, β -catenin and c-myc can be used as markers to identify the non-healing tissue within a chronic ulcer.

Methods: Our experimental design involved obtaining debrided skin tissue from consented patients with pressure ulcers, diabetic foot ulcers, and venous stasis ulcers (n=20). Exclusion criteria included those patients who had systemic disease, were on systemic medications or who were treated with biological therapy within four weeks. The skin was processed for paraffin and frozen sectioning. The samples were then analyzed for the following biological markers: H&E (histology), immunofluorescence (β -catenin) and immunoperoxidase staining (c-myc).

Results: In marked contrast to normal skin, biopsies of non-healing edges obtained from patients with all three types of chronic wounds showed a thick and hyper-proliferative epidermis with mitosis present in the suprabasal layer, and no epithelial migration. **(Fig.1A)** In addition, hyperkeratosis and parakeratosis was evident in the non-healing edges of all types of chronic ulcers. **(Fig. 1B)** We found activation and nuclear presence of β -catenin throughout the epidermis of the non-healing edges in all three types of ulcers. In normal skin, the staining is membranous and along the basal layer. Positive nuclei stain green. **(Fig. 2)** When we tested biopsy specimens obtained from the wound

edge immediately post-debridement, we found marked reduction of c-myc expression and absence of nuclear β -catenin similar to that seen in normal skin (**Fig 3**) We then looked at c-myc one of the downstream targets of β -catenin, we showed that there is increased expression of c-myc throughout the epidermis of chronic ulcers before debridement. Positive nuclei are brown and negative nuclei are blue. (**Fig. 4A**) When we looked at post debridement skin we saw a marked reduction in c-myc expression similar to that of normal skin. (**Fig. 4B**)

Conclusions: This work sheds light on the molecular mechanisms underlying the development of chronic wounds and identifies molecules that can be utilized as pathogenic markers. Histology, β -catenin and c-myc can potentially be utilized in determining the margin of debridement in the future. (**Fig.5**)

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Year-Out Research



Vasisht Srinivasan, MS4

Preceptor:

Edward Vates, M.D., Ph.D.

Department of Neurosurgery

University of Rochester Medical Center

Capillary Pulsatility Is Decreased After Subarachnoid Hemorrhage

Abstract: Subarachnoid hemorrhage (SAH) is a devastating injury to the brain, commonly resulting from rupture of an aneurysm. The dreaded sequella of SAH is vasospasm, which can result in delayed ischemic neurological deficits (DIND) and stroke due to arterial spasm and a decrease in cerebral perfusion. However, The effects of SAH on the microvasculature remain largely unexplored. We used *in-vivo* 2-photon laser scanning microscopy (LSM) to document capillary pulsatility and determine the effects on this by SAH. Normal and SAH animals underwent craniotomies to measure microvascular blood flow using LSM. Pulsatility index (PI), calculated using the ratio peak red blood cell (RBC) velocity:mean RBC velocity was found to be significantly decreased in SAH animals, correlating with a drop in brain tissue oxygenation. Further work needs to be performed to fully understand the effects and implications of reducing pulsatility in the microcirculation.

Objectives: SAH causes vasospasm of large intracranial arteries, but its effects on the microcirculation remains largely unexplored. We used *in-vivo* two-photon laser scanning microscopy (LSM) to document pulsatility in capillaries, and to determine if SAH affects capillary pulsatility.

Methods: Normal and SAH mice (cisterna magna injection model, 48 h post injection) were examined using LSM. Arterial blood pressure (AB), pulse, pCO₂, pO₂, and temperature were measured and maintained constant among all animals. LSM was used to identify “arterial” and “venous” capillaries. Arterial capillaries were defined as capillaries immediately branching off of a feeder arteriole. Venous capillaries were similarly defined as those draining directly into a venule. Line scans of multiple individual arterial and venous capillaries were used to calculate RBC velocity for 1-2 seconds, and this data was used to calculate capillary pulsatility. Pulsatility index (PI) was defined as the ratio peak RBC velocity:mean RBC velocity (non-pulsatile flow would have PI = 1).

Results: Capillaries in both normal and SAH animals showed pulsatile flow through arterial and venous capillaries. Compared to normal mouse brain (arterial PI=1.41, venous = 1.31), SAH brain arterial and venous capillaries showed significantly reduced pulsatility (arterial PI = 1.29, venous 1.23, $p < 0.05$). This correlated with observations that brain tissue oxygenation was dramatically reduced after SAH (normal brain oxygen 29.14 mmHg vs. SAH brain oxygen = 10.03 mmHg).

Conclusions: Capillary pulsatility is reduced after SAH, and this does not appear to be due to elevated ICP. This correlates with reduced oxygen tension within the brain after SAH. Reduced pulsatility could be a reflection of proximal arterial vasospasm or distal venous distention, both of which are seen in our animal model, or it could be due to changes in how RBCs are able to move through capillaries. Pulsatility has been implicated in maintaining capillary patency, and this

change in pulsatility may play a role in microcirculatory failure after SAH. Studies have demonstrated widespread organ damage following long-term non-pulsatile flow (i.e. while on cardiopulmonary bypass) in animals and further work needs to be done to fully understand the effects of microvascular pulsatility on end-organ function.

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