



SCHOOL OF  
**MEDICINE &  
DENTISTRY**

UNIVERSITY *of* ROCHESTER  
MEDICAL CENTER

Medicine of the Highest Order

2010

**Annual  
Medical Student  
Abstract Journal**

*Sponsored by:*

Center for Advocacy, Community Health, Education and Diversity

Offices for Medical Education

Medical Student Research Faculty Advisory Committee

Community Outreach Faculty Advisory Committee

International Medicine Faculty Advisory Committee Medical

Humanities Faculty Advisory Committee

# Basic Science & Clinical Research

**Bryce Allio, MS2**

## **Neuropeptides Coordinate the Complex Inflammatory Cascade During Wound Healing.**

Keywords: Neuropeptides, Diabetic Neuropathy, Wound Healing, SubstanceP

### **ABSTRACT**

The last decade of inflammation research has been dedicated to discovering the role of cytokines in disease process and pharmaceutical use. Neuropeptides are now becoming increasingly identified as major players and regulators in the inflammatory cascade. Nowhere is this more evident than in the case of diabetic neuropathy and the occurrence of foot ulcerations. Diabetic peripheral neuropathy is the number one indicator of a patient developing an ulceration that resists healing. Wound healing requires the integration of complex cellular and molecular events in successive phases of inflammation, cell proliferation, cell migration, angiogenesis and re-epithelialisation. Neuropeptides released from peripheral nerves such as Substance P and Neuropeptide Y have been shown in a number of studies to help orchestrate the cytokines and migratory cells. This poster will serve as a review, and for many, an introduction to the recently realized neuroimmune system.

Considerations: Please note this intended to present a “current state” of the research in which I was involved this year. Unfortunately my experience this summer was limited to knowledge gain as opposed to experimental outcome gain. As I was not involved personally in a project, I have no successful or failed experiment to present in the typical format. However, the subject matter in which I intend to review and present in poster form is universally applicable to all inflammation and is surprisingly unknown to most due to its relatively new beginnings. I am confident that this topic will be most interesting to poster session attendees.

Information and results for this poster will be pulled mainly from the work of my research mentors A. Veves and FW. LoGerfo.

# Basic Science & Clinical Research

Nicole Altorelli, MS2

**Preceptors:**

**Dr. John Olschowka, PhD and Dr. Kerry O'Banion, MD, PhD Department of Neurobiology and Anatomy  
University of Rochester Medical Center**

## **The Role of COX-1 in Radiation Induced Neuroinflammation**

**Introduction:** Normal tissue irradiation in the brain causes both acute and delayed effects, including induction of neuroinflammation. The neuroinflammatory response consists of the activation of microglia and astrocytes and upregulation of mediators such as chemokines, cytokines, prostanoids, reactive oxygen and nitrogen species. These changes in the tissue are thought to contribute to long-term damage such as disruption of the blood-brain barrier, demyelination, and white matter necrosis. Neuroinflammation is seen following many types of injury and may contribute to CNS disorders such as Alzheimer's, Parkinson's, ALS, and dementia [Choi 2008]. Indeed, epidemiological studies indicate that individuals taking nonsteroidal anti-inflammatory drugs that target prostaglandin production by cyclooxygenase (COX) show reduced risk for Alzheimer's disease [Klegeris 2005]. Previously, the inducible isoform COX-2 was thought to be the primary producer of prostaglandins after CNS damage and was presumed to be the target for many anti-inflammatory drugs [Choi 2009]. More recently COX-2 has been shown to have protective effects on the cells of the brain and COX-1 appears to be the enzyme that is most relevant to CNS inflammation.

**Objective:** To determine the role of COX-1 in neuroinflammation after radiation injury in the mouse brain.

**Background:** COX-1 is primarily found in microglia, which are responsible for innate immune responses by producing proinflammatory molecules [Gao 2009]. In contrast, COX-2 is primarily found in neurons. Activated microglia numbers increase significantly 24 after brain irradiation and persist out to one year [Olschowka and O'Banion unpublished data]. Activated microglia produce a range of pro-inflammatory molecules that alone or through the activity of other cells can lead to neural damage, oxidative stress and cell death [Hailer 2008]. COX-1 has been implicated in several diseases associated with neuroinflammation, including Alzheimer's and Parkinson's disease [Yermakova et al 1999, Teismann 2003]. Recently, COX-1 deficient mice injected with lipopolysaccharide were found to have significant reductions in neuroinflammatory markers such as iNOS, chemokines, cytokines, prostaglandins, thromboxanes and microglial activation relative to wild-type control mice [Choi 2008]. This suggests that COX-1 inhibitors might be therapeutically beneficial in diseases associated with neuroinflammation [Choi 2009].

**Methods:** B6;129P2 mixed background (WT or COX-1<sup>-/-</sup>) mice (8-10 weeks old) were anesthetized, cranially irradiated using a Cesium-137 source at doses of 35 Gray (Gy), and sacrificed 6 months following irradiation. Mice were anesthetized and perfused with

4% paraformaldehyde. Brains were immersion fixed, frozen, sectioned to 30  $\mu\text{m}$  and stored in cryoprotectant. Sections were subjected to standard immunohistochemical protocols with antibodies to assess radiation-associated activation of microglia (MHC-II and Iba-1), astrocytes (GFAP - fluorescent), and endothelial cells (ICAM-1). Stained sections were quantified from captured images by direct cell counting (MHC-II) or by threshold analysis and calculation of area occupied by stain using ImageJ (NIH). 2-Way ANOVA followed by Bonferroni Post Hoc Test was used to establish statistical significance at a level of  $p < 0.05$ .

**Results:** Numbers of MHCII<sup>+</sup> stained per  $\text{mm}^2$  were significantly increased by radiation in both wild-type ( $p < 0.05$ ) and COX-1<sup>-/-</sup> ( $p < 0.001$ ) mice. Interestingly, irradiated COX-1 deficient mice showed greater numbers of MHC-II positive cells relative to irradiated control mice ( $p < 0.01$ ). Although the morphology of Iba-1 positive microglia clearly changed with radiation, our quantitative approach failed to detect differences in total area stained with no difference between strains detected. ICAM-1 staining was significantly increased following 35 Gy irradiation in both wild-type ( $p < 0.01$ ) and COX-1 knockout ( $p < 0.05$ ) mice, but no significant differences between the two strains was observed. Cells of unknown type were consistently seen on ICAM1 stained sections. Double labeling immunofluorescence of ICAM1 with GFAP or IBA1 demonstrated co-localization in both astrocytes and microglia.

**Conclusions:** Our results confirm that neuroinflammation occurs following irradiation and is prominent for the time (6 months) and dose (35 Gy) examined here. COX-1<sup>-/-</sup> showed neuroinflammatory responses and in the case of MHCII, appeared to have a more robust response to radiation than wild-type mice. These results are not consistent with other studies suggesting a pro-inflammatory role for COX-1. This discrepancy could well be due to differences in eliciting agents (i.e. radiation vs. LPS) or in the time points examined (days vs. months). Additional work will be required to more fully dissect the role of COX-1 in neuroinflammation following radiation injury.

#### References:

1. Chiang CS, McBride WH, Withers HR. Radiation induced astrocytic and microglial responses in mouse brain. *Radiother Oncol* 1993; 29:60-68.
2. Choi S, Langenbach R, Bosetti F. Genetic deletion or pharmacological inhibition of cyclooxygenase-1 attenuate lipopolysaccharide-induced inflammatory response and brain injury. *The FASEB Journal* 2008; 22:1491-1500.
3. Choi S, Aid S, Bosetti F. The distinct roles of cyclooxygenase-1 and -2 in neuroinflammation: implications for translational research. *Cell Press* 2009; 30: 174-181.
4. Gao, H.M. and Hong, J.S. (2008) Why neurodegenerative diseases are progressive: uncontrolled inflammation drives disease progression. *Trends Immunol.* 29, 357–365.
5. Hailer NP. Immunosuppression after traumatic or ischemic CNS damage: it is neuroprotective and illuminates the role of microglial cells. *Prog Neurobiol.* 2008 Mar;84(3):211-33.
6. Klegeris A, McGeer PL. Non-steroidal anti-inflammatory drugs (NSAIDs) and other anti-inflammatory agents in the treatment of neurodegenerative disease. *Curr Alzheimer Res.* 2005 Jul;2(3):355-65.

8. Kyrkanides S, Olschowka JA, Williams JP, *et al.* TNF and IL-1 mediate intercellular adhesion molecule-1 induction via microglia-astrocyte interaction in CNS injury. *J Neuroimmunol* 1999;95:95–106.
9. Teismann, P. et al. (2003) Cyclooxygenase-2 is instrumental in Parkinson's disease neurodegeneration. *Proc. Natl. Acad. Sci. U. S. A.* 100, 5473–5478
10. Yermakova, A.V. et al. (1999) Cyclooxygenase-1 in human Alzheimer and control brain: quantitative analysis of expression by microglia and CA3 hippocampal neurons. *J. Neuropathol. Exp. Neurol.* 58, 1135–1146.

# Basic Science & Clinical Research

Rachel Anolik, MS2

**Preceptor:**

**Matija Snuderl, MD**

**Neuropathologist at Massachusetts General Hospital, Boston, MA.**

## **Inhibition of Placental Growth Factor (PlGF) in Medulloblastomas Does Not Inhibit Neurosphere Formation**

Rachel Anolik<sup>1</sup>, Matija Snuderl, MD<sup>2</sup>, Nathaniel Kirkpatrick, PhD<sup>2</sup>, Ana Batista, PhD<sup>2</sup>, Elisa Walsh<sup>2</sup>, Euiheon Chung, PhD<sup>2</sup>, Walid Kamoun, PhD<sup>2</sup>, Teresa Peterson<sup>2</sup>, Lance L. Munn, PhD<sup>2</sup>, Dan G. Duda, PhD<sup>2</sup>, Dai Fukumura, PhD<sup>2</sup>, Peter Carmeliet, PhD<sup>2</sup>, Lei Xu, PhD<sup>2</sup>, Rakesh K. Jain, PhD<sup>2</sup>

<sup>1</sup>University of Rochester, School of Medicine and Dentistry

<sup>2</sup>Department of Radiation Oncology, Edwin L. Steele Laboratory, Harvard Medical School

**Objective:** To determine whether anti PlGF therapy has an effect on stem cell properties in medulloblastoma regression.

**Methods:** D283Med and D341Med human medulloblastoma cells were transfected with Gaussia luciferase cDNA and implanted orthotopically into cerebelli of SCID mice. Tumor growth was followed by whole body imaging and blood Gluc assay. Murine PlGF was blocked by anti-PlGF antibody (PL5D11D4, ThromboGenics) or silenced by siRNA. Immunohistochemistry (IHC) for nestin, a stem cell marker, was performed on tissue sections of dissected tumors. In vitro, to evaluate the role of PlGF for neurosphere formation, human and murine D283, D341 and 283Mbm medulloblastoma cell lines were cultured in Neurocult media and treated with anti-PlGF antibody and murine and human PlGF recombinant protein. Sphere formation was monitored and recorded for 10 days. 3-(4,5-Dimethylthiazol-2-Yl)-2,5-Diphenyltetrazolium Bromide (MTT) assay was performed in vitro to explore viability and proliferation.

**Results:** Mice with implanted medulloblastoma cells with PlGF silenced by siRNA or blocked by the antibody from the day of implantation showed a significant delay in tumor growth ( $p < 0.0001$ ) and prolonged survival ( $p = 0.003$ ) when compared to IgG-treated controls. Treatment of established tumors 3 weeks post-implantation with anti-PlGF antibody showed stabilization of disease and regression of medulloblastomas ( $p = 0.017$ ) by Gluc and whole body imaging measurements, and prolongation of survival ( $p = 0.0009$ ). Immunohistochemistry showed nestin upregulated in sections from siRNA PlGF knockdown tumors and those treated with anti-PlGF antibody compared to IgG treated controls. Sphere formation was not prevented by anti-PlGF antibody treatment in vitro. Viability and proliferation were also not inhibited by anti-PlGF antibody treatment in vitro.

**Conclusions:** Pharmacological or genetic blockade of -PlGF leads to regression of medulloblastoma in vivo and upregulation of stem cell marker nestin. However, anti-PlGF blockade does not inhibit neurosphere formation in vitro suggesting that PlGF blockade does not affect medulloblastoma stem cells.

# Basic Science & Clinical Research

Isabel Bazan, MS2

**Preceptor:**  
**Hsiang Shonna Yin, MD Assistant Professor**  
**Department of Pediatrics**  
**NYU School of Medicine / Bellevue Hospital Center**

## **Dissemination of a Health Literacy Intervention to Improve Provider-Patient Communication of Medication Instructions and Decrease Outpatient Pediatric Errors**

**Introduction:** According to the Institute of Medicine (IOM), almost half of all US adults have trouble understanding and utilizing health information, or low health literacy.<sup>1</sup> Health literacy has been recognized as a critical quality and patient safety issue, and has been specifically linked to poor medication management.<sup>5-9</sup> A recent study found that 70% of preventable adverse drug events (ADEs) in pediatric outpatients are attributable to errors in medication administration;<sup>10</sup> barriers to provider communication of medical instructions, including limited health literacy skills, play an important role.<sup>11-13</sup> This issue is particularly concerning given the high prevalence of dosing errors (>50%; liquid medications)<sup>14-16</sup> and nonadherence<sup>17</sup> in children. To address these issues, a bilingual (English/Spanish), plain language, pictogram-based health literacy intervention was developed at NYU School of Medicine / Bellevue Hospital to facilitate provider communication of medication information. A randomized controlled trial in Bellevue's pediatric ED demonstrated the efficacy of the intervention, with decreased dosing errors (intervention vs. control: 5.4% vs. 47.8%, p=0.0002) and non-adherence (9.3% vs. 38.0%, p=0.002).<sup>18</sup> The current study builds on this prior work by seeking to examine the effectiveness and feasibility of the pictogram-based intervention as it is implemented in 2 public hospital pediatric emergency department settings for use by pediatric providers.

### Objectives:

To assess the effectiveness of the pictogram-based health literacy tool in decreasing revisit rates, improving medication dosing and adherence by parents, and improving the quality of provider-parent communication.

To assess the feasibility of incorporating the pictogram-based tool into routine practice in the pediatric ED, including assessing utilization rates, as well as the fidelity with which providers perform each component of the health literacy tool.

**Background:** This study is consistent with a growing national focus on the development of evidence-based strategies to address low health literacy and reduce medical errors.<sup>1,2</sup> Medication errors are a particularly critical concern in children, given the high prevalence of misdosing,<sup>16-18</sup> and a 2.4x increased rate of adverse events when medication errors occur in children.<sup>21</sup> Of further concern is an overall poor adherence rate of 50%,<sup>19</sup> with implications for treatment failure and drug resistance.<sup>19,22</sup> Effective communication is critical; the ED, given its often chaotic nature, is an especially high risk site for miscommunication / error.<sup>23</sup>

The HELPix tool was designed to facilitate accurate dosing and adherence to the prescribed medication schedule by directly addressing the communication needs of caregivers with low literacy. HELPix has three components: 1) medication instruction and log sheets, 2) teachback, and 3) provision of a standardized dosing instrument (liquid medications only).

**Methods:** This study employs a pre- / post- implementation study design. We will compare findings from 2 public hospital EDs, Bellevue and Woodhull Hospitals, serving patients with similar sociodemographics, one of which will undergo implementation of the HELPix tool, while the other will continue to provide routine medication counseling.

We have begun to enroll and assess parent/children and providers in the pre-implementation phase. Chart reviews at each site are performed consecutively to assess parent-child dyads for eligibility. *Inclusion criteria:* child  $\leq 8$  years, child prescribed a daily dose short course ( $\leq 14$  day) liquid medication. *Exclusion criteria:* caregiver non-English/ Spanish language (due to HELPix instruction sheets available in English/ Spanish only).

*Assessments by Chart review:* Child diagnosis / prescription information are obtained by chart review, hospital revisits are assessed, and sociodemographic information is collected.

*Assessments by telephone interview:* Parent medication-related practices (report of medication dose, adherence (start/end time, missed doses), and use of standardized instrument), report of provider strategies used to communicate medication instructions (e.g. teachback), report of perceived quality of provider communication, and sociodemographic information.

*Observed assessments:* Those parents enrolled by telephone are asked to return for an observed dosing assessment utilizing a previously established protocol.<sup>20</sup> Parents are also asked to complete health literacy (STOFHLA (short Test of Functional Health Literacy in Adults), NVS (Newest Vital Sign)) and numeracy (WRAT (Wide Range Achievement Test) Arithmetic) assessments.<sup>3</sup>

**Results:** To date, we have enrolled 79 subjects (Bellevue n=34; Woodhull n=45), which represents approximately 25% of the total number we plan to enroll for Phase I of the study.

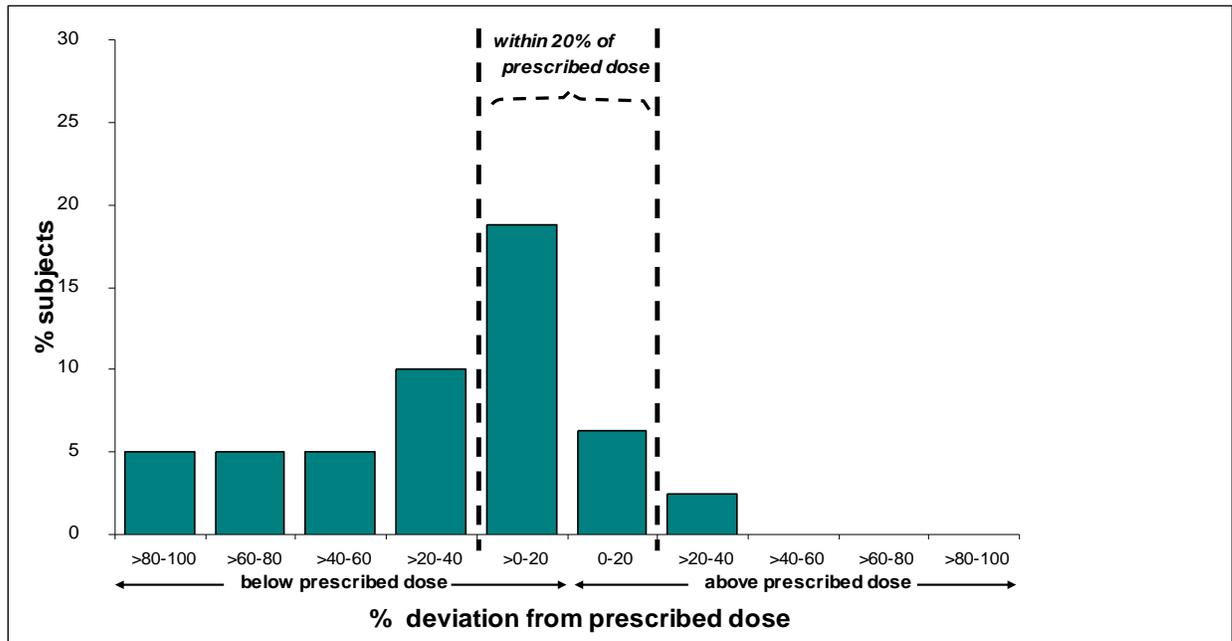
#### Caregiver health literacy and numeracy

A significant proportion of caregivers fell into the marginal or inadequate HL categories. Statistically significant differences in TOFHLA categorization was seen between sites, with 15.8% at Bellevue vs. 48.0% at Woodhull falling in to the inadequate category ( $p=0.04$ ). No statistically significant differences between sites were seen in NVS categorization ( $p=0.8$ ). Caregiver numeracy, assessed using the WRAT-3 Arithmetic, was poor, with 86.4% scoring below a 5<sup>th</sup> grade level. No statistically significant differences in numeracy category were seen between parents at Bellevue compared to parents at Woodhull ( $p=1.0$ ).

#### Dosing errors and adherence

51.2% made a dosing error, defined as 20% or more deviation from the prescribed dose (**Figure 1**). 23.3% of parents made an error greater than a 50% deviation from the prescribed dose. The vast majority, approximately 90% of doses, involved underdosing rather than overdosing. Thus far, approximately 40.4% of parents were non-adherent (80% adherence rate considered to be acceptable). We have not yet examined correlations between dosing error and adherence and the caregiver health literacy / numeracy variables.

**Figure 1:** Caregiver dosing accuracy, observed



**Conclusion:** It has become increasingly evident that strategies to prevent medication errors are needed, particularly ones which take into account the widespread level of low health literacy in the US. Strategies targeting errors in children are especially needed, given the high prevalence of misdosing and non-adherence.<sup>16-18</sup> Unfortunately, there has been limited development or evaluation of interventions to prevent parent medication administration errors in children.

Prior work has already found the HELPix intervention to be efficacious in improving caregiver dosing accuracy and adherence in the ‘ideal’ world where the intervention was performed by trained members of the research team. This current study aims to assess how effective and feasible HELPix will be in the ‘real’ world, where each child’s health care provider administers the intervention. The low resource requirements for this intervention, along with a large reduction in risk and a small number needed to treat, support its potential utility in clinical practice.<sup>20</sup>

We have only just begun to gather data for phase I of our study. Our findings reveal that a large number of caregivers are categorized as having ‘marginal’ or ‘inadequate’ health literacy, and a significant percentage have poor numeracy skills, below a 5<sup>th</sup> grade arithmetic level. Dosing errors were frequent and non-adherent rates were high, consistent with findings from our previous studies. These results illustrate that HELPix may be particularly effective with this population of low literate patients. HELPix integrates proven communication strategies to improve provider- parent communication of medication instructions, providing specific support for parents with low health literacy. The pictogram-based materials help parents to focus on key concepts, with a particular emphasis on appropriate measurement of liquid medications. Ultimately, we hope to disseminate the intervention across NYC and nationally. We also hope to expand the scope of HELPix to include additional medication types, including those for chronic diseases, adult medication regimens, as well as additional languages.

## REFERENCES

1. Nielson-Bohlman L, Panzer A, Kindig D, eds. *Health literacy: a prescription to end confusion*. Washington, DC: Institute of Medicine - National Academies Press; 2004.
2. Schwartzberg JG, Van Geest JB, Wang CC, eds. *Understanding Health Literacy: Implications for*

- Medicine and Public Health*: AMA Press; 2005.
3. Berkman ND, DeWalt DA, Pignone MP, et al. *Literacy and health outcomes*. Rockville, MD: Agency for Healthcare Research and Quality; 2004.
  4. Baker DW, Wolf MS, Feinglass J, Thompson JA, Gazmararian JA, Huang J. Health literacy and mortality among elderly persons. *Archives of Internal Medicine*. Jul 23 2007;167(14):1503-1509.
  5. Vernon JA, Trujillo A, Rosenbaum S, DeBuono B. Low health literacy: implications for national health policy. Partnership for Clear Health Communication at the National Patient Safety Foundation ([http://npsf.org/askme3/pdfs/Case\\_Report\\_10\\_07.pdf](http://npsf.org/askme3/pdfs/Case_Report_10_07.pdf); accessed August 15, 2008); 2007:1-12.
  6. Commission J. "What did the doctor say?": Improving health literacy to protect patient safety. *Health Care at the Crossroads report*. 2007.
  7. Davis TC, Wolf MS, Bass PF, et al. Low literacy impairs comprehension of prescription drug warning labels. *Journal of General Internal Medicine*. 2006;21(8):847-851.
  8. Persell SD, Osborn CY, Richard R, Skripkauskas S, Wolf MS. Limited health literacy is a barrier to medication reconciliation in ambulatory care. *Journal of General Internal Medicine*. Nov 2007;22(11):1523-1526.
  9. Davis TC, Wolf MS, Bass PF, 3rd, et al. Literacy and misunderstanding prescription drug labels. *Annals of Internal Medicine*. Dec 19 2006;145(12):887-894.
  10. Wolf MS, Davis TC, Tilson HH, Bass PF, 3rd, Parker RM. Misunderstanding of prescription drug warning labels among patients with low literacy. *American Journal of Health-System Pharmacy*. Jun 1 2006;63(11):1048-1055.
  11. Yin HS, Dreyer BP, Foltin GL, van Schaick L, Mendelsohn AL. Association of low caregiver health literacy with reported use of non-standardized dosing instruments and lack of knowledge of weight-based dosing. *Ambulatory Pediatrics*. 2007;7(4):292-298.
  12. Zandieh SO, Goldmann DA, Keohane CA, Yoon C, Bates DW, Kaushal R. Risk factors in preventable adverse drug events in pediatric outpatients. *Journal of Pediatrics*. Feb 2008;152(2):225-231.
  13. Ad Hoc Committee on Health Literacy for the Council on Scientific Affairs AMA. Health Literacy: Report of the Council on Scientific Affairs. *JAMA*. February 10, 1999; 281(6):552-557.
  14. Hardin LR. Counseling patients with low health literacy. *American Journal of Health- System Pharmacy*. Feb 15 2005;62(4):364-365.
  15. Castro CM, Wilson C, Wang F, et al. Babel babble: physicians' use of unclarified medical jargon with patients. *American Journal of Health Behavior*. Sep-Oct 2007;31 Suppl 1:S85-95.
  16. Frush KS, Luo X, Hutchinson P, Higgins JN. Evaluation of a method to reduce over-the-counter medication dosing error. *Archives of Pediatrics & Adolescent Medicine*. Jul 2004;158(7):620-624.
  17. Li SF, Lacher B, Crain EF. Acetaminophen and ibuprofen dosing by parents. *Pediatric Emergency Care*. Dec 2000;16(6):394-397.
  18. McMahon SR, Rimsza ME, Bay RC. Parents can dose liquid medication accurately. *Pediatrics*. Sep 1997;100(3 Pt 1):330-333.
  19. Winnick S, Lucas DO, Hartman AL, Toll D. How do you improve compliance? *Pediatrics*. Jun 2005;115(6):e718-724.
  20. Yin HS, Dreyer BP, van Schaick L, Foltin G, Dinglas C, Mendelsohn AL. Randomized controlled trial of a pictogram-based intervention to reduce liquid medication dosing errors and improve adherence among caregivers of young children. *Archives of Pediatrics & Adolescent Medicine*. 2008;162(9):814-822.
  21. Santell JP, Hicks R. Medication errors involving pediatric patients. *Joint Commission Journal on Quality & Patient Safety*. Jun 2005;31(6):348-353.
  22. Sawyer SM, Aroni RA. Sticky issue of adherence. *Journal of Paediatrics & Child Health*. 2003;2003(39):2-5.
  23. Croskerry P, Shapiro M, Campbell S, et al. Profiles in patient safety: medication errors in the emergency department. *Academic Emergency Medicine*. 2004;11(3):289-299

# Basic Science & Clinical Research

Michael Bourne, MS2

**Preceptor:**

**J. Kimble Frazer, MD/PhD Assistant Professor of Pediatrics**

**Division of Pediatric Hematology-Oncology**

**Adjunct Research Instructor in Oncological Sciences Huntsman Cancer Institute, University of Utah**

## **Valproate-Induced Remission of Zebrafish T Cell Lymphomas**

**Introduction:** Treatment of pediatric T cell lymphoblastic lymphoma (T-LBL) is highly effective but requires 2 years of morbid and intensive therapy that also confers risks for long-term side effects to survivors. Molecularly targeted treatments carry the promise of less toxic—yet still highly efficacious—therapies for T-LBL, with several classes of agents currently in development. Using transgenic murine *Myc* (*mMyc*) zebrafish, as well as *shrek* (*srk*), *hulk* (*hlk*), and *oscar the grouch* (*otg*) mutants, Dr. Frazer's lab has piloted g-irradiation (XRT) and dexamethasone (DXM) treatments in *D. rerio* T-LBL. Their results demonstrate that both interventions can induce high rates of remission, and show that zebrafish and human T-LBL are similarly susceptible to these therapies, alluding to their common biologic features. **Objective:** To determine if valproate induces T-LBL and T-ALL remission in *mMyc*, *srk*, *hlk*, and *otg* lines of *D. rerio* *in vivo*.

**Background:** Dr. Frazer and colleagues recently published their findings in *Leukemia, Heritable T-Cell malignancy models established in a zebrafish phenotypic screen*<sup>i</sup>. Their work uses zebrafish genetic models to better understand the molecular abnormalities that lead to T cell acute lymphoblastic leukemias and lymphoblastic lymphomas. Although many T cell cancers have lesions in known genetic loci, like well-characterized mutations in *NOTCH1* and *c-MYC*, many other unknown genetic lesions likely cause or contribute to malignant transformation. Dr. Frazer and his team used transgenic fish with T-lymphocyte specific expression of Enhanced Green Fluorescent Protein (EGFP), rendering their T cells visible by fluorescent microscopy. In a 'forward-genetic' approach, these fish were subjected to chemical mutagenesis with a DNA-damaging agent, ENU (N-ethyl-N-nitrosourea). Subsequent generations of fish were screened for tumors expressing EGFP, and 3 lines with heritable predisposition to T cell malignancy were obtained. The morphologic appearance of these cancers resemble human varieties of T-cell acute lymphoblastic leukemia (T-ALL) and lymphoblastic lymphoma (T-LBL).

**Methods:** *Wild-type* and *mMyc D. Rerio* were used to find a suitable therapeutic and non-lethal dose of valproate of 7.5µg/ml. Zebrafish with a positive screen for cancer from *mMyc* and *hlk* lines were used in the various trials. Trials in June and July 2010 had the following protocol: Four *mMyc* and two *hlk* were photographed on day 0 (d0) with UV light to fluoresce the EGFP expressing lymphocytes and visualize disease burden. Fish were then placed in separate containers with 200 ml of water with a valproate concentration of 7.5µg/ml. Subsequent photographs were taken around every 3-4 days. Treatment was continued until day 14 and the fish were followed with weekly photographs to see when/if remission occurred. Alongside this project, previous studies in which tamoxifen is used to induce *mMyc* leukemia at a much younger age were successfully duplicated<sup>ii</sup>. This will increase the number of available *D. rerio* with T cell lymphomas for further studies<sup>iii</sup>.

**Results:** Photographs of each fish during the treatment period from the various trials were given a rating of *complete response* (EGFP fluorescence disappears), *partial response*, or *no response*. The *mMyc* fish

responded better than the *hlk* fish to valproate. As of July 2010 around 70% of them *Myc* fish had a *complete response* (100% in some trials) and the rest displayed *partial responses*. Most of the *hlk* had a *partial response*.

**Conclusion:** *In vivo* valproate treatment effectively induces remission in T-LBL *D. rerio* lines, especially *mMyc*.

#### References:

<sup>1</sup> JK Frazer, ND Meeker, L Rudner, DF Bradley, ACH Smith, B Demarest, D Joshi, EE Locke, SA Hutchinson, S Tripp, SL Perkins and NS Trede. Heritable T-cell malignancy models established in a zebrafish phenotypic screen. *Leukemia* 2009;23:1825-1835.

<sup>1</sup> Lara Stevanato, Randolph L Corteling, Paul Stroemer, Andrew Hope, Julie Heward, Erik A Miljan and John D Sinden. C-MycER transgene silencing in a genetically modified human neural stem cell line implanted into MCAo rodent brain. *BMC Neuroscience* 2009;10:86.

<sup>1</sup> Francois Vaillant, Karen Blyth, Anne Terry, Margaret Bell, Ewan R Cameron, James Neil and Monica Stewart. A full-length Cbfa1 gene product perturbs T-cell development and promotes lymphomagenesis in synergy with MYC. *Oncogene* 1998;18:7124-7134.

## Basic Science & Clinical Research

**Darren Bryan, MS2**

**Preceptor:**

**Christopher L. Skelly MD FACS**

**Assistant Professor of Surgery and Vascular Research**

**The malignant course of carotid artery occlusion: risk factor and outcomes**

Darren Bryan BA, John Carson MD, Qi He MD, Khalil Qato BA, Christopher L. Skelly MD

Objective: The long term outcome of patients with carotid artery occlusion has demonstrated continued risk for neurologic events. The purpose of this study was to evaluate the long-term outcomes of these patients and to determine risk factors that were predictive of death, neurological event or contralateral carotid intervention.

Methods: Patients with 100% carotid occlusion as shown by duplex ultrasound were retrospectively identified and followed between January 2002 and June 2010 (follow-up range 1 to 93 months, mean follow-up 52 months) at a tertiary care hospital. All duplex exams were performed at an ICAVL approved vascular lab and were available for analysis. All patients had a minimum of three duplex exams available for review. Chi-square analysis was used to determine risk factors for death, neurologic event or contralateral intervention. Multivariate Cox proportional hazard analysis was conducted for those risk factors with P values (<0.1). Survival was estimated using the Kaplan-Meier method with  $p < 0.05$  considered significant.

Results: 80 patients with carotid occlusion were identified and available for analysis with a median follow up of 51 months (range 1-101 months). Co-morbidities were commensurate with a tertiary care referral center. On initial encounter, 30 patients (38%) were symptomatic with 23(29%) patients having symptoms referable to the occluded carotid. During the follow-up period, 7 patients (9%) had a neurologic event, of which 6(86%) were referable to the occluded carotid artery; 14 (18%) patients underwent a contralateral operation and 19(24 %) died. Significant Risk factors for contralateral operation, neurologic event in follow up, or Death are included in the table. Multivariate analysis revealed that amurosis fugax at initial presentation was a risk factor for contralateral operation ( $p=0.05$ ); although numerous variables of multi- vessel disease were significant with Chi-square analysis, there was no significant risk factor associated with neurologic event with multivariate analysis. Both neck radiation ( $p=0.05$ ) and stenosis or occlusion of the external carotid artery ipsilateral to the occlusion on follow up exam ( $p < 0.027$ ) were associated with an increased risk of death. Kaplan-Meier analysis showed that 7 year survival for patients with stenosis or occlusion of the ECA at follow up compared to those without was significantly worse ( $16.2\% \pm 10.3\%$  vs.  $79\% \pm 8.7\%$ ;  $p < 0.00001$ )

Conclusions: Patients presenting with carotid occlusion frequently present with symptoms referable to the occlusion. 86% of neurologic events originated from the occluded carotid artery, indicating that it is not a benign process. Multivariate analysis revealed no factor predictive of subsequent neurologic event, specifically, concurrent extracranial arterial disease. Given the significant risk of death in patients found to have ipsilateral ECA stenosis in follow up, it seems reasonable to continue surveillance of the occluded carotid.

<b>Risk Factor</b>	<b>Contralateral operation</b>	<b>Neurologic Event in follow up</b>	<b>Death</b>
<b>Prior Neck irradiation</b>	0.68	0.17	.054‡
<b>Symptoms present at initial presentation</b>	0.57	0.47	0.075
<b>Amurosis Fugax at initial presentation</b>	.078‡	0.76	0.44
<b>Contralateral ICA progression in follow up</b>	0.20	0.47	0.49
<b>Ipsilateral ECA at presentation*</b>	0.17	0.19	0.005
<b>Contralateral ECA at presentation</b>	0.005	0.56	0.014
<b>Ipsilateral Vert in follow up*</b>		0.019	0.29
<b>Ipsilateral ECA in follow up*</b>	0.033	0.073	<0.0001†
<b>Contralateral ECA in follow up</b>	0.62	0.46	0.061
<b>Any ECA/Vertebral stenosis or occlusion at presentation</b>	0.053	0.098	0.007
<b>ECA/Vertebral stenosis or occlusion progression in follow up</b>	0.29	0.427	0.31

Table 1. P values from Chi squared analysis of risk factors predictive of contralateral operation, neurologic event in follow up, and death. P values <0.01 were then put in a multivariate analysis: †p<0.05 in multivariate analysis. ‡p=0.05 in multivariate analysis.

<sup>i</sup>JK Frazer, ND Meeker, L Rudner, DF Bradley, ACH Smith, B Demarest, D Joshi, EE Locke, SA Hutchinson, S Tripp, SL Perkins and NS Trede. Heritable T-cell malignancy models established in a zebrafish phenotypic screen. *Leukemia* 2009;23:1825-1835.

<sup>ii</sup>Lara Stevanato, Randolph L Corteling, Paul Stroemer, Andrew Hope, Julie Heward, Erik A Miljan and John D Sinden. C-MycER transgene silencing in a genetically modified human neural stem cell line implanted into MCAo rodent brain. *BMC Neuroscience* 2009;10:86.

<sup>iii</sup>Francois Vaillant, Karen Blyth, Anne Terry, Margaret Bell, Ewan R Cameron, James Neil and Monica Stewart. A full-length Cbfa1 gene product perturbs T-cell development and promotes lymphomagenesis in synergy with MYC. *Oncogene* 1998;18:7124-7134.

# Basic Science & Clinical Research

Stephen Carr, MS2

**Preceptor:**

**Joseph P. Walton, Ph.D. Research Associate Professor**

**Departments of Otolaryngology and Neurobiology and Anatomy**

**University of Rochester Medical Center**

**Effects of Varying Stimulus Frequency and Rate on the ABR of the Developing Rat Introduction:**

The Auditory Brainstem Response (ABR) consists of a series of electrical potential peaks and troughs generated at various levels of the central auditory pathway<sup>(4,6,9)</sup>. While human full-term neonates can hear at birth, previous studies have shown that auditory function in the rat as measured by the ABR begins at postnatal day (PND) 12-14 and adult thresholds are reached by PND 22<sup>(1,3,9)</sup>. It has been demonstrated that latencies decrease and amplitudes increase as a function of maturation of the CNS<sup>(2,5)</sup>. Factors thought to explain these maturational changes are progressive myelination of nerve fiber tracts, fiber diameter growth, facilitation of synaptic transmission and improved synchronization<sup>(9)</sup>. In this study, the developmental time course of the Auditory Brainstem Response (ABR) was measured in the developing rat from PND 14 to PND 40 to characterize the effects of varying the rate and frequency of stimuli on the latency and amplitude of the ABR waveform. Peaks analyzed in this study were P1, corresponding to the cochlear nerve, and P4, corresponding to the inferior colliculus<sup>(9)</sup>.

**Methods:** Rat pups were analyzed to determine the ABR latency and amplitude at PND 14, 21 and 40. Prior to recording, rats were anesthetized with Avertin (200 mg/kg I.P.), and placed on a heating pad to maintain normothermia. The stimulus presentation hardware consisted of a RP2.1 Enhanced Real Time Processor (Tucker-Davis Technologies, (TDT)) functioning as a digital-to- analog converter connected to a Leader LAT-45 attenuator. The output from the attenuator connected to a Kenwood Stereo Powered Amplifier (BASIC MID), which drove a Leaf Tweeter (EAS-10TH400A, Matsushita Electronic Components Corp, Japan). Evoked potentials were recorded with needle electrodes connected to a HS4 BioAmp head-stage. Subcutaneous electrodes were inserted behind the ipsilateral ear (recording electrode), contralateral ear (indifferent) and at the vertex above the nose. The rat was placed so that the speaker was 22 cm from the left ear, in the same horizontal plane. The frequencies tested on each animal were 6, 12, 24, and 36 kHz. The rates tested were 19, 29, 39, 49, 59, 69, and 79 clicks/sec. Both frequency and rate tests were performed at 60, 70 and 80 dB intensities. Artifact rejection was enabled. The recorded waveforms were amplified (x10,000), filtered (3 – 100 kHz) and digitized. Latency and amplitude measurements were made after peak identification, and values were averaged for each age and compared using SPSS analytical software.

**Results:** Analysis of P4 for PND 14 rats was not performed due to the inconsistency of the waveform after P1. ANOVA testing of averaged waveform latency and amplitude values showed the following results (a p <0.05 was considered statistically significant):

- 1. Effects of stimulus rate on latency:** In P14 rats, a longer P1 latency was measured at 29 clicks/sec compared to rates of 69 and 79 clicks/sec at every intensity level; this effect disappeared by PND 21. Other latencies from slower rates were longer than those measured at higher rates for various intensities for the P14 age group. There was no effect of rate on P1 latency at any intensity level for PND 21 or 40. As expected, P1 latency measurements at PND 14 were longer than those at PND 21 and 40 for every rate and at every intensity. No significant differences in P4 latency due to age or rate were found between PND 21 and PND 40 measurements.
- 2. Effects of stimulus rate on amplitude:** The amplitude of P1 in PND 14 rats was significantly

smaller than that measured in PND 21 and 40 rats at every rate and intensity. P1 amplitudes for 19 and 29 clicks/sec were greater than the 79 clicks/sec amplitude at every intensity level for PND 40 and for 80 dB at PND 21. Other P1 amplitudes from slower rates were greater than those measured at higher rates for various intensities for the P40 age group. The P4 amplitude response to the 19 clicks/sec stimulus was greater than the corresponding response to the 69 and 79 clicks/sec stimuli at both PND 21 and 40. The effects of age were largely insignificant for P4 amplitude.

3. **Effects of stimulus frequency on latency:** P1 latency shortened as age increased, consistent with maturation of the CNS. Higher frequencies and greater intensities of the stimulus trended toward shorter P1 latency for each age except for the latency measurements for 24 and 36 kHz at 60 dB for PND 14 rats. All other comparisons held true to the trend but not all were statistically significant. Differences in intensity level showed little effect in P4 latency for both PND 21 and PND 40.
4. **Effects of stimulus frequency on amplitude:** P1 amplitudes increased with intensity level for all ages and frequencies. The effects of age were largely insignificant. P4 amplitudes showed little change from PND 21 to PND 40, although the increase in amplitude was sharper for 6 and 12 kHz than for 24 and 36 kHz as the intensity level increased.

Unless stated otherwise, latencies decreased and amplitudes increased as a function of maturation, consistent with previously reported data.

**Discussion:** This study provides further support for the validity of the rat as a model for human perinatal auditory development. Though the ABR has been shown to be a powerful instrument for the study of the maturation of the human auditory system<sup>(8)</sup>, the variability and difficulty in detectability during the preterm period limits its use<sup>(7)</sup>. Whereas most full-term human neonates show an ABR response, adult values may not be obtained until 1-2 years after birth or longer<sup>(9)</sup>. Differing responses to rate and frequency in the juvenile rat likely parallel the human pre- and post-natal course of development. This study also confirms previously published data<sup>(5)</sup> concerning the effect of rate and frequency on the rat ABR. It provides normative data and a baseline for similar frequency and rate interaction experiments to study environmental insults or nutritional deficiencies in the developing rat.

## References

1. Blatchley, B. J., W. A. Cooper, et al. (1987). "Development of auditory brainstem response to tone pip stimuli in the rat." Brain Research 429(1): 75-84.
2. Church, M. W., H. L. Williams, et al. (1984). "Postnatal development of the brainstem auditory evoked potential and far-field cochlear microphonic in non-sedated rat pups." Brain Research 316(1): 23-31.
3. Geal-Dor, M., S. Freeman, et al. (1993). "Development of hearing in neonatal rats: air and bone conducted ABR thresholds." Hearing Research 69(1-2): 236-242.
4. Jewett, D. L. and M. N. Romano (1972). "Neonatal development of auditory system potentials averaged from the scalp of rat and cat." Brain Research 36(1): 101- 115.
5. Newton, E. H., W. A. Cooper, et al. (1992). "Rate and frequency interactions in the auditory brain-stem response of the adult-rat." Hearing Research 60(1): 73-79.
6. Rotteveel, J. J., E. J. Colon, et al. (1987). "The maturation of the central auditory conduction in preterm infants until three months post term. I. Composite group averages of brainstem (ABR) and middle latency (MLR) auditory evoked responses." Hearing Research 26(1): 11-20.
7. Rotteveel, J. J., R. de Graaf, et al. (1987). "The maturation of the central auditory conduction in preterm infants until three months post term. II. The auditory brainstem responses (ABRs)." Hearing Research 26(1): 21-35.
8. Salamy, A. (1984). "Maturation of the auditory brainstem response from birth through early childhood." Journal of Clinical Neurophysiology 1(3): 293-329.
9. Shaw, N. A. (1988). "The auditory evoked potential in the rat--a review." Progress in Neurobiology 31(1): 19-45.

## Basic Science & Clinical Research

Michael Cluff, MS2

**Preceptor:**

**Robert Garfield, Ph. D Senior Staff**

**Scientist**

**Director of Division of Research**

**Department of Obstetrics and Gynecology**

**St. Joseph's Hospital and Medical Center, Phoenix, AZ**

### **Noninvasive Uterine Electromyography can Predict Preterm Delivery**

Introduction: Second only to childbirth, “threatened preterm labor” is the most common diagnosis that leads to hospitalization during pregnancy.<sup>1</sup> Of those admitted to the hospital for threatened preterm labor, up to 50% are not in true labor and will deliver at term.<sup>2</sup> Of those who are diagnosed as not in preterm labor, 20% will deliver prematurely.<sup>3</sup> This leads to excessive hospitalizations, and missed opportunities to improve neonatal outcome. It is known that myometrial activation is required for effective contractions and true labor. This is characterized by uterine molecular changes that lead to an increase in coupling and excitability of cells.<sup>4,5</sup> These cellular changes lead to a change in the overall electrical activity of the uterus.<sup>6</sup>

Background: Previous studies have shown that the myometrial activation, and the subsequent myometrial electrical activity changes can be monitored by uterine electromyography (EMG).<sup>6</sup> It has also been observed that increases in peak amplitude and frequency, along with wave propagation velocity changes coincide with true labor.<sup>7,8</sup>

Objective: To determine if there is directionality associated with the increased electrical activity of the uterus during true labor, compared with false labor.

Methods: Women presenting with regular contractions with intact membranes at term (>37 weeks of gestation) were included in the term group. Delivery within 24 hours of EMG measurement was defined as being in labor (term labor groups) and those delivering after 24 hours were defined as not being in labor (term non-labor group).

Women with a diagnosis of preterm labor (at least 6 contractions in a 60 minute period assessed by TOCO and/or maternal perception and a cervical dilation of at least 2 cm or effacement of at least 80% assessed by digital cervical examination) at less than 34 weeks of gestation were included in the preterm labor group. Delivery within 7 days of EMG measurement was classified as preterm labor, while those delivering after 7 days were placed in the non-preterm labor group.

For the uterine EMG measurements, a standard 4-electrode arrangement, symmetric around the navel, was used. Uterine EMG was measured for 30 minutes from each patient. The patients were asked to remain still while supine without disturbing any of the probes and wires for the recordings.

Once the uterine EMG data was collected, it was analyzed, comparing voltage peaks between two leads. The average time difference, velocity and directionality of corresponding voltage peaks were determined for each of the four groups. Results:

pending

Conclusion: Although it has previously been shown that uterine EMG propagation velocity and power spectrum peak frequency can more accurately identify true preterm labor than current clinical methods, the determination of more parameters that differentiate between true and false labor will allow better specificity and sensitivity in clinical testing.

## References:

1. Bennett TA, Kotalchuck M, Cox CE, Tucker MJ, Nadeau DA: Pregnancy-associated hospitalizations in the United States in 1991 and 1992: a comprehensive view of maternal morbidity. *Am J Obstet Gynecol* 178. 346-354. 1998
2. McPheeters ML, Miller WC, Hartmann KE, Savitz DA, Kaufman JS, Garrett JM, Thorp JM: The epidemiology of threatened preterm labor: a prospective cohort study. *Am J Obstet Gynecol* 192. 1325-1329. 2005
3. Iams JD, Romero R. Preterm Birth. In: Gabbe SG, Niebyl JR, Simpson JL, editors. *Obstetrics: Normal and Problem Pregnancies*. 5<sup>th</sup> ed. Philadelphia (PA): Churchill Livingstone Elsevier; 2007. P. 668-712.
4. Balducci J, Risek B, Gilula NB, Hand A, Egan JF, Vintzileos AM. Gap junction formation in human myometrium: a key to preterm labor. *Am J Obstet Gynecol* 1993; 168: 1609-1615.
5. Garfield RE, Blennerhassett MG, Miller SM. Control of myometrial contractility: role and regulation of gap junctions. *Osf Rev Reprod Biol* 1988;10:436-490
6. Buhimschi C, Garfield RE. Uterine contractility as assessed by abdominal surface recording of electromyographic activity in rats during pregnancy. *Am J Obstet Gynecol* 1996; 174: 744-754.
7. Maner WL, Garfield RE, Maul H, Olson G, Saade G. Predicting term and preterm delivery with transabdominal uterine electromyography. *Obstet Gynecol* 2003; 101:1254- 1260
8. Lucovnik M, Maner WL, Chambliss LR, Blumrick R, Balducci J, Novac-Antolic Z, Garfield RE. (2010). Noninvasive uterine electromyography can predict preterm labor. Manuscript submitted for publication.

# Basic Science & Clinical Research

Jason Costa, MS2

**Preceptor:**

Arthur J. Moss, M.D. Professor of Medicine  
Department of Cardiology  
University of Rochester Medical Center

## Gender-Specific Risk Factors for Life-Threatening Events in Type-I Long QT Syndrome

**Introduction:** Long QT Syndrome Type 1 (LQT1) is the most commonly occurring of the congenital Long QT syndromes.<sup>1</sup> It is caused by deficiency of the slow-acting potassium channel, IKs, due to mutations in the *KCNQ1* gene which encodes the channel's alpha subunit. The resulting prolongation of ventricular repolarization often results in cardiac events, such as syncope or cardiac arrest, and is exacerbated by adrenergic stimulation. Accordingly, treatment of LQT1 patients often involves beta-blocker therapy, and for intractable cases, left cardiac sympathetic denervation.<sup>2</sup>

**Background:** The phenotypic expression of LQT1 has been shown to be affected by gender and age. Previous studies have focused on gender-related risk over all LQTS 1 genotypes, and have demonstrated that, during childhood, males have a higher incidence of cardiac events, while females display a higher incidence thereafter.<sup>3</sup>

To date, there have been no known studies examining gender-related risk according to LQTS 1 mutation location. Furthermore, previous gender studies have focused on the endpoint of cardiac events that include syncope as well as the more severe events of aborted cardiac arrest (ACA) and sudden cardiac death (SCD). In such studies, syncope served as the largest component of the combined end point due to its higher incidence relative to ACA or SCD in LQTS 1.

**Objective:** In this study, we chose to examine the gender-specific risk for the more clinically important life-threatening events, comprising ACA or SCD, within patient subsets based on LQTS1 mutation location. These subsets included the cytoplasmic loop (C-loop) region, the transmembrane region not including the C-loops, and the non-transmembrane region. We were interested in examining the C-loop region, as recent work in our group has shown that mutations in this region are correlated with significantly increased risk for life-threatening cardiac events.<sup>4</sup>

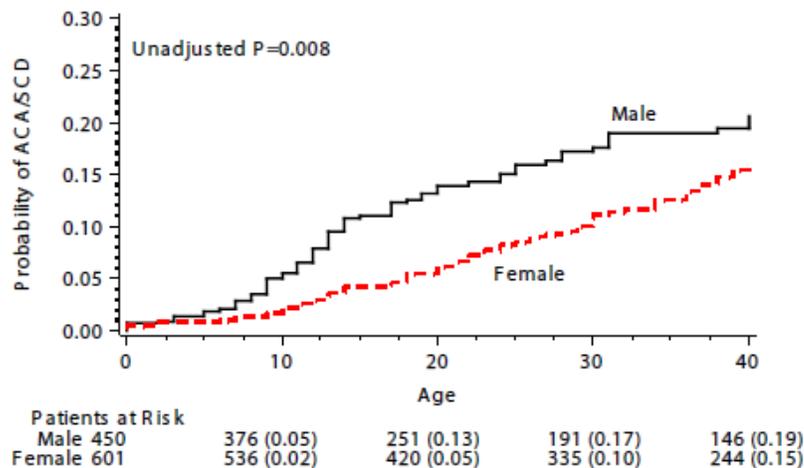
**Methods:** The study population comprised 1086 genetically-confirmed LQTS1 patients from the International LQTS registry. Follow-up was censored at age 41 years to minimize the influence of coronary disease on incidence of cardiac events. We examined the risk of ACA or SCD by gender and by mutation-location in the total population and in males and females separately. Mutation-location within the *KCNQ1*-encoded channel was categorized as: the C-Loop region (C-Loop), the transmembrane region not including the C-Loop region (Non-C-Loop TM), and the non-transmembrane region (Non-TM). The Kaplan-Meier life-table method was used to assess the time to first occurrence of the end point of ACA or SCD and the cumulative event rates by gender and mutation-location. The results were compared using the log-rank statistic. Multivariate Cox proportional hazards regression modeling was used to assess the independent contribution of gender and mutation-location, after further adjustment for QTc duration and time-dependent beta-blocker therapy, to development of the end points during follow-up.

## Results:

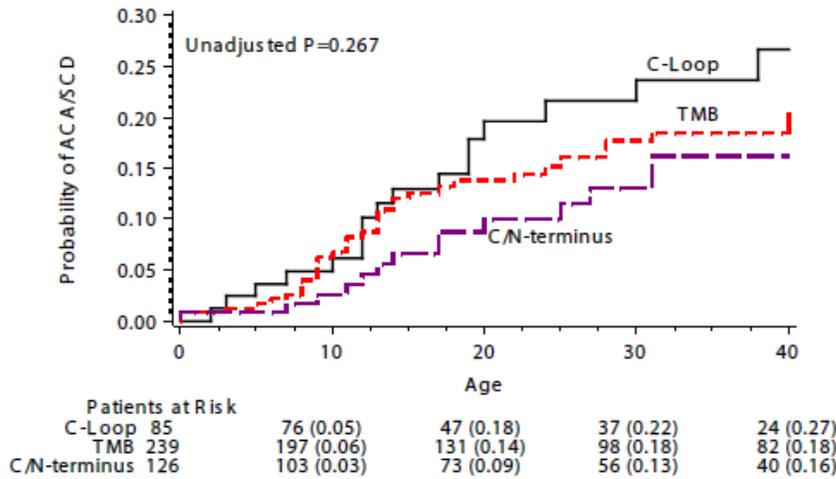
- 1. General Risk Factors for Life-Threatening Cardiac Events:** Multivariate analysis in the total population showed that LQT1 males had a significantly higher risk for ACA or SCD as compared with females (HR= 1.44 [p=0.03]). Accordingly, the cumulative probability of ACA or SCD at age 40 years was significantly higher in males than in females (19% vs. 15%, respectively; p=0.008 [Figure 1]). In addition, LQT1 patients with C-loop mutations were shown to have significantly higher risk of life-threatening events as compared with patients with both non-C-loop TM mutations (HR = 1.92 [P=0.01]) and those with non-TM mutations (HR= 1.87 [P=0.01]).
- 2. Gender-specific factors for life-threatening cardiac events:** Analysis of gender-specific risk factors showed that among LQT1 males the risk of life-threatening events was high regardless of mutation-location (Figure 2), whereas LQT1 females with C-loop mutations had a significantly higher rate of life-threatening events as compared with LQT1 females with other mutations (Figure 3). Consistent with those findings, multivariate analysis showed that among males, the presence of C-loop mutations was not associated with a statistically significant higher risk for ACA or SCD as compared with the presence of both non-C-loop TM mutations (HR = 1.34 [P=0.38]) and non-TM mutations (HR= 1.31 [P=0.59]). In contrast, among females the presence of C-loop mutations was associated with a pronounced increase in the risk of ACA or SCD as compared with both non-C-loop TM mutations (HR = 2.53 [P=0.01]) and non-TM mutations (HR= 2.64 [P=0.01]).

**Conclusions:** In this study, we have shown that among LQT1 patients, males have a significantly higher risk for life-threatening cardiac events from birth through age 40 years as compared with females. However, our findings suggest that the gender-related risk in LQT1 is affected by mutation-location. Thus, among males the risk for ACA or SCD was high regardless of the location of the mutation in the *KCNQ1* channel, whereas among females the presence of C-loop mutations was associated with a pronounced risk increase. The present results suggest that sex hormones have a location-specific effect on the expression of the *KCNQ1* channel. These findings can be used for improved gender-specific risk stratification and management of patients with this inherited cardiac arrhythmic disorder.

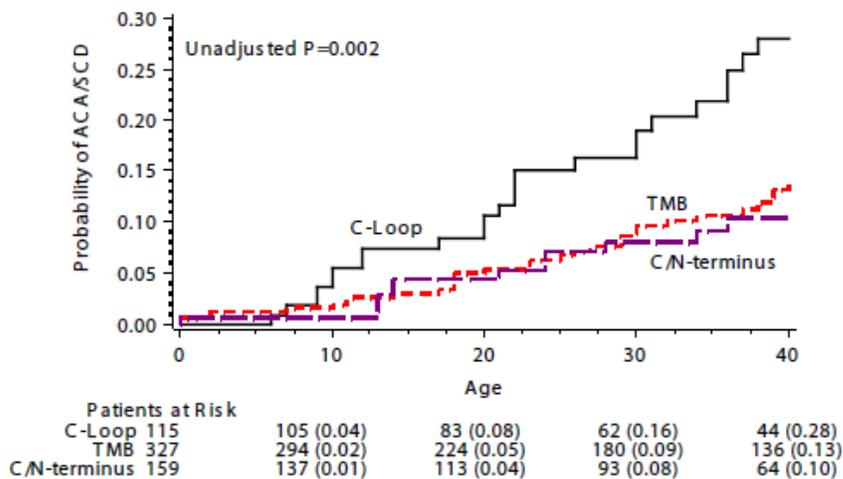
**Figure 1:** Cumulative probability of ACA or SCD in LQT1 patients by gender



**Figure 2:** Cumulative probability of ACA or SCD in LQT1 males by mutation location



**Figure 3:** Cumulative probability of ACA or SCD in LQT1 females by mutation location



**References:**

1. Goldenberg I, Moss AJ. Long QT syndrome. *J Am Coll Cardiol* 2008; 51:2291-300.
2. Goldenberg I, Zareba W, Moss AJ. Long QT Syndrome. *Curr Probl Cardiol* 2008; 33(11): 629-94.
3. Zareba W, et al. Modulating Effects of Age and Gender on the Clinical Effects of Long QT Syndrome by Gender. *J Am Coll Cardiol* 2003; 42(1): 103-109
4. Basheshet A, Goldenberg I, Moss AJ, et al. Mutations in Cytoplasmic Loops are Associated with Increased Risk for Cardiac Events in Type-1 Long QT Syndrome [Abstract]. *American Heart Association Scientific Sessions*, Nov. 2010, Chicago, IL

# Basic Science & Clinical Research

Megan de Grouchy, MS2

**Preceptor:**

**William Bowers, PhD Associate Professor**  
**Center for Neural Development and Disease**  
**University of Rochester Medical Center**

**Effect of VIP on Disease Pathology in an Animal Model of Alzheimer's Disease Introduction:**

Alzheimer's Disease (AD) is a neurodegenerative disorder associated with progressive functional decline and dementia. Inflammation has been shown to have a role in AD pathophysiology, likely mediated by cells of the central nervous system (CNS) that produce pro-inflammatory mediators. Vasoactive intestinal peptide (VIP) elicits an anti-inflammatory response in the CNS, and has been demonstrated to have a neuroprotective effect.

**Objective:** To determine if VIP elicits a protective effect in an animal model of Alzheimer's disease, as measured by AD pathology.

**Background:** AD progression is marked by extracellular amyloid- $\beta$  ( $A\beta$ ) peptide accumulation, tau pathology, deficits in synaptic function, and neuronal loss, initiated primarily in the hippocampus, amygdala and the cerebral cortex. Inflammation has been demonstrated to contribute to the pathophysiology of AD, though it is not clear if it is etiological or a secondary effect. The cells of the CNS responsible for producing pro-inflammatory mediators include astrocytes, microglia, and neurons. In the AD brain, focal and diffuse astrocytosis is highly evident in areas of AD pathology, including at sites of ghost tangles, amyloid-bearing plaques, and angiopathic capillaries. Acute and chronic models of brain inflammation have been developed to probe how this process affects AD pathology, and synaptic integrity/neuronal activity. Cytokines secreted by astrocytes, microglia, and neurons in response to an insult (e.g., LPS infusion, transgenic  $A\beta_{1-42}$  overexpression) have been implicated as the likely mediators of brain inflammation. Vasoactive intestinal peptide (VIP), originally discovered in the porcine intestinal tract, is present in the brain and CSF.<sup>1</sup> VIP has an important role in embryonic CNS development and has been demonstrated to have a role in learning.<sup>2,3,4</sup> VIP has been shown to decrease inflammation, both by inducing the release of anti-inflammatory mediators from astrocytes and by reducing microglial activation.<sup>5,6,7</sup> Decreased levels of VIP have been shown in the aging brain, and AD patients were found to have significantly decreased levels of VIP compared with controls, though it is not clear if this is etiological or a secondary effect of the disease. An animal model of AD, treated with VIP delivered intranasally, demonstrated increased memory and learning compared with untreated controls.<sup>8</sup>

**Methods:** A triple transgenic mouse model of AD (3xTg-AD) that harbors three mutant genes (hPS<sup>1M146V</sup>, hAPP<sup>Swe</sup>, hTau<sup>P301L</sup>) was created on a mixed 129/C57BL/6 background. The 3xTg-AD mice develop both plaques and tangles in a progressive and age-dependent fashion. Two recombinant adeno-associated virus (rAAV) vectors were constructed: one expressing human VIP fused to the pro-sequence of the neurotrophin nerve growth factor (NGF) to optimize the secretion profile of VIP (rAAV2-NGF-VIP) and a second expressing the reporter gene product enhanced green fluorescent protein (rAAV2-eGFP). The individual transgenes were placed under the transcriptional control of the human cytomegalovirus (CMV) promoter. Both rAAV2-NGF-VIP and rAAV2-eGFP vectors were subsequently packaged into serotype-2 virions using a baculovirus-based rAAV vector production method. The rAAV2-NGF-VIP and rAAV2-eGFP vectors were stereotactically delivered to the left and right CA1 layer, respectively, of the 3xTg-AD at 6 months of age (N=9). Mice were sacrificed 6 months post-injection and brains sectioned on a sliding

microtome. Immunohistochemistry was performed on the sections using: microglia/macrophage specific protein (anti-Iba-1); astrocyte-specific protein (anti-glia fibrillary acidic protein); AT180 specific human tau phosphorylated at the Thr231 residue; 6E10 specific human amyloid beta peptide, epitope in amino acids 3-8. Staining intensities of the CA1 region of the hippocampus were quantified. Fluorescent immunohistochemical staining was performed to assess presence of GFP and VIP, using anti-GFP and anti-VIP antibodies. Images were visualized using fluorescent microscopy. A competitive ELISA was performed to assess transduction of the vector.

**Results:** No differences were found between sides treated with eGFP and NGF-VIP using microglia and astrocytes as markers of inflammation, and A $\beta$  plaques as a marker of AD pathology. Tau pathology was not quantified, due to poor staining. Immunofluorescent staining of both GFP and NGF-VIP was poor, suggesting that there may not have been adequate expression of NGF-VIP to impart an effect. NGF-VIP production from transduced cells was confirmed by ELISA. Injection site damage leading to poor vector uptake, or the use of a stereotactic injection method that promotes a more focal rather than diffuse distribution, could account for the results.

**Conclusions:** VIP remains an important anti-inflammatory mediator in a variety of inflammatory conditions. Future studies will utilize convection-enhanced delivery (CED) methodology to enhance vector distribution and minimize tissue trauma, hopefully attenuating the limitations of the current study.

#### References:

1. Said S, Rosenberg R. Vasoactive intestinal polypeptide: abundant immunoreactivity in neural cell lines and normal nervous tissue. *Science* 1976, 192: 907-8.
2. Hill JM, Mehnert J, McCune SK, Brenneman DE. Vasoactive intestinal peptide regulation of nerve growth factor in the embryonic mouse, *Peptides* 2002, 23: 1803- 8.
3. Moody TW, Hill JM, Jensen RT. VIP as a trophic factor in the CNS and cancer cells, *Peptides* 2003, 163-77.
4. Yang K, Lei G, Jackson MF, MacDonald JF. The involvement of PACAP/VIP system in the synaptic transmission in the hippocampus. *J Mol Neurosci* 2010, in print.
5. Brenneman DE, Hauser J, Spong CY, Phillips TM, Pert CB, Ruff M. VIP and D- ala-peptide T-amide release chemokines which prevent HIV-1 GP120-induced neuronal death. *Brain Res* 1999, 838: 27-36.
6. Steingart RA, Solomon B, Brenneman DE, Fridkin M, Gozes I. VIP and peptides related to activity-dependent neurotrophic factor protect PC12 cells against oxidative stress. *J Mol Neurosci* 2001, 15: 137-45.
7. Tunçel N, Şener E, Cerit C, Karasu U, Gürer F, Şahintürk V, Bayçu C, Ak D, Filiz Z. Brain mast cells and therapeutic potential of vasoactive intestinal peptide in a Parkinson's disease model in rat: Brain microdialysis, behavior, and microscopy. *Peptides* 2005, 26:827-37.
8. Gozes I, Bardea A, Reshef A, Zamostiano R, Zhukovsky S, Rubinstein S, Fridkin M, Brenneman DE. Neuroprotective strategy for Alzheimer disease: Intranasal administration of a fatty neuropeptide. **PNAS** 1996, **93**:427-32.

# Basic Science & Clinical Research

Daniel Feiler, MS2

**Preceptor: Kane Pryor, M.D. Assistant Professor**  
Department of Anesthesiology  
Weill Cornell Medical Center

## **An Investigation of the Relationship between Theta Phase at the Time of Encoding and the Time Domain Characteristics of Amnesia for Multiple Intravenous Anesthetic Drugs In Humans**

**Introduction:** Several commonly used intravenous anesthetics possess the ability to cause selective amnesia, even when administered at barely perceptible doses. The exact mechanism(s) by which this occurs remain poorly understood. One dominant theory is that the drugs interfere with processes in the hippocampus, a region in the medial temporal lobe that is integral to the consolidation (early stabilization) of conscious memories<sup>1</sup>. A possible mechanism is that the drugs specifically interfere with the synchrony of theta (5-8 Hz) oscillations, a phenomenon that has been linked to hippocampo-cortical feedback loops<sup>2-3</sup>, successful memory function<sup>4-5</sup>, and memory decay<sup>6</sup>, and which can be measured by processing of the electroencephalogram.

**Objective:** To characterize the nature of anesthetic amnesia by investigating the relationship between the time domain characteristics of amnesia and theta activity and phase at the time of encoding.

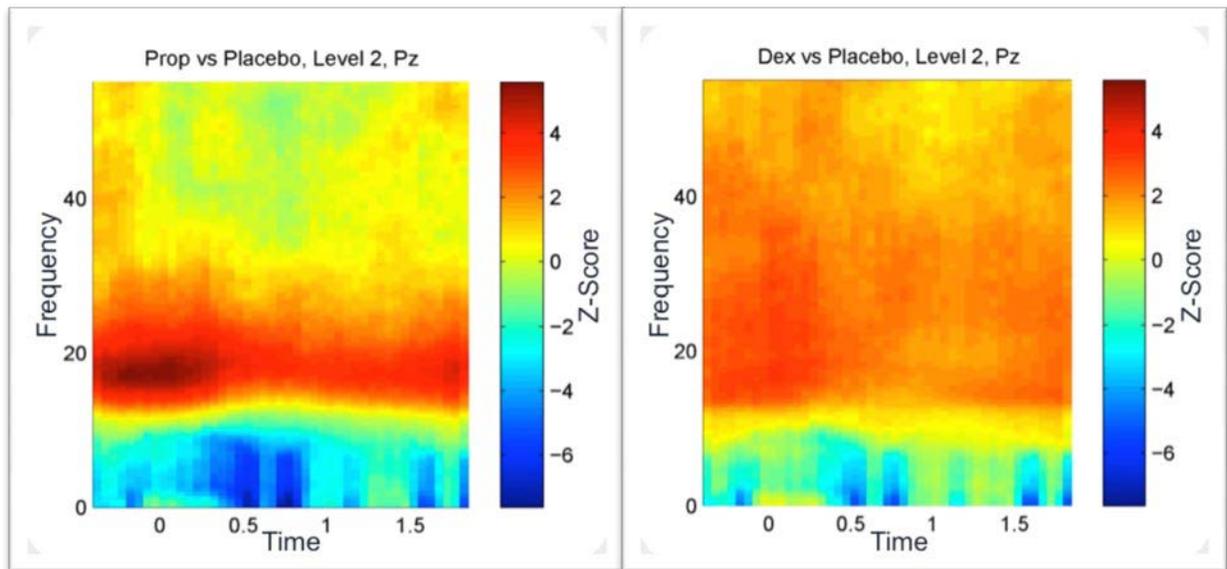
**Background:** One approach to evaluate memory function in humans is to mathematically model what happens to memories over time. In normal memory function, a trace is established rapidly and then progressively decays. Previous studies show that this temporal course can be described by a negative power function<sup>7-8</sup>, approximated under typical assumptions by the simple equation<sup>9</sup>  $m_t = \lambda t^{-\psi}$  where  $m$  is the memory strength at time  $t$ ,  $\lambda$  describes the strength of the initial memory trace, and  $\psi$  describes the subsequent rate of decay of that trace. Any intervention that alters memory function, such as an amnesic anesthetic drug, will modulate these parameters.

The objective of this study is to determine whether components of the mathematical model can be linked to dynamic changes in theta activity and phase. Previously, Pryor et al<sup>9</sup> demonstrated that the degree of memory consolidation failure caused by anesthetic drugs (as measured by the parameter  $\psi$ ) is closely associated with loss of the parietal P2-N2 complex, which is a surrogate measure of theta phase<sup>10</sup>. The object of the current study is to conduct a far more sophisticated analysis of the electroencephalographic data to directly examine the association between changes in theta activity and phase across all brain regions and drug-induced consolidation failure.

**Methods:** Sixty-one healthy volunteers were randomized to receive propofol ( $n = 12$ ), thiopental ( $n = 13$ ), midazolam ( $n = 12$ ), dexmedetomidine ( $n = 12$ ), or placebo ( $n = 12$ ). At two separate drug concentrations, subjects encoded pictures into memory using a 375-item continuous recognition task. Recognition for these items was later tested with drug absent, covering a broad time series. Memory function was then modeled over the time domain using a two-parameter, first-order negative power function (for full methodology, see Pryor et al<sup>15</sup>). Theta activity at the time of encoding was extracted from the electroencephalogram at 20 nodes, using a standard 10-20 montage sampled at 1000 Hz. Using custom-programmed MATLAB matrices, the raw electroencephalogram for the first 2400 ms after exposure to the picture was transformed into narrow-bandwidth spectral measures of power (dB and Z-values relative to 600 ms of baseline electroencephalogram activity prior to image presentation).

**Results and Conclusions:** The project has not been completed yet, and final results and conclusions are therefore pending. However, sufficient processing has been performed to preliminarily assess the quality of data and validity of the hypothesis. Figure 1 shows the power spectra (in Z-Scores) over the precuneus region for subjects receiving propofol 0.90 mcg/mL (panel A) and subjects receiving dexmedetomidine 0.40ng/mL (panel B), and clearly demonstrated a far greater loss of theta power with propofol that is consistent with the mathematical measures of consolidation failure.

**Figure 1.** (Panel A) (Panel B)



## References

1. Squire LR. Memory systems of the brain: a brief history and current perspective. *Neurobiol Learn Mem*, 2004; 82(3): 171-7.
2. Siapas AG, Lubenov EV, Wilson MA: Prefrontal phase locking to hippocampal theta oscillations. *Neuron* 2005; 46: 141-51
3. Young CK, McNaughton N: Coupling of theta oscillations between anterior and posterior midline cortex and with the hippocampus in freely behaving rats. *Cereb Cortex* 2009; 19:24-40
4. Klimesch W, Doppelmayr M, Russeger H, Pachinger T: Theta band power in the human scalp EEG and the encoding of new information. *Neuroreport* 1996; 7:1235-40
5. Klimesch W, Doppelmayr M, Schimke H, Ripper B: Theta synchronization and alpha desynchronization in a memory task. *Psychophysiology* 1997; 34:169-76
6. Klimesch W, Hanslmayr S, Sauseng P, Gruber W, Brozinsky CJ, Kroll NE, Yonelinas AP, Doppelmayr M: Oscillatory EEG correlates of episodic trace decay. *Cereb Cortex* 2006; 16:280-90
7. Wixted JT, Carpenter SK: The Wickelgren power law and the Ebbinghaus savings function. *Psychol Sci* 2007; 18: 133-4
8. Wickelgren WA: Single-trace fragility theory of memory dynamics. *Mem Cognit* 1974; 2:775-80
9. Pryor KO, Reinsel RA, Mehta M, Li Y, Wixted JT, Veselis RA: Visual P2-N2 complex and arousal at the time of encoding predict the time domain characteristics of amnesia for multiple intravenous anesthetic drugs in humans. *Anesthesiology*. 2010; 113(2):313-26.
10. Freunberger R, Klimesch W, Doppelmayr M, Holler Y: Visual P2 component is related to theta phase-locking. *Neurosci Lett* 2007; 426:181-6

## Basic Science & Clinical Research

Jenie George, MS2  
Gregory Ouellet  
Scott McNitt

**Preceptor:**

Arthur J Moss, M.D. Ilan Goldenberg, M.D  
University of Rochester Medical Center Department of Cardiology

### **Response to Cardiac Resynchronization Therapy among Diabetic Patients with Ischemic and Non-Ischemic Cardiomyopathy**

**Objective:** The present study was designed to assess differences in the clinical and echocardiographic response to cardiac resynchronization therapy-defibrillator (CRT-D) between diabetic patients with ischemic and nonischemic-cardiomyopathy (ICM and NICM, respectively).

**Background:** CRT-D therapy has been shown to reduce the risk of heart failure or death in patients with both ICM and NICM. However, currently there is limited information regarding differences in echocardiographic and clinical response to cardiac resynchronization therapy among patients with diabetes mellitus who have cardiomyopathy of ischemic or nonischemic etiology.

There is limited information regarding the clinical course of patients with diabetic cardiomyopathy of ischemic compared to non-ischemic etiology; and differences in echocardiographic and clinical response to cardiac resynchronization therapy in this population.

**Methods:** The study population comprised patients with diabetes mellitus (n=552) with ICM (n=347) and NICM (n=205) who were enrolled in the Multicenter Automatic Defibrillator Implantation-Cardiac Resynchronization Therapy ([MADIT-CRT) Multivariate analysis was used to evaluate the clinical response to CRT-D (defined as CRT-D vs. ICD-only reduction in the risk of heart failure [HF] or death) and the echocardiographic response to CRT-D (defined as percent reduction in left ventricular end diastolic and systolic volume volumes [LVEDV and LVESV, respectively] at 12 month of follow-up compared with baseline values) within the 2 subgroups of patients with diabetes mellitus.

**Results:** Multivariate Cox proportional hazards regression analysis showed that CRT-D was associated with a significant reduction in the risk of HF or death among diabetic patients with both ICD and NICM. The clinical response to CRT was more pronounced among patients with NICM (HR=0.21 [p=0.002] than among those with ICM (HR=0.50 [p=0.005]). Consistently, Kaplan-Meier analysis showed that the reduction in the rate of

HF or death was more pronounced among patients with diabetic NICM (Figure 1) as compared with those with diabetic ICM (Figure 2). Treatment with CRT-D was also associated with significantly greater reductions in both LVEDV and LVESV at 12 months of follow-up among diabetic patients with NICM as compared with those with ICM ( $p < 0.001$  for both comparisons – Figure 3). Interaction-term analysis showed that treatment with CRT-D was conferred a significant reduction in the risk of HF or death in both NICM and ICM patients who had a body mass index [BMI]  $\leq 30 \text{ kg/m}^2$  (HR = 0.19 [ $p = 0.01$ ] and 0.35 [ $p = 0.005$ ], respectively), whereas the clinical benefit of treatment with CRT-D within the 2 subgroups was attenuated among obese patients (BMI  $> 30 \text{ kg/m}^2$ )

**Conclusions:** Cardiac resynchronization therapy is associated with a significant reduction in the risk of HF or death among diabetic patients with both ICM and NICM. The response to treatment with CRT-D is more pronounced among diabetic patients with a non-ischemic etiology of cardiomyopathy and among those who have a lower BMI.

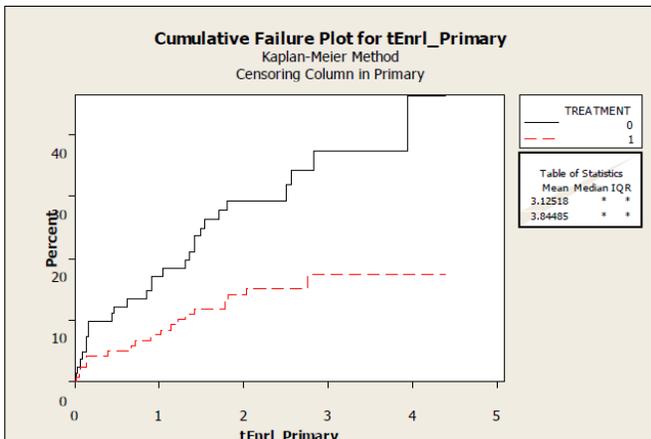


Figure 1: Time to first event (heart failure or death) in diabetics with non-ischemic cardiomyopathy stratified by treatment (ICD or CRT)

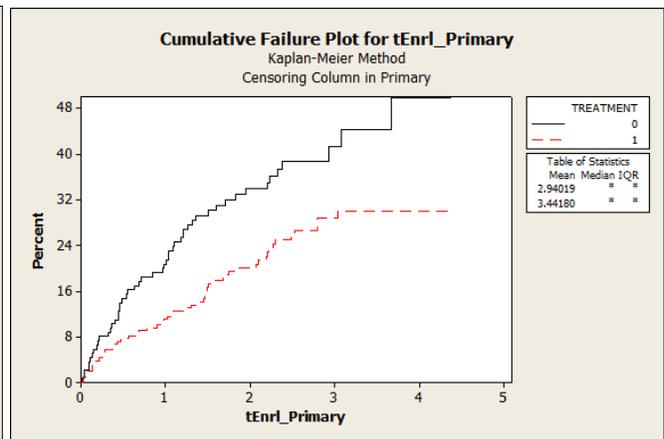


Figure 2: Time to first event (heart failure or death) in diabetics with ischemic cardiomyopathy stratified by treatment (ICD or CR)

**Percent changes in echocardiographic parameters at 12 months of treatment with CRT**

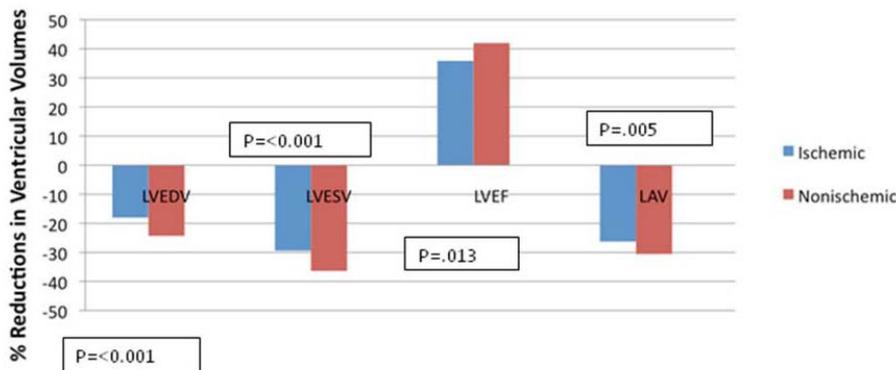


Figure 3. The Effect of CRT-D on echocardiographic parameters in diabetic patients with ischemic or non-ischemic cardiomyopathy

## References

1. Singh S, Dhingra S, Ramdath DD, Vasdev S, Gill V, Singal PK. Risk Factors Preceding Type 2 Diabetes and Cardiomyopathy. *J Cardiovasc Transl Res*. Jul 1 2010.
2. Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, Grishman A. New type of cardiomyopathy associated with diabetic glomerulosclerosis. *Am J Cardiol*. Nov 8 1972;30(6):595-602.
3. Das SR, Drazner MH, Yancy CW, Stevenson LW, Gersh BJ, Dries DL. Effects of diabetes mellitus and ischemic heart disease on the progression from asymptomatic left ventricular dysfunction to symptomatic heart failure: a retrospective analysis from the Studies of Left Ventricular Dysfunction (SOLVD) Prevention trial. *Am Heart J*. Nov 2004;148(5):883-888.
4. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med*. Oct 1 2009;361(14):1329-1338.
5. Moss AJ, Brown MW, Cannom DS, et al. Multicenter automatic defibrillator implantation trial-cardiac resynchronization therapy (MADIT-CRT): design and clinical protocol. *Ann Noninvasive Electrocardiol*. Oct 2005;10(4 Suppl):34-43.
6. Dries DL, Sweitzer NK, Drazner MH, Stevenson LW, Gersh BJ. Prognostic impact of diabetes mellitus in patients with heart failure according to the etiology of left ventricular systolic dysfunction. *J Am Coll Cardiol*. Aug 2001;38(2):421- 428.
7. Sajad A. HAYAT BP, Rajdeep S. KHATTAR and Rayaz A. MALIK. Diabetic cardiomyopathy: mechanisms, diagnosis and treatment. *Clinical Science*. 2004:539-557.
8. Boudina S, Abel ED. Diabetic cardiomyopathy revisited. *Circulation*. Jun 26 2007;115(25):3213-3223.
9. Boudina S, Abel ED. Diabetic cardiomyopathy, causes and effects. *Rev Endocr Metab Disord*. Mar 2010;11(1):31-39.

# Basic Science & Clinical Research

Janna Gewirtz, MS2

**Preceptor:**

**Rear Admiral Susan Blumenthal, M.D., M.P.A.**

**Director, Health and Medicine Program, Center for the Study of the Presidency and Congress**

**Former Assistant Surgeon General of the United States**

**Former Deputy Assistant Secretary for Women's Health, U.S. Department of Health and Human Services**

**Rear Admiral, USPHS (ret.)**

## **The Impact of Recent Health Reform Legislation on the Prevention of Illness in the United States**

**Introduction:** Over the past half century, preventable chronic illnesses have taken an enormous toll on our Nation's health. In 1960, an estimated 46% of American adults (ages 20 to 74) were either overweight or obese; by 2008, those ranks had grown to 74%, a sobering number that continues to swell. In 2007, obesity was associated with 162,000 excess deaths each year, over two thirds of which are attributable to cardiovascular disease. Tobacco is another major contributor to the chronic disease epidemic. In spite of the science linking smoking to premature death and disability, 1 in 5 women and 1 in 4 men still smoke, an addiction that increases the risk of lung cancer by thirteen times for women and twenty-three times for men.

These unhealthy habits are also taking a financial toll. The 133 million Americans that currently have a chronic disease are the most frequent users of the health care system in the United States, at a cost of over \$1.5 trillion annually. More than 96% of Medicare and 83% of Medicaid funds are spent on the treatment of chronic disease. American businesses in particular bear the burden of chronic illnesses, with an estimated \$13 billion dollars spent each year on obesity-related medical costs alone, and even more on reduced workforce productivity.

A cornerstone of the recently passed health reform legislation, The Patient Protection and Affordable Care Act (ACA) is a comprehensive approach to the prevention of illness, mobilizing all sectors of society to promote the health of the public.

**Objective:**

To evaluate those provisions in the Patient Protection and Affordable Care Act (ACA) that aim to transform our system into one that is oriented to prevent illness and promote wellness and to assess what remains to be done at the National level in order to make this transformation a reality.

**Background:**

In the months preceding the passage of the ACA, many organizations with expertise in public health and health policy issued recommendations for prevention-focused provisions to be incorporated into the health reform law, with the ultimate goal of shifting our system from a "sick-care system" into a more comprehensive "health-care system". Throughout the legislative process, these recommendations helped shape the emerging bill. Some were accepted directly, others were incorporated in a modified form and many were left out of the bill entirely. In the context of these recommendations, we aimed to evaluate those provisions that were ultimately incorporated into the new law and provide insight regarding what remains to be done at the national level with respect to disease prevention.

**Methods:**

We reviewed the recommendations and statements from various organizations with expertise in public health and health policy regarding prevention provisions that should be incorporated in health reform

legislation submitted to the Obama administration and/or Congress prior to the signing by the President of the Affordable Care Act (ACA) on March 23, 2010. We then evaluated the prevention provisions that were incorporated into the ACA in the context of these recommendations. In particular, for each recommendation, we analyzed whether it had been directly included in the new law, included in some modified form or not included in the legislation.

**Results:**

Based on our findings, we assessed the impact that the ACA will have on the prevention of illness and the promotion of wellness in the United States and generated a set of recommendations regarding a prevention agenda that still remains to be implemented at the National level.

**Conclusion:**

The prevention of illness is imperative for both the financial and physical health our nation. While the passage of recent health reform legislation is an important and revolutionary step in the creation of a U.S. health care system that prevents illness and promotes wellness, more remains to be done in order to fully transform our system from an emphasis on sickness to health.

# Basic Science & Clinical Research

Stephanie Guo, MS2

**Preceptor:**

**Paul S. Brookes, Ph.D** Department of Anesthesiology  
University of Rochester Medical Center

## High-Throughput Screening of Cardioprotective Drugs Against Ischemia-Reperfusion Injury

**Introduction:** Myocardial infarction (MI) afflicts 1 million patients and claims 200,000 lives annually in the United States. Despite decades of research and numerous clinical trials, as of 2010, there is not a single FDA-approved drug for the reduction of myocardial infarct size in humans. Furthermore, in addition to MI, cardiac ischemia-reperfusion (IR) injury is a complicating factor during surgeries. Therefore, cardiac IR injury remains a major unaddressed clinical problem. One of the major obstacles to the development of cardioprotective drugs is the limited number of efficient cardiac IR models.

**Objective:** To develop a novel, high-throughput approach to screening for compounds protective against IR injury.

**Background:** Currently, the most physiologically relevant model is in-vivo LAD occlusion in mice. This approach, however, requires animal survival surgery and achieves a maximum throughput of 1 animal/day. A somewhat faster model is the Langendorff perfused heart; nonetheless, the throughput of this model is also low. Recently, the Seahorse Bioscience XF analyzer has emerged as a novel methodology for screening mitochondrial function in intact cells, in a 24-well plate format.

**Method:** The Seahorse Bioscience XF-24 extracellular flux analyzer is adapted to include controlled, argon gas flow. The H9C2 cardiomyocyte cell line is exposed to ischemia, simulated by the apparatus, which is programmed to undergo a 30-minute, 4-step cycle to bring oxygen levels down to 12% of that of room air. A transient micro-chamber is then created to allow cellular respiration to bring oxygen levels down to just 4% of that of room air. The development of ischemia is monitored by the built-in ability of the instrument to measure both O<sub>2</sub> and pH levels. Following ischemia, the H9C2 cells are then exposed to a 60-minute reperfusion. Following injury, cell viability was measured using the CytoTox-Glo™ method (Promega). The screen was first tested with known cardioprotective compounds: cyclosporin A, FCCP, and diazoxide, at physiologically relevant concentrations. Next, the screen was done on various nitro lipids shown to be cardioprotective on Langendorff perfused mice hearts in the Brookes lab. Finally, using this model, a 2000 compound library (Spectrum™ collection) is screened, at a concentration of 5uM, for the ability to protect cells against simulated IR injury in cardiomyocytes.

**Results:** The screen was validated with 0.2uM cyclosporine A, 50nM FCCP and 10uM diazoxide, which showed a decrease in cell death by 14% ± 1.71%, 19% ± 3.1%, and 21% ± 3.0%, respectively, as compared to control cells. The screen also indicated protection by nitrolinoleic and nitrooleic acids, showing a decrease in cell death by 27% ± 2.1% and 40% ± 2.8%, respectively. Screening of the Spectrum™ collection is ongoing. Thus far, results indicate protection by a number of known protective drugs (eg. Adenosine, estrogen and amiloride) as well as numerous novel compounds.

**Conclusion:** This high-throughput, in-vitro model can appropriately simulate IR injury and effectively detect compounds that increase cell viability following this injury. The novel hits will be pursued in the

established, more physiologically-relevant models of ischemia injury, which includes the Langendorff perfused heart and a murine in-vivo coronary artery occlusion model.

**References:**

1. "Cardiovascular Disease Statistics". American Heart Association
2. JM Downey and MV Cohen. "Why do we still not have cardioprotective drugs?"  
*Circulation*. 2009; 73:1171-1177
3. CE Murry, RB Jennings and KA Reimer. "New insights into potential mechanisms of ischemic preconditioning". *Circulation*. 1991;84:442-445.
4. KA Reimer, CE Murry and RB Jennings. "Cardiac adaption to ischemia: Ischemic preconditioning increases myocardial tolerance to subsequent ischemic episodes". *Circulation*. 1990;82:2266-2268
5. SM Nadtouchiy, PR Baker, BA Freeman and PS Brookes. "Mitochondrial nitroalkene formation and mild uncoupling in ischemic preconditioning: implications for cardioprotection". *Cardiovascular Research*. 2009; 82(2):333-40.
6. DA Ferrick, A Neilson, C Beeson. "Advances in measuring cellular bioenergetics using extracellular flux". *Drug Discovery Today*. 2008; 13(5-6):268-274
7. "How the XF24 extracellular flux analyzer works". *Seahorse Bioscience*. 2009.  
<<http://www.seahorsebio.com/products/xf24-analyzer/how-does-the-xf24-work.php>>

# Basic Science & Clinical Research

Tamara John, MS2

**Preceptor:**

**Gregg Nicandri, M.D. Department of Orthopaedics  
University of Rochester Medical Center**

## **Assessing the Arthroscopic Training Resources Utilized in Orthopaedic Resident Education**

**Introduction:** Arthroscopic surgical procedures substantially differ from open surgical procedures and require unique skill sets to address limitations. These limitations include altered tactile sensation, lack of depth perception, requirement to work in 3-dimensions while visualizing in 2-dimensions, limited degrees of freedom of arthroscopic instruments, increased length of the instrumentation, and the varying levels of eye-hand coordination that are required during arthroscopic surgery. The operating room is not an ideal setting for teaching basic arthroscopic skills due to patient safety concerns, limited resident education time, and cost of operating room time. Enhancement and development of skills such as anatomy, instrumentation, palpating with instruments, and intracorporeal knot tying is not limited to the operating room. Alternatives to apprenticeship training include instructional courses, CD, video, or web based media, artificial models, cadavers, and virtual reality. However, the prevalence, perceived effectiveness and preferences for each of these modalities remains unknown.

**Objective:** The purpose of this study was to assess the educational preferences of surgeons and trainees who wish to enhance their arthroscopic skill as well as to assess the perceived effectiveness of common methods being used in knee and shoulder arthroscopic skills training.

**Background:** Although the true costs of training residents in the operating room is unknown, a study by Farnworth et. al showed that resident operating times were, on average 42.47 minutes longer than attending operating times. This average difference in procedural time translates to a cost increase of about \$661.85 per patient if a resident is performing a surgery<sup>1</sup>. In 2008 the Residency Review Committee (RRC) in surgery stated that there needed to be an increased emphasis on simulation in surgical training, and the American College of Surgeons (ACS) recently endorsed the effort to “move the learning curve outside of the operating room”<sup>2</sup>. As a result, surgical skills training outside of the operating room is becoming more common and a variety of methods have been employed. Traditionally, clinical medical education has included a mixture of didactic lessons combined with an apprentice-like experience<sup>3</sup>. The assumption is made that by the end of their clinical education, these apprentices will become competent physicians. Several teaching methodologies, such as virtual reality simulators and web based instruction including video, lectures, or e-modules, may be effective alternatives to the traditional “see one, do one, teach one” apprenticeship.

**Methods:** A thirty item survey, constructed through “survey monkey”, was created with the intent of addressing and ranking issues related to orthopaedic resident arthroscopic skills training. An e-mail was sent to 3170 United States orthopaedic residents, 152 residency program directors, 426 orthopaedic sports medicine attending physicians practicing at institutions affiliated with residency programs, asking them to participate in the online survey. The email contained a link to the survey on “survey monkey” in addition to an “Introductory Statement/Consent” form. The section involving demographic data consisted of five items designed to assess the arthroscopic experience of the residents. In the arthroscopic skills training section, the effectiveness of nine common methods of arthroscopic skills training was assessed using a five point Likert scale, ranging from “least effective” (1 point) to “most effective (5 points). The nine common methods included practice on dry models, cadaveric specimens, virtual reality simulators, web

based instruction including video, lectures, or e-modules, lecture or didactic only instructional courses, observing in live surgery, assisting or performing live surgery, reading industry technique guides, and reading published material.

In the survey distributed to the residents, the confidence section required each resident to rate their confidence in performing fifteen basic orthopaedic procedures. The survey distributed to the attending physicians consisted of a confidence section which required each physician to estimate their level of confidence in graduating chief resident's ability to perform the same fifteen common orthopaedic procedures previously stated. A ten-point Likert scale, ranging from "not confident" (1 point) to "very confident" (10 points), will be used for self-assessment of confidence. The positive control in this study was applying a short leg splint because it is a basic skill that all residents should be confident about performing. Contrastingly, performing an Open Reduction Internal Fixation (ORIF) of a both column acetabular fracture was used as a negative control because few if any residents should be confident about performing this procedure. This approach has been used in many other studies that focused on the confidence of medical practitioners<sup>4</sup>.

Each recipient was sent an e-mail link to the survey web address and, one week later, a reminder e-mail was sent to those who did not complete the email. Two months after the original e-mail, data collection was considered complete and any subsequent responses were no longer collected. A similar method has been used successfully in the past to assess training resources used in arthroscopic rotator cuff repair<sup>5</sup>.

**Results:** The response rate of the survey was 31 out 152 (20.4%) contacted orthopaedic residency program directors, 73 out of 426 (17.1%) contacted sports medicine attendings, and 254 out of 3170 contacted orthopaedic residents. 31 out of 31 (100%) responding residency program directors indicated that their program included a dedicated sports rotation. The mean duration of the sports medicine rotation was 8.7 months (CI 5.26-12.09). The percentage of programs that utilized various techniques utilized in resident arthroscopic education ranged from 5% to 100% of the orthopaedic residency programs. In fact, all programs offered observation in live surgery and assistance or performing of live surgeries. Alternatively, very few programs (n= 6) offered practice on virtual reality simulators. The average effectiveness, was assessed by the residents and attendings, on each arthroscopic learning technique. The assessment was based on a five point Likert scale, ranging from "least effective" (one point) to "most effective" (five points). Interestingly, the opinions were similar among most techniques. However, residents had an overall lower rating of observation in live surgery than the attendings. The most effective method with an average score of 5.65 among residents and attendings is assisting or performing live surgery while the least effective method, with an average score of 3.6 among residents and attendings is reading industry technique guides. Resident confidence levels were compared between residents without cadaver training and residents with cadaver training. For nearly all fifteen procedures, residents who did not have cadaver training reported a lower confidence level than those who did have cadaver training. Applying a short leg splint was the positive control and performing an Open Reduction Internal Fixation was the negative control.

**Conclusion:** Arthroscopic educational curriculum varies significantly across residency programs. However, the preferred methodology of choice among most orthopaedic residency programs is the traditional methodology of observation and assisting or performing live surgeries. Nonetheless, dry model training was perceived to be almost as effective as traditional observation. Cadaveric training remains the preferred method of adjunctive arthroscopic education and individuals training on cadavers demonstrate increased confidence in their ability to perform arthroscopic procedures.

**References:**

1. Farnsworth LR, Lemay DE, Wooldridge T, Mabrey JD, Blaschak MJ, DeCoster TA, Wascher DC, Schenck RC Jr. A Comparison of Operative Times in Arthroscopic ACL Reconstruction Between Orthopaedic Faculty and Residents: The Financial Impact of Orthopaedic Surgical Training in the Operating Room. *The Iowa Orthopaedic Journal* 2001; 21: 31-35.
2. Michelson JD. Simulation in orthopaedic education: an overview of theory and practice. *The Journal of Bone and Joint Surgery* 2006; 88: 1405-1411.
3. Kohn KT, Corrigan JM, Donaldson MS. *To Err Is Human: Building a Safer Health System*. Washington, DC: National Academy Press; 1999.
4. Leopold SS, Morgan HD, Kadel NJ, Gardener GC, Schaad DC, Wolf FM. Impact of Educational Intervention on Confidence and Competence in the Performance of a Simple Surgical Task. *Journal of Bone and Joint Surgery* 2005; 87:1037-1037.
5. Vitale MA, Kleweno CP, Jacir AM, Levine WN, Bigliani LU, Ahmad CS. Training Resources in Arthroscopic Rotator Cuff Repair. *Journal of Bone and Joint Surgery* 2007; 89: 1393-1398.

## Basic Science & Clinical Research

Ross Hanson, MS4, India Johnson, MS2

**Preceptor:**

**John Markman, M.D. Director**  
**Neuromedicine Pain Management Center**  
**University of Rochester Medical Center**

### **Characterization of Neuropathic Pain in Post Laminectomy Pain Syndromes**

**Introduction:** Low back pain is the third leading indication for surgery in the United States [1, 2]. Despite the growing rates and complexity of surgical treatments, the vast majority of patients are left with residual painful symptoms following these interventions [3, 4]. In a substantial minority, these chronic symptoms are moderate to severe in intensity and cause significant activity limitation. The diagnostic category of post laminectomy pain encompasses a highly prevalent and diverse set of chronic, low back pain syndromes. Roughly 20% of patients experience more severe pain syndromes after surgery, and this is a leading cause of referral for subspecialty pain care [3]. Given the surging prevalence of low back pain and associated growth of complex spine surgery [4], it is important to refine the characterization of these post operative pain syndromes.

**Objective:** To demonstrate the feasibility of adapting DN4 and LEEDS questionnaires to the evaluation of post laminectomy pain syndrome.

**Background:** Although post operative pain syndromes tend to have varied anatomic precipitants and underlying pain mechanisms, patients with more severe back pain are more likely to have a neuropathic component [5]. The presence of a neuropathic mechanism may adversely affect patient outcomes, since this type of pain strongly correlates with decreased quality of life, increased functional impairment, and more severe pain intensity [6]. Consequently, patients with neuropathic pain are more likely to lack response to conventional therapies and endorse greater pain intensity and reduced health related quality of life compared to patients with non-neuropathic pain syndromes. We hypothesized that post laminectomy pain syndromes frequently have a neuropathic component and that patients experiencing this type of pain may be identified using instruments validated in other chronic neuropathic pain conditions.

**Methods:** This was a cross-sectional study with an embedded chart review of patients with chronic pain after spine surgery, designed to examine characteristics of post-laminectomy pain syndrome (PLPS). Eligible patients were between 18 and 85 years of age, spoke English, had previous lumbar laminectomy with or without instrumentation within the past 7 years, and demonstrated persistent pain of greater than 3/10 intensity at the time of initial referral for pain management. Patients were recruited initially by mail with telephone follow-up between October 2009 and January 2010. Of 157 patients identified using IDXAnalyzer and recruited for the study, 43 patients (20 male, 23 female, age range: 28-79 years) were enrolled in the single visit. Subjects completed a panel of self-report measures validated to assess pain and pain-related interference. These included the following: Visual Analog Scale (VAS), Roland-Morris Disability Questionnaire (RMDQ), and Modified Brief Pain Inventory, Short-Form (mBPI-sf). In addition to questionnaires, patients were examined by trained personnel at the time of study visit to complete the following objective measures: Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), and Neuropathic Pain Diagnostic Questionnaire (DN4).

**Results:** In this sample 43 chronic pain patients were evaluated for the presence of neuropathic pain using the validated DN4 cut-off score of 4 or greater [7]. 67.4% were categorized in the  $\geq 4$  neuropathic pain

group (29 patients), and 32.6 % were in the <4 non-neuropathic pain group (14 patients). The same 43 patients were also stratified according to the presence of neuropathic pain using the previously validated LANSS cut-off score of 12 or greater [8]. In this sample of 43 chronic pain patients, 25.6% were categorized in the  $\geq 12$  neuropathic pain group (11 patients), and 74.4 % were in the <12 non-neuropathic pain group (32 patients).

DN4 positive patients scored significantly worse in all pain and disability metrics than those in the DN4 negative category. These included VAS pain intensity (59.7mm vs. 33.3mm,  $p < 0.01$ ), RMDQ (16.3 vs. 10.9,  $p < 0.01$ ), and mBPI-sf (60.9 vs. 33.1,  $p < 0.01$ ). LANSS positive patients also scored significantly worse in the majority of pain and disability metrics than those in the LANSS negative category, although not as markedly as seen with the DN4. LANSS positive patients demonstrated worse pain as demonstrated by VAS (63.5mm vs. 46.9mm,  $p = 0.04$ ). LANSS positive patients also exhibited increased disability as judged by RMDQ (17.9 vs. 13.4,  $p = 0.02$ ) although not by mBPI-sf (63.2 vs. 47.9,  $p = 0.08$ ). Patients with axially-distributed pain predominated (60.5%), though there were no significant differences in pain distribution observed between groups in either neuropathic pain measure (DN4:  $p = 0.76$ , LANSS:  $p = 0.24$ ).

**Conclusion:** The presence of neuropathic pain according to both the DN4 and LANSS was associated with significantly higher pain intensity, increased level of disability, and greater pain-related activity interference. This constellation of findings is concordant with the presence of neuropathic symptoms in other chronic pain syndromes such as post herpetic neuralgia (PHN). Surprisingly, the presence of neuropathic pain was equally distributed among patients with axial predominant syndromes and those with a classic, lateralized radicular distribution of symptoms regardless of the painful region they identified as most bothersome. Neither axial nor radicular-predominant patterns were associated with positive outcomes to the DN4 or LANSS. This finding challenges the historical presumption that axial predominant back pain conforms to the end organ dysfunction model of lumbar back pain. It may be inferred that the mechanism of the underlying pain syndrome may be more valuable with regard to identifying subpopulations of responders to specific treatments than anatomic symptom distribution. Identification of this subpopulation of patients with neuropathic pain offers a foundation for enriched enrollment strategies for clinical trials and enhanced treatment matching in clinical practice for procedures targeting neuropathic pain such as spinal cord stimulation.

## References:

1. Hart, L.G., R.A. Deyo, and D.C. Cherkin, *Physician office visits for low back pain. Frequency, clinical evaluation, and treatment patterns from a U.S. national survey*. Spine (Phila Pa 1976), 1995. **20**(1): p. 11-9.
2. Taylor, V.M., et al., *Low back pain hospitalization. Recent United States trends and regional variations*. Spine (Phila Pa 1976), 1994. **19**(11): p. 1207-12; discussion 13.
3. Fritzell, P., et al., *2001 Volvo Award Winner in Clinical Studies: Lumbar fusion versus nonsurgical treatment for chronic low back pain: a multicenter randomized controlled trial from the Swedish Lumbar Spine Study Group*. Spine (Phila Pa 1976), 2001. **26**(23): p. 2521-32; discussion 2532-4.
4. Weinstein, J.N., et al., *Surgical vs nonoperative treatment for lumbar disk herniation: the Spine Patient Outcomes Research Trial (SPORT): a randomized trial*. JAMA, 2006. **296**(20): p. 2441-50.
5. Schmidt, C.O., et al., *Modelling the prevalence and cost of back pain with neuropathic components in the general population*. Eur J Pain, 2009. **13**(10): p. 1030-5.
6. Freynhagen, R., et al., *painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain*. Curr Med Res Opin, 2006. **22**(10): p. 1911-20.
7. Bouhassira, D., et al., *Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4)*. Pain, 2005. **114**(1-2): p. 29-36.
8. Bennett, M., *The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs*. Pain, 2001. **92**(1-2): p. 147-57

## Basic Science & Clinical Research

**Sarah Keller, MS2**

**Preceptor:**

**Jonathan Friedberg, MD**

**Chief of the Division of Hematology/Oncology of the Department of Medicine University of Rochester Medical Center**

### **Late Relapses Following Autologous Stem Cell Transplantation (ASCT) for Hodgkin Lymphoma (HL) in the ABVD Therapeutic era**

Sarah Keller, Jennifer Kelly, Elizabeth Sensenig, Jennifer Andreozzi, Jamie Oliva, Lynn Rich, Louis Constine, Michael Becker, Gordon Phillips, Jane Liesveld, Richard I. Fisher, Steven H. Bernstein, and Jonathan W. Friedberg

ASCT is the standard therapy for relapsed and refractory HL. To determine the long-term outcome of ASCT in the modern “ABVD era,” and the impact of allogeneic transplantation in pts who fail ASCT, we reviewed all pts with HL who were treated with ASCT between 1990 and 2005 at the University of Rochester. Median follow-up is 10 years. 113 pts (44% female; 88% Caucasian) with documented HL were treated with ASCT for relapsed/refractory HL. At ASCT, median age was 34 years (range 19-66). 73% of these pts were treated initially with ABVD or MOPP-ABVD-hybrid therapy. Histology was: NS (n=79), mixed cellularity (n=19), LP (n=6), LD (n=3), and classical NOS (n=6). 57% of patients were in first clinical relapse at time of ASCT, and 32% were refractory to therapy prior to ASCT. Conditioning regimens at ASCT were BEAC (n=77); BEAM (n=28); Cy/TBI (n=8). 50% of pts received XRT following ASCT. At 5 years, overall survival (OS) for the entire population was 55%, and event-free survival (EFS) was 45%. In total, 67 pts have died; of these 38 died of HL. Notably, 16 (24%) of the deaths occurred more than 5 years after ASCT, and 6 of these 16 patients (38%) died directly from HL; other causes of death were acute leukemia (n=3); 1 each from cardiomyopathy, complications of pulmonary fibrosis, non-Hodgkin Lymphoma, myelodysplastic syndrome, acute myocardial infarction, and 2 unknown causes. Furthermore, 20% of the 55 relapses occurred beyond 3 years, with 5 relapses documented 5 years post ASCT. 12 patients received an allogeneic transplant following ASCT relapse: 9 (75%) have died, and only 1 patient remains in remission. In contrast to other studies, we do not observe a plateau in EFS following ASCT. Patients appear to be at continuous risk of recurrence through at least 5 years after ASCT. While it is well-known that there are late events resulting from ASCT, late deaths attributable to HL have not previously been documented. Our results have important implications in defining success of maintenance strategies after ASCT for HL, and emphasize the importance of long-term follow-up for both toxicity and recurrence.

# Basic Science & Clinical Research

Ryan Koehler, MS2

**Preceptor:**

**Gregg Nicandri, M.D. Assistant Professor**

**Department of Orthopaedics**

**University of Rochester Medical Center**

## **Validation of a Video-based Model for Evaluating Live Diagnostic Knee Arthroscopy Performance**

**Introduction:** General surgery training programs have utilized task-specific checklists, global rating scales, and motion analysis as methods to assess competency in simulated and live laparoscopic surgery.<sup>1-3</sup> These tools have been shown to be valid models for assessing surgeon performance and have led to the development of a standardized surgical skills curriculum.<sup>4</sup> In orthopaedic surgery, arthroscopic procedures require a skill set similar to laparoscopic surgery yet the validity of utilizing similar methods of competency assessment is unknown.

**Objective:** The purpose of the current study was to determine the feasibility and validity of using an arthroscopic surgery assessment tool to evaluate surgeon proficiency when performing diagnostic knee arthroscopy.

**Background:** Recently, the use of a task-specific checklist and a global rating scale to assess surgeon performance of arthroscopic partial meniscectomy in cadaveric specimens was shown to demonstrate construct validity.<sup>5</sup> Subjects' performance scores were positively correlated to previous number of procedures performed and year-in-training. Additionally, Howells et al. found that transfer validity could be demonstrated for skills obtained using a bench-top knee model to improve proficiency at performing diagnostic knee arthroscopy in the operating theater.<sup>6</sup> These studies suggest that arthroscopic surgery can indeed be assessed similar to laparoscopic surgery and identified potential areas for improvement. Incorporating video analysis into a model of assessment has been identified as a way to strengthen the previously mentioned tools.<sup>5,6</sup> The use of video-based analysis has been shown to be a valid, feasible, and reliable way to assess performance of laparoscopic cholecystectomy.<sup>7</sup>

**Methods:** Thirteen residents, two sports medicine fellows, and two attending physicians were recruited from the department of Orthopaedic Surgery at Duke Medical Center. Participants were grouped into novice surgeons (PGY-1,2), intermediate surgeons (PGY-3,4,5), and expert surgeons (PGY-6+). Subjects were asked to record the intra-articular portion of a diagnostic knee arthroscopy in a patient undergoing arthroscopic meniscectomy without prior history of knee injury. Each arthroscopic video was reviewed by a single rater who was blinded to the identity and level of experience of the operating surgeon. Each subjects' proficiency was determined using the Basic Arthroscopic Knee Scoring System modified for analysis of intra-operative video (BAKSS-V). The BAKSS-V was composed of a task-specific checklist and a global rating scale.

**Results:** No novice surgeons, two (33%) of six intermediate surgeons, and four (100%) of four expert surgeons had at least one case which achieved a maximum BAKSS-V score of 60 points. Moderate positive correlation was shown between total BAKSS-V score and postgraduate year (PGY) ( $r=0.68$ ,  $p < 0.01$ ). BAKSS-V variance was shown to be statistically significant across all groups ( $p < 0.01$ ). Pair-wise comparison of scores grouping novices (PGY1,2), intermediates (PGY 3,4,5), and experts (PGY6+) demonstrated significant differences between all groups ( $p = < 0.01$ ). The average score of the

novice (PGY 1-2) group was 29.21 (95% CI, 24.75-33.68). The average score of the intermediate (PGY 3,4,5) group was 52.35 (95% CI, 50.32-54.38). The average score of the expert (PGY 6+) group was 58.85 (95% CI, 57.59-60.10). Analysis of the task-specific checklist score alone did not demonstrate any appreciable difference between groups.

**Conclusion:** This study demonstrates the feasibility and validity of using the BAKSS-V assessment of intraoperative video as a method of assessing arthroscopic proficiency. This has implication in bridging the gap between assessment of lab acquired skills and their translation into surgical proficiency.

#### **References:**

1. Michelson JD. Simulation in orthopaedic education: an overview of theory and practice. *J Bone Joint Surg Am.* 2006;88:1405-11.
2. Aggarwal R, Darzi A. From scalpel to simulator: a surgical journey. *Surgery.* 2009;145:1-4.
3. Michelson JD, Manning L. Competency assessment in simulation-based procedural education. *Am J Surg.* 2008;196:609-15.
4. Fundamental of Laparoscopic Surgery Program. <<http://www.flsprogram.org/>>
5. Insel A, Carofino B, Leger R, Arciero R, Mazzocca AD. The development of an objective model to assess arthroscopic performance. *J Bone Joint Surg Am.* 2009;91:2287-2295.
6. Howells NR, Gill HS, Carr AJ, Price AJ, Rees JL. Transferring simulated arthroscopic skill to the operating theatre. *J Bone Joint Surg Br.* 2008;90-B:494-9.
7. Aggarwal R, Grantcharov T, Moorthy K, Milland T, Darzi A. Toward feasible, valid, and reliable video-based assessments of technical surgical skills in the operating room. *Ann Surg.* 2008;247:372-9.

## Basic Science & Clinical Research

Dmitriy Migdalovich, MS2

**Preceptors:**

**Arthur J. Moss, M.D.**  
Professor of Medicine (Cardiology)  
Heart Research Follow-up Program

**Ilan Goldenberg, M.D.**  
Research Associate Professor Associate Director,  
Heart Research Follow-up Program

### **Gender Differences in Mutation-Location Dependent Risk of Life Threatening Cardiac Events in LQT2 Patients**

**Introduction** Long QT syndrome (LQTS) is a congenital disorder caused by mutations in several cardiac ion channel genes, and is clinically identified by abnormal QT interval prolongation on the ECG<sup>1</sup>. LQTS is associated with clinical outcomes of arrhythmogenic syncope and sudden arrhythmic death<sup>2</sup>. Type 2 LQTS, the second most common variant of LQTS, is characterized by mutations in the  $I_{Kr}$  cardiac channel, which is encoded by the *KCNH2* gene<sup>3</sup>. Previous studies found an effect of gender among LQT2 patients, showing that although there was no significant difference in cardiac event rate between male and female carriers  $\leq 15$  years, female LQT2 carriers ages 16-40 years had a significantly higher risk of cardiac events than their male counterparts<sup>4</sup>. However, no studies had investigated how mutation-location within the  $I_{Kr}$  channel contributed to the gender differences in cardiac event rate.

**Objective** The goal of this study was to investigate how mutation location, specifically locations within pore-loop, the transmembrane nonpore region, the N-terminus, and the C-terminus of the  $I_{Kr}$  cardiac channel, would influence the gender dependent risk of life threatening events in adult patients with LQT2 syndrome.

**Methods** We examined the occurrence of a first cardiac event of either aborted cardiac arrest (ACA) or sudden cardiac death (SCD) among 1188 LQT2 patients enrolled in the U.S. portion of the International LQTS Registry. The baseline and follow up clinical characteristics of the study population were evaluated using the chi-square test for categorical variables and the t-test for continuous variables. The cumulative probability of a first life-threatening cardiac event from birth through age 40 years was assessed by the Kaplan-Meier method, and significance was tested by the log-rank test. Multivariate Cox proportional-hazards regression models were used to evaluate the independent contribution of clinical and genetic factors to the first occurrence of ACA or SCD.

**Results** Although there was no difference in event rates between male and female patients during childhood, the rate of life threatening events was higher among LQT2 females after the onset of adolescence (Fig. 1). Significant differences in the risk for life-threatening events were identified between males and females by mutation-location. Among males, pore-loop mutations were associated with a significantly higher rate of ACA or SCD as compared with mutations which were located in other regions of the *KCNH2* channel (Fig. 2). In contrast, among females the rate of ACA or SCD was high regardless of mutation location (Fig. 3). Consistent with those findings, multivariate analysis showed that pore-loop mutations were associated with a significantly higher risk for life-threatening events among males as compared with other mutations (HR=3.46, p=0.003), whereas the presence of pore-loop mutations was not associated with a significant increase in the risk of ACA or SCD among females (HR=0.949, p=0.820).

Figure 1: Cumulative probabilities of ACA and SCD in LQT2 patients by gender

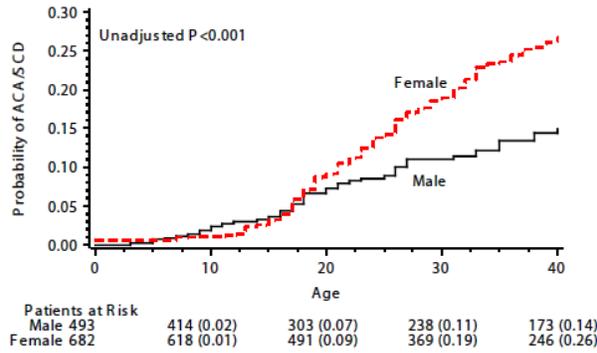


Figure 2: Cumulative probabilities of ACA and SCD in LQT2 males by mutation-location

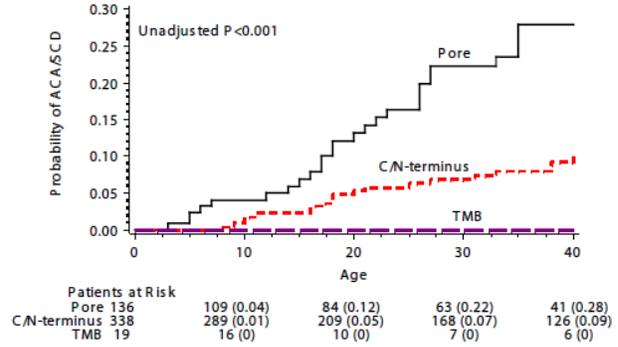
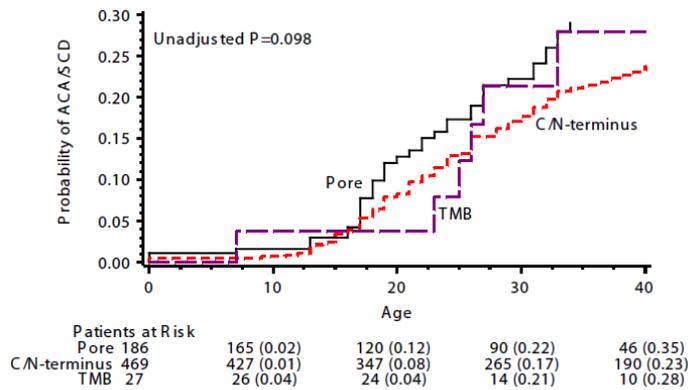


Figure 3: Cumulative probabilities of ACA and SCD in LQT2 females by mutation-location



**Conclusion** Our findings provide mutation-specific data regarding gender differences in the risk for life-threatening events in LQT2 patients. We have shown that the rate of ACA or SCD after the onset of adolescence is significantly higher among LQT2 females as compared with the respective males. However, further analysis by mutation-location demonstrated that despite the overall lower-risk of LQT2 males, those who harbored mutations in the pore-loop region still exhibited a high rate of ACA or SCD as compared with other mutation-locations, whereas the rate of life-threatening events among LQT2 females was shown to be high regardless of mutation- location. Further investigation of the mechanisms of the different mutations in the  $I_{Kr}$  channel, especially how testosterone and estrogen may alter the functioning of the channel depending on the type of mutation within the channel, may explain why LQT2 males exhibit a lower incidence of ACA or SCD associated with transmembrane nonpore and N-terminus/C-terminus mutations and have a lower incidence of life threatening cardiac events in adulthood than LQT2 females.

## References

1. Moss AJ, Kass RS. Long QT Syndrome: from channels to cardiac arrhythmias. *J Clin Invest* 2005; 115:2018-24.
2. Goldenberg I, Zareba W, Moss AJ. Long QT Syndrome. *Curr Probl Cardiol*. 2008; 33:629- 694.
3. Sanguinetti MC. HERG1 channelopathies. *Eur J Physiol*. 2010; 460:265-276.
4. Zareba W, Moss AJ, Locati EH, et al. Modulating Effects of Age and Gender on the Clinical Course of Long QT Syndrome by Genotype. *JACC*. 2003;42:103-109.

## Basic Science & Clinical Research

Christine Neeb, MS2

**Preceptor:**  
**Margaret Altemus, MD Associate**  
**Professor**  
**Department of Psychiatry**  
**Weill Cornell Medical College**

**Introduction:** Hormonal changes are hypothesized to play a role in the onset of depression during pregnancy and the postpartum period. During pregnancy, levels of  $\beta$ -endorphin, CRH, cortisol, HCG, prolactin and gonadal steroids are unusually high. In the postpartum period, however, women experience a sudden drop in most pregnancy hormones, particularly the gonadal steroids estrogen and progesterone due to the removal of the placenta as well as elevation in brain levels of lactational hormones, oxytocin and prolactin, depending on breastfeeding status.<sup>iii iii</sup> Over 10% of postpartum depression appears to onset during pregnancy, but there has been little attention given to potential differences in risk factors, clinical features or treatment response.<sup>iii</sup> If there are pathophysiological differences in depression which onsets during pregnancy as opposed to postpartum, these differences would be important to consider in genetic studies and in design of prevention and treatment efforts.

**Objective:** To determine if there are differences in symptomatology, risk factors, and demographics between women with a major depressive episode of postpartum onset versus pregnancy onset and if so, to determine if these differences indicate if either pregnancy-onset or postpartum-onset depression is a distinct illness from major depressive disorder (MDD).

**Methods:** Medical records of 185 women who were evaluated in a reproductive psychiatry specialty clinic and three private practices during an episode of peripartum depression were examined. Psychiatric history variables were recorded and included personal and family history of depression or bipolar disorder, personal history of panic disorder, OCD, GAD, premenstrual symptoms, suicide attempts, and discontinuation of antidepressant medication less than one year prior to symptom onset. Psychosocial variables included history of physical or sexual abuse, current social support, partner discord, partner status, infant health problems or premature delivery, and planned vs. unplanned pregnancy. Reproductive history variables included number of prior deliveries, elective terminations, pregnancy losses, infertility treatment, prior or current pregnancy complications, and nausea during pregnancy. Non reproductive medical conditions were recorded. Current symptom variables included agitation, psychomotor retardation, suicidal ideation, insomnia, hypersomnia, panic, OC symptoms, psychotic symptoms, intrusive violent thoughts, and response to treatment. Results for all patients were analyzed, as well as those for an exclusive subgroup, from which patients with ongoing MDD, dysthymia, bipolar disorder, and those who discontinued their antidepressant less than one year prior to symptom onset were excluded.

**Results:** Women experiencing a new onset of depression during pregnancy had a higher rate of history of MDD than women experiencing a new onset of depression postpartum. When the exclusive groups were examined, 46% of women with pregnancy onset depression had experienced a previous episode of MDD, while 14% of those in the postpartum onset group had experienced a previous episode ( $X^2=9.4$ ,  $p<0.01$ ). In the overall group, 84% of the pregnancy onset group and 46% of the postpartum onset group had a history of MDD ( $X^2=28.47$ ,  $p<0.001$ ). In the overall analysis, multiparous women who were depressed during pregnancy had a higher incidence of history of "postpartum" depression (53%) than multiparous women with postpartum onset (19%) ( $X^2=9.25$ ,

$p < 0.01$ ). The incidence of obsessive compulsive (OC) symptoms was significantly higher in women with postpartum onset depression than those with pregnancy onset. In the exclusive group, 29% of women in the postpartum onset group experienced OC symptoms during their current depressive episode, while 7.7% of women in the pregnancy onset group experienced such symptoms ( $X^2 = 4.41$ ,  $p < 0.05$ ). In the overall group, 28% of women in the overall postpartum onset group and 13% of women in the overall pregnancy onset group experienced OC symptoms ( $X^2 = 6.30$ ,  $p < 0.02$ ). In the overall analysis, reported history of physical and/or sexual abuse was significantly higher in the pregnancy onset group (29%) than the postpartum onset group (14%) ( $X^2 = 6.44$ ,  $p < 0.02$ ). Psychotic symptoms were significantly more common among patients with postpartum onset depression when examining both the overall and exclusive groups. In the analysis of the exclusive groups, 14% of women in the postpartum onset group experienced symptoms of psychosis, as compared to 0% in the pregnancy onset group ( $X^2 = 4.10$ ,  $p < 0.05$ ). Overall, 11% of patients with postpartum onset experienced psychosis, while 0% of those with pregnancy onset experienced such symptoms ( $X^2 = 11.57$ ,  $p < 0.001$ ). Women experiencing pregnancy onset depression were more likely to have discontinued antidepressant pharmacotherapy less than one year prior to symptom onset when results were examined overall. 35% of women in the pregnancy onset group had discontinued medication less than a year prior to symptom onset, as opposed to 12% of the postpartum onset group ( $X^2 = 13.66$ ,  $p < 0.001$ ).

**Discussion:** Our data suggest that women with a history of MDD are more susceptible to a peripartum depression, but that this depression will onset during pregnancy and not be delayed until the postpartum period. Similarly, more women in the pregnancy onset group had a history of postpartum depression than those in the postpartum onset group, indicating again that if a woman is at risk for a peripartum depressive episode, that episode is more likely to happen during pregnancy than postpartum. It seems that women who are already at risk for MDD based on past medical history should be on the lookout for depressive symptoms long before the arrival of the new baby. This finding is important given the general belief that women with a history of MDD are more at risk for postpartum depression. In addition, the increased rate of obsessive compulsive symptoms during postpartum depression indicates an inherent difference in at least some aspects of the symptomatology of postpartum depression compared to MDD. According to one study, 9.9% of outpatients with MDD had concurrent OCD.<sup>iii</sup> While this statistic fits with the 7.7% of women with pregnancy onset MDD found to have OC symptoms, the rate of 29% in the postpartum onset group is staggeringly higher. While depression during pregnancy and postpartum are currently both considered episodes of MDD, these data indicate that while symptomatology and risk factors for pregnancy onset depression fit the MDD criteria, postpartum onset may be different. These findings have important implications in the early diagnosis and treatment of MDD relapse in pregnant women.

## References

- <sup>iii</sup> McLean, M., A. Bisits, et al. (1995). "A placental clock controlling the length of human pregnancy." *Nat Med* **1**(5): 460-3.
- <sup>iii</sup> Hendrick, V., L. L. Altshuler, et al. (1998). "Hormonal changes in the postpartum and implications for postpartum depression." *Psychosomatics* **39**(2): 93-101.
- <sup>iii</sup> Stowe, Z. N., A. L. Hostetter, et al. (2005). "The onset of postpartum depression: Implications for clinical screening in obstetrical and primary care." *Am J Obstet Gynecol* **192**(2): 522-6.
- <sup>iii</sup> Zimmerman, M., W. McDermt, et al. (2000). "Frequency of anxiety disorders in psychiatric outpatients with major depressive disorder." *Am J Psychiatry* **157**(8): 1337-40.

## Basic Science & Clinical Research

Tambetta Ojong, MS2

**Preceptor:**

**Katie Malbon, MD**

**Clinical Fellow in Adolescent Medicine Mount Sinai Adolescent Health Center**

*What's on the street? What do adolescents and young adults know about STDs and how do they think we can promote routine screening for STDs using technological innovations?*

**Introduction:** In response to a survey completed by adolescents at the beginning of seven focus groups at the Mount Sinai Adolescent Health Clinic (MSAHC), the data demonstrated that almost all adolescents owned a cell phone, and were mostly minority females and almost all were sexually active. Chlamydia trachomatis was the most common sexually transmitted disease among this sample of adolescents. Finally almost all the sampled adolescents did respond quicker to text messaging than voicemail and therefore this could be a plausible method to provide annual screening reminders among sexually active adolescents as well as a means of sexual health education.

**Objective:** To determine if adolescents respond faster to voicemails or text messages as well as their interest in receiving health education via text messages.

**Background:** Chlamydia trachomatis is the most widespread bacteria sexually transmitted disease in the United States with over fifty percent of cases affecting women ages 15-25 years.<sup>1</sup> Despite recommended annual screening among sexually active young women, the majority of adolescents and young adults are still not routinely tested for Chlamydia<sup>2</sup> and other STDs. The widespread adoption of cell phone text messaging and email among adolescents and young adults make these channels an attractive tool to launch new strategies to promote Chlamydia education testing and treatment. Preliminary results in the UK and Australia using text messaging to deliver lab results are encouraging,<sup>3,4</sup> however, little has been done in the US to evaluate the feasibility of such technologies to effect behavior change and address key barriers to STD testing and treatment among adolescents and young adults.<sup>5</sup> The barriers to STD screening are complex and not completely understood. The beliefs of patients, providers and practices are important variables one should consider,<sup>9</sup> additionally, patients' demographic variables like lack of health insurance, race/ethnicity,<sup>10,11,9</sup> all play a role in barriers to STD screening. However, failure to present for preventive health services is likely the most significant factor. A recent study using 1994-2003 National Ambulatory Medical Care Survey (NAMCS) data for adolescents ages 11 to 21 years, found that only 9% of adolescent visits to physician offices were for preventive care, with an even lower rate of 3% among late adolescent females.<sup>10</sup> In a complementary study using the 1996-2006 NAMCS and National Hospital Ambulatory Medical Care Survey data for young adults ages 20 to 29 years, researchers found that only 17% of young women ambulatory care visits were for preventive care and only 2.7% of visits included counseling about STIs.<sup>11</sup> Barriers to treatment are multi-faceted and include lack of knowledge among adolescents and young adults about asymptomatic disease, where to get tested, and complications associated with disease. Additional patient concerns include fear of positive test implications as well as testing confidentiality.

**Methods:** 31 English-speaking patients of Mount Sinai Adolescent Health Clinic between the age of 15 and 23 participated in the 7 held focus groups and answered this survey. Each patient was assigned to the 'pm walk-in' clinic and had to wait for the providers to commence clinic session at 1pm, so the patients

would have been sitting in the waiting area until that time. Recruiting in this way is done routinely at MSAHC and found to be successful. Participants were approached in the waiting area at 11:30 and given verbal and written information regarding the purpose and content of the focus groups. At the beginning of the focus groups they each completed a brief survey and could choose to not answer questions as well as select more than one answer for some questions and this quantitative data was entered into an Excel spreadsheet from which basic frequencies and cross tabulations was done.

**Results:** From the survey data it was shown that there was a difference between the two proposed methods of communications that adolescents respond to. 30/30 adolescents stated that they would respond faster to text than to email. CI { .9049661, 1.0000000 } **p-value < .0001**. The survey results also demonstrated that there was a significant difference between adolescents that owned a cell phone and had unlimited text versus those that did not. It was determined that 29/31 adolescents owned a cell phone and had unlimited text when compared to those without a cell phone and unlimited text. CI { .8105355, 1.0000000 } **p-value < .0001**. A significant difference was observed among young adults that would be interested in receiving health information via text messages and the ones that were not. The results demonstrated that 19/28 adolescent wanted to receive health education messages via text CI { .4764836, .8412240 } **p-value 0.001335**. There was also a marked significant difference between adolescents who are sexually active versus those that are not. It was determined that 28/31 adolescents were sexually active CI { .768497, 1.0000000 } **p-value < .0001**. This survey showed that there was a significant difference between the genders of the adolescents completing the survey. More females were part of the survey in comparison to male counterparts 30/31 CI { .8559096, 1.0000000 } **p-value < .0001** Likewise it was determined that there was significance in the age at onset on intercourse between the three proposed aged groups. The number of adolescents with onset of intercourse was both 15/30 in the 16-19 and 13-15 age groups and 0/30 in the 20-24 age group.  $\chi$ -squared 15 df= 2 **p-value = 0.0005531**. However when the two groups with earlier onset of intercourse where compared no significant difference was found. The results were both 15/30 for both the 13-15 and 16-19 age group. CI { 0.3129703, 0.6870297 } **p-value = 1**. When looking at the demographics of the adolescents sampled once again there was a significant difference between the races. The proportions were 16/31 African Americans, 15/31 Hispanic, and 0/31 Mixed or Caucasian.  $\chi$ -squared 31.0645 df 3 **p-value < .0001**. When a binomial test was performed to compare the proportion of the African American respondents to the Hispanic respondents there was no significant difference. CI { 0.3306006, 0.6984543 } **p-value = 0.7239**. When, looking at the prevalence of Chlamydia compared to gonorrhea, syphilis, herpes, HPV, trichomoniasis there was no statistically significant difference. The proportions were 7/11 for Chlamydia, 3/11 for Trichomoniasis and 1/11 for Herpes.  $\chi$ -squared = 0.8182 df = 1 **p-value = 0.3657**. Finally when asked where adolescents get their health information about STDs there was a significant difference in distribution of sources. The proportions were 12/76 for family 13/76 for friends, 6/76 for teachers, 19/76 for the Internet, 6/76 for books, 5/76 for magazines and 15/76 from the Internet.  $\chi$ -squared 15.7368 df= 6 **p-value = 0.01524**.

**Conclusion:** From this survey it was determined that female minorities do make up a larger population of the MSAHC. They stated that they do respond faster to text messages in comparison to voicemails and do want to get health information via text messages and therefore since some of these individuals are already sexually active, text messaging may be a potential new venue to provide reminders of preventative care such as STD screening, or be used as a reminder for an upcoming appointment or even as a method to ensure compliance with birth control as well as a potential educational tool for their sexual health.

## References

1. Centers for Disease Control and Prevention: Chlamydia Screening Among Sexually Active Young Female Enrollees of Health Plans ---United States, 2000-2007: MMRW April 17 2009 58 (14) 362-365
2. Source: Gutmacher Institute. Facts on sexually transmitted infections in the United States. June,2009
3. Menon-Johansson AS, McNaught F, Mandalia S, Sullivan AK. Texting decreases the time to

- treatment for genital Chlamydia trachomatis infection. *Sex Transm Infect* 2006;82:49–51.
4. E J Lim, J Haar and J Morgan Can text-messaging results reduce time to treatment of Chlamydia trachomatis? *Sex Transm Infect* 2008 84: 563-564 originally published online August 22, 2008
  5. Levine D, McCright J, Dobkin L, Woodruff AJ, Klausner JD. SEXINFO: a sexual health text messaging service for San Francisco youth. *Am J Public Health*. 2008 Mar;98(3):393-5.
  6. Washington AE, Johnson RE, Sanders LL Jr. Chlamydia trachomatis infections in the United States. What are they costing us? *JAMA*. 1987 Apr 17;257(15):2070-2.
  7. Source: Centers for Disease Control and Prevention : Chlamydia- CDC Fact Sheet. Sexually Transmitted Diseases. <http://www.cdc.gov/std/chlamydia/STDFact-chlamydia.htm>. Last accessed 12/2/2009
  8. U.S. Preventive Services Task Force: Screening for Chlamydia infection: recommendations and rationale. *Am J Prev Med* 2001; 20 (3 Suppl). 90
  9. Centers for Disease Control Academy for Educational Development: Summary of a Review of the Literature: Programs to Promote Chlamydia Screening; April 12, 2007
  10. Rand CM, Shone LP, Albertin C, Auinger P, Klein JD, Szilagyi PG. National health care visit patterns of adolescents: implications for delivery of new adolescent vaccines. *Arch Pediatr Adolesc Med*. Mar 2007;161(3):252-259.
  11. Fortuna RJ, Robbins BW, Halterman JS. Ambulatory Care Among Young Adults in the United States. *Ann Intern Med*. 2009;151:379-385.
  12. Chiardonna, C. “ The Chlamydia Cascade: Enhanced STD Prevention Strategies for Adolescents”; *J Pediatr Adolesc Gynecol* (2008) 21; 233-241

# Basic Science & Clinical Research

**Louis Okafor MS2**

**Preceptors:**

**James Sanders, M.D. Department of Orthopaedics  
University of Rochester Medical Center**

**Stephen Cook, M.D., MPH Department of Pediatrics  
University of Rochester Medical Center**

**John Faust, M.D. Department of Orthopaedics  
University of Rochester Medical Center**

## **Demographic Risk of Slipped Capital Femoral Epiphysis and Adolescent Tibia Vara Among Obese Children**

**Introduction:**

Adolescent Tibia Vara (ATV) is a growth disorder involving the medial portion of the proximal tibial growth plate that produces a localized varus deformity. The incidence is greater if the child is obese, has an affected family, and resides in certain geographical locations. The cause is unknown, but it has been theorized that in susceptible individuals, mechanical stress damages the proximal medial growth plate during the normal stage of bowing thus converting physiological bowlegs into tibia vara.<sup>18</sup>

Slipped capital femoral epiphysis (SCFE) is a failure of the upper femoral epiphysis allowing displacement of the femoral head on the neck. The condition is often associated with genetic and geographic factors. The causes of SCFE are complex. Multiple factors contribute to a mechanical failure of the growth plate. Growth plate failure occurs when mechanical stress exceeds the strength of the plate. The hip is anatomically vulnerable because of the biomechanics of the joint. Loading across the hip joint is about four times body weight. The growth plate is relatively weaker than other skeletal components during puberty. Overloading of a vulnerable hip, as such with obese individuals, leads to a failure of the growth plate and SCFE.<sup>18</sup>

**Objective:**

To determine if patients with SCFE or ATV that cannot be attributed to a congenital, endocrine, or metabolic bone disorder are more likely to reside in a demographically high risk areas than other children.

**Background:**

SCFE and ATV result in a decreased tendency to participate in physical activities due to the pain associated with each disease. These diseases occur far more frequently in obese than in slender children<sup>1-17</sup>. Subsequent weight gain and long term disability often ensue later in life due to the inability to exercise.

The University Rochester has developed a database of the community with the goal of identifying populations at risk for nutritional related disorders. This database may provide further understanding of the role demographics play in these two musculoskeletal disorders of childhood obesity. If this is the case, then it should allow more targeted prevention of these lifetime disorders.

**Methods:**

The billing records of the Department of Orthopaedics and Rehabilitation were searched for the

ICD-9 codes for slipped capital femoral epiphysis (732.20) and adolescent tibia vara (736.42) from 2000-2010. Males and females aged 7 to 16 years old were selected. This search returned 98 patients with SCFE and 14 patients with ATV were found. The charts were then reviewed for specific data points to include: date of injury, diagnosis, or surgery; age; height and weight; gender; race; address; insurance type; medications; and previous medical diagnoses. After chart review patients with SCFE or ATV secondary to a congenital, endocrine, or metabolic bone disorder were excluded. 93 SCFE patients and 7 ATV patients met inclusion criteria for the study.

The billing records of the Department of Orthopaedics and Rehabilitation were searched for the ICD-9 codes for distal radius/ulna fractures (813.40, 813.41, 813.42, 813.44) from 2000-2010 in order to design the control population. Children with distal radius/ulna fractures were selected as a control population because there is no association with these fractures and obesity or BMI. The aim was to choose a control group that represented "normal" children. Males and females aged 8-16 years old were selected. This search returned 15,023 patients. For statistical purposes four control patients were chosen for every patient with SCFE or ATV. Patients with distal radius/ulna fractures were separated by gender and age. The fracture patients were then placed into random order using a random sequence of numbers generated by a free program available on [www.random.org](http://www.random.org). The charts were then reviewed for specific data points to include: date of injury, diagnosis, or surgery; age; height and weight; gender; race; address; insurance type; medications; and previous medical diagnoses. Patients with distal radius/ulna fractures secondary to a congenital, endocrine, or metabolic bone disorder were excluded. This generated a control group of 400 patients randomly selected from the 15,023 patients found on the initial search. This control group was age and gender matched to SCFE and ATV patients. Controls were deliberately not filtered by geographic location. This method allowed us to obtain a truly random sample of age and gender matched from controls without a congenital, endocrine, or metabolic bone disorder and of all heights and weights from the entire geographic area treated by our department.

Data from the charts reviews were collected on a form designed for this study. The data from the forms was entered into Microsoft Access to create a database. The patient database was then analyzed and compared to a demographic database to determine the demographic risk factors for SCFE and ATV compared to the control group. Standard statistical techniques were utilized to evaluate the data.

### **Results/Conclusion:**

Pending completion of project.

### **References:**

1. **Benson, E. C.; Miller, M.; Bosch, P.; and Szalay, E. A.:** A new look at the incidence of slipped capital femoral epiphysis in New Mexico. *J Pediatr Orthop*, 28(5): 529-33, 2008.
2. **Beskin, J. L.; Burke, S. W.; Johnston, C. E., 2nd; and Roberts, J. M.:** Clinical basis for a mechanical etiology in adolescent Blount's disease. *Orthopedics*, 9(3): 365-70, 1986.
3. **Bowen, J. R.; Assis, M.; Sinha, K.; Hassink, S.; and Littleton, A.:** Associations among slipped capital femoral epiphysis, tibia vara, and type 2 juvenile diabetes. *J Pediatr Orthop*, 29(4): 341-4, 2009.
4. **Chan, G., and Chen, C. T.:** Musculoskeletal effects of obesity. *Curr Opin Pediatr*, 21(1): 65-70, 2009.
5. **Davids, J. R.; Huskamp, M.; and Bagley, A. M.:** A dynamic biomechanical analysis of the etiology of adolescent tibia vara. *J Pediatr Orthop*, 16(4): 461-8, 1996.
6. **Dunbar, J., and Goulding, A.:** Slipped capital femoral epiphysis: more New Zealand cases likely as obesity rises in children and adolescents? *N Z Med J*, 114(1145): 559-60, 2001.

7. Gordon, J. E.; Hughes, M. S.; Shepherd, K.; Szymanski, D. A.; Schoenecker, **P. L.**; **Parker, L.**; and **Uong, E. C.**: Obstructive sleep apnoea syndrome in morbidly obese children with tibia vara. *J Bone Joint Surg Br*, 88(1): 100-3, 2006. **Henderson, R. C.**: Tibia vara: a complication of adolescent obesity. *J Pediatr*, 121(3): 482-6, 1992.
8. **Lim, Y. J.**; **Kagda, F.**; **Lam, K. S.**; **Hui, J. H.**; **Lim, K. B.**; **Mahadev, A.**; and **Lee, E. H.**: Demographics and clinical presentation of slipped capital femoral epiphysis in Singapore: comparing the East with the West. *J Pediatr Orthop B*, 17(6): 289-92, 2008.
9. **Loder, R. T.**: The demographics of slipped capital femoral epiphysis. An international multicenter study. *Clin Orthop Relat Res*, (322): 8-27, 1996.
10. **Loder, R. T.**; **Aronson, D. D.**; and **Greenfield, M. L.**: The epidemiology of bilateral slipped capital femoral epiphysis. A study of children in Michigan. *J Bone Joint Surg Am*, 75(8): 1141-7, 1993.
11. **Manoff, E. M.**; **Banffy, M. B.**; and **Winell, J. J.**: Relationship between Body Mass Index and slipped capital femoral epiphysis. *J Pediatr Orthop*, 25(6): 744-6, 2005.
12. **Murray, A. W.**, and **Wilson, N. I.**: Changing incidence of slipped capital femoral epiphysis: a relationship with obesity? *J Bone Joint Surg Br*, 90(1): 92-4, 2008.
13. **Poussa, M.**; **Schlenzka, D.**; and **Yrjonen, T.**: Body mass index and slipped capital femoral epiphysis. *J Pediatr Orthop B*, 12(6): 369-71, 2003.
14. **Restrepo, R.**, and **Reed, M. H.**: Impact of obesity in the diagnosis of SCFE and knee problems in obese children. *Pediatr Radiol*, 39 Suppl 2: S220-5, 2009.
15. **Sorensen, K. H.**: Slipped upper femoral epiphysis. Clinical study on aetiology. *Acta Orthop Scand*, 39(4): 499-517, 1968.
16. **Wills, M.**: Orthopedic complications of childhood obesity. *Pediatr Phys Ther*, 16(4): 230-5, 2004.
17. **Staheli, Lynn T.** *Practice of Pediatric Orthopedics*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2006. Print. Pg. 84-85; 188

## Basic Science & Clinical Research

Millicent Okereke, MS2

**Preceptor:**

**Lourdes Oriana Linares, PhD Associate Professor of Pediatrics  
Associate Professor of Psychiatry  
Mount Sinai Adolescent Health Center**

**Nudel, M., Okereke, M., Phillip, G. Linares, L.O. & Diaz, A. A Preliminary Study of Cortisol Reactivity among High Risk Adolescent Females engaged in Perpetration Teen Dating Aggression. *Mount Sinai Adolescent Health Center (MSAHC).***

**Introduction.** Given that the ability to respond to an acute stressor by raising cortisol is important for health, the identification of underlying physiological dysregulation among female adolescent patients engaged in acts of teen dating aggression has high public health significance. Previous studies have shown that adolescent girls engage in high levels of physical dating aggression toward their romantic partners both as perpetrators and victims. It is also known that aggressive youth and those with histories of child maltreatment are at highest risk for altered cortisol responses in response to a laboratory stressor (cortisol reactivity). Altered cortisol slopes among these high-risk youth have been characterized by not showing an increase in levels of cortisol following a stressor, nor do they have a gradual flattening of response (i.e., flattening slopes).

**Purpose.** Using an ecologically valid stressor test in the laboratory, this pilot study explored resting and reactivity cortisol levels among female adolescents served at an inner city adolescent health clinic in New York City. We hypothesized that teen females engaged in perpetrating physical aggression (PDA) toward their romantic partners are more likely to show hypothalamic- pituitary-adrenal (HPA)-axis dysregulated cortisol reactivity (i.e., flattening of slopes) as compared to those who were not (No PDA).

**Methods.**

The sample. The preliminary sample comprised of N = 20 female teen patients ages 14- 17 who were recruited from waiting rooms at MSAHC. 79% of those eligible (sexually active, not pregnant, with a sibling +/-in the home) agreed to participate. Mean age was 16.9 (.9) years; they lived in a single parent household (77%), and mostly belong to ethnic minority backgrounds (53% Latina, 27% African American). Self-reports gathered face-to-face showed that in the past 30-days 20% drank alcohol weekly, and 47% smoked marijuana at least once. In regard to child maltreatment history, 20% reported moderate to severe physical abuse, 47% sexual abuse, 47% physical neglect, with 75% reporting at least one child maltreatment type (CTQ); 57% experienced sibling physical aggression (SAS); and 80% reported CES depression scores above clinical cutoff (>16). Thus, the sample is characterized as showing high levels of exposure to family violence, health-related risk behaviors, and psychological distress symptoms.

Procedures. Participants provided written parental consent (and child assent) or adolescent informed consent. Safeguards to protect the safety of subjects approved by the IRB were in place. Participants completed a 2-hour clinic visit which included face-to-face health risk self-reports (AddHealth, CTQ, SAS, CTS2, CES, PTSD), behavioral ratings following the lab stressor (attitudes toward violence and emotional distress), and cortisol samples at resting and reactivity periods. An independent clinician met with each participant to discuss her reactions to the test and give her the opportunity for a referral to the on-site mental health clinic. Participants were asked to refrain from eating, drinking, or smoking during the visit

The stress test. The *Attitudes toward Interpersonal Violence Assessment (AIVA; Reese- Weber, 2008)* was administered to assess cortisol reactivity. This 3-minute assessment provides visual stimuli for

the observation of adolescent dating violence. The AIVA uses standardized video vignettes of increasingly violent interactions between a male and a female adolescent (age 15). About half of subjects viewed the female aggressor version while the other half viewed the male aggressor version.

**Cortisol collection.** Native saliva was collected using Salivette synthetic rolls; six salivary cortisol samples were gathered at identical time intervals in minutes before (at -45, -25, -5) and after (at +20, +40, and +60) viewing the AIVA stressor (0). The time prior to the administration of the stress test was defined as the resting measure of log cortisol, while the post- AIVA was considered log cortisol reactivity. To reduce diurnal variability, testing was done between 1-5 pm when cortisol is most stable. To ensure quality of specimen we also tracked use of birth control pills (27%), medications (13%), inhaler for asthma (20%), hydrocortisone cream (13%), and physical activity (7%) and verbal disagreement (50%) in the past 24-hours.

**Cortisol assays.** Assessment of unbound salivary cortisol concentrations (in nmol/l) reflected the level of unbound cortisol as determined by DELFIA enzyme immunoassay conducted at the University of Trier. Container was centrifuged at 2000g for 10 minutes and assaying was done in duplicate. The coefficients of variation were between 4.0% and 6.7% and the corresponding inter-assay coefficients of variation were between 7.1% and 9.0%.

## Results

In the CTS2, 53% of the sample reported at least one severe physical assault act towards partner such as slamming against a wall, kicking, beat-up (perpetration group), while 27% reported being victimized by partner (pushing, grabbing, slapping) at least once. Intercorrelation between PDA perpetration and victimization was .30. Higher scores in female perpetration of severe PDA were associated with victimization by their partners ( $r = .24$ ), perceived emotional distress following the stressor ( $r = .25$ ), association with deviant friends ( $r = .32$ ), PTSD symptoms ( $r = .25$ ), and 30-day marijuana use ( $r = .36$ ).

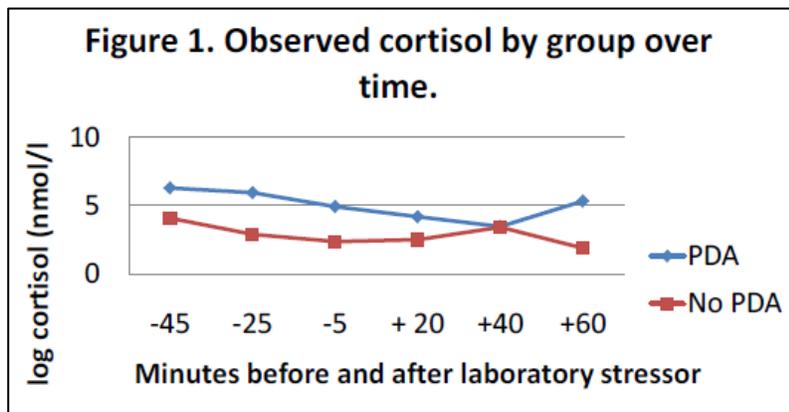


Figure 1 shows that perpetrators (PDA group) and non-perpetrators (No PDA group) showed a descending slope at resting (before the stressor) which continued over time following the presentation of the stressor. After exposure to the stressor, teens in the PDA group tend to show a delayed increase of cortisol at +60 minutes, while teens in the No PDA group showed no such increase and instead showed flattening of cortisol over time.

## Conclusions

High levels of perpetration of physical dating aggression and exposure to family violence were reported in this sample. Preliminary results suggest that overall female adolescents were largely non-reactive to the laboratory stressor (i.e., flattening of cortisol concentration at resting which continued at the reactivity phase). Our findings are consistent with those recently found by Mac Millan et al., 2009 (Biological Psychiatry 66:62-68) for female adolescents with histories to child maltreatment. Furthermore, as compared to the No PDA group, a delayed increase in cortisol concentration found in the PDA group deserves further scrutiny.

# Basic Science & Clinical Research

**Ben Peterson, MS2**

**Preceptor: Robert Frisina, Ph.D.**

**Otolaryngology Assoc. Chair Professor of Otolaryngology, Biomedical Engineering and Neurobiology & Anatomy  
Assoc. Director - International Center for Hearing & Speech  
University of Rochester Medical Center**

## **The Aging Auditory System: Presbycusis and Hormonal Influences**

**Introduction:** Aldosterone is a steroid hormone secreted from the adrenal cortex. It plays a critical role in the regulation of Na and K balance throughout the body, inducing transcription and translation of Na/K ATPase and NKCC. This particular effect has been observed in the inner ear (Pitovski et al., 1993). Several studies have shown that serum aldosterone levels decrease with age in humans as well as in rodents (e.g. Mulkerin et al., 1995; Kau et al., 1999).

**Objective:** The aim of this study was to gather new data on the range of aldosterone levels in young adult and aged mice. By doing so, we hoped to quantify age-related declines in serum aldosterone levels and their relations to presbycusis, as has been done in humans. This is to prepare for potential future experiments in which aldosterone supplementation could be explored as a possible treatment for presbycusis for mice with naturally decreased serum aldosterone levels.

**Background:** Cochlear function is highly dependant upon the maintenance of an appropriate endocochlear potential. The stria vascularis maintains this potential by transporting and cycling K<sup>+</sup> ions through the endolymph (Salt et al., 1986-87). Na/K ATPase channels as well as Na/K/2Cl Co-transporters (NKCC) are crucial for K<sup>+</sup> transport from the perilymph and from the surrounding cells. Previous studies have shown that individuals with imbalanced Na/K-ATPase and NKCC channels in the cochlea experience defective K<sup>+</sup> transport in the endolymph and hearing loss (e.g. Schmidt et al., 2002).

While no direct connection has been made regarding the effect of serum aldosterone levels on presbycusis, a recent study has shown a correlation between low serum aldosterone levels and severity of presbycusis in aged humans (Tadros et al., 2005). In CBA/CaJ mice, we hope to directly investigate the role of aldosterone in cochlear K<sup>+</sup> transport, and its possible protective effects against presbycusis.

**Methods:** We measured auditory brainstem responses (ABRs) and otoacoustic emissions (DPOAE) levels in young adult (3-4 mon, N=10) and old (22-24 mon, N=2) CBA mice, along with their serum aldosterone levels upon sacrifice after the completion of the hearing tests.

Mice were anesthetized with a mixture of ketamine/xylazine (120 and 10 mg/kg body weight, respectively, intraperitoneal injection) prior to all experimental sessions. All recording sessions were completed in a soundproof acoustic chamber (IAC lined with Sonex) with body temperature maintained with a heating pad. ABR and DP-grams were acquired and 2 or more trials were obtained for each mouse, with the recording session duration limited by depth of anesthesia. Duration of testing was up to one hour per animal. DP grams and ABR recordings were obtained in a manner similar to previous publications (Jacobson et al., 2003; Guimaraes et al., 2004; Varghese et al., 2005). The mice were then allowed to lie undisturbed for one hour before they were sacrificed by carotid arterotomy for sample collection, followed by cervical dislocation. Samples were allowed to coagulate at room temperature for 45 minutes and then spun at 3000 Hz for 30 minutes. Serum was collected in eppendorf tubing and sent to ARUP laboratories

in Salt Lake City, Utah for analysis.

**Results/Discussion:** Eight of the young animals' samples had to be combined among litter-mates because of sample size smaller than 0.5 cc, producing only four samples. They ranged from 19.4-35.4 ng/dl (within the expected range). However, the other two young animals as well as the two old animals produced samples just under 0.6cc. These samples were unable to be read reliably. While the two old animals showed Presbycusis by their DPOAE and ABR thresholds, we were unable to correlate their serum aldosterone levels with their hearing loss due to insufficient blood sample size. Two more young animal samples as well as six more old (24-30 months) animal samples are needed to complete the study. Each sample will need to be significantly greater than 0.6cc, requiring two animals per sample.

### **References:**

Guimaraes, P., Zhu, X., Cannon, T., Kim, S-H., Frisina, R.D. (2004) Sex Differences in Distortion Product Otoacoustic Emissions as a Function of Age in CBA Mice. *Hearing Research*. 192:83-89.

Jacobson M., Kim SH., Romney J., Zhu X., Frisina R.D. (2003) Contralateral suppression of distortion-product otoacoustic emissions declines with age: A comparison of findings in CBA mice with human listeners. *Laryngoscope*. 113:1707-1713.

Kau MM, Chen JJ, Wang SW, Cho WL & Wang PS, (1999) Age-related impairment of aldosterone secretion in zona glomerulosa cells of ovariectomized rats. *J. Invest. Med.* 47:425- 432.

Mulkerrin E, Epstein FH & Clark BA, (1995) Aldosterone responses to hyperkalemia in healthy elderly humans. *J. Am. Soc. Nephrol.* 6:1459-1462.

Pitovski, D.Z., Drescher, M.J., Kerr, T.P. & Drescher, D.G. (1993) Aldosterone mediates an increase in [3H] ouabain binding at Na<sup>+</sup>, K<sup>+</sup>-ATPase sites in the mammalian inner ear. *Brain Res.* 601, 273-278.

Salt, A.N., Thalmann, R., Marcus, D.C., Bohne, B.A. (1986) Direct measurement of longitudinal endolymph flow rate in the guinea pig cochlea. *Hear. Res.* 23:141-151.

Salt, A.N., Melichar, R., Thalmann, R. (1987) Mechanisms of endocochlear potential generation by stria vascularis. *Laryngoscope*. 97: 984-991.

Schmiedt RA, Lang H, Okamura H, Schulte BA. (2002) Effects of furosemide applied chronically to the round window: A model of metabolic presbycusis. *J Neurosci* 22:9643-9650.

Tadros, S.F., Frisina, S.T., Mapes, F., Frisina, D.R., Frisina, R.D. (2005) High Serum Aldosterone Levels Correlate with Lower Hearing Thresholds in Aged Humans: A Possible Protective Hormone against Presbycusis. *Hearing Research*. 209:10-18.

Varghese, G.I., Zhu, X., Frisina, R.D. (2005) Age-related declines in contralateral suppression of distortion product otoacoustic emissions utilizing pure tones in CBA/CaJ mice. *Hearing Res.* 209:60-67.

## Basic Science & Clinical Research

Clifford A. Pierre, MS2

**Preceptor:**

**G. Edward Vates, M.D., Ph.D.**

**Assistant Professor of Neurological Surgery Department of Neurosurgery  
University of Rochester Medical Center**

### **The Effect of Bradykinin on Astrocyte Regulation of Blood Flow**

**Introduction:** Post-subarachnoid hemorrhage (SAH) vasospasm cause of stroke resulting in neurologic injury in a younger patient population than is typically seen for ischemic stroke. Cerebral vasospasm is the reversible process of reduction in vessel diameter that occurs several days after SAH, intracerebral hemorrhage, or brain trauma. Vasospasm induced by SAH can lead to ischemia and infarction and thus poor neurologic outcome or death. Preliminary studies have demonstrated that microcirculatory dysfunction due to SAH is also associated with local hypoxia, astrocytosis, and decreased function of astrocyte to initiate  $Ca^{2+}$  dependent vasodilation.

**Objective:** Bradykinin is a highly active proinflammatory peptide hormone that is released during various kinds of tissue injury. SAH causes astrocytes to have abnormal calcium metabolism, leading to impaired astrocyte regulation of blood flow, and this may be mediated by bradykinin that is released in the brain as part of the inflammatory response initiated within 24-48 hours of SAH. Recent work has suggested that bradykinin may mimic some of the effects of SAH on microcirculation. In the present study, we directly analyzed whether bradykinin effects calcium signaling and brain perfusion in both normal and SAH mice.

**Methods:** FVB/NJ mice were injected with SAH and arranged for *in vivo* imaging using techniques previously described. We monitored astrocyte calcium signaling using calcium-sensitive fluorescent dyes. The effects of bradykinin superfusion onto the brain surface on astrocyte calcium signaling, and perfusion was then studied in both SAH and control animals using stereologic techniques.

**Results:** Astrocyte calcium signaling was quantified as change over baseline fluorescence and cerebral blood perfusion was measured. We observed that bradykinin superfusion caused elevation of astrocyte intracellular calcium as compared to mice superfused with phosphate buffered saline, although this change was qualitative; we are in the process of developing quantitative techniques to more rigorously define this effect. Bradykinin treatment also appeared to cause an increase in capillary blood perfusion in normal mice, but in SAH mice bradykinin treatment caused variable changes in capillary perfusion, suggesting that the effect was either not as robust, or was variable due to reasons yet unknown.

**Conclusion:**

Qualitatively, it appeared that astrocytic intracellular calcium signaling increased after the superfusion of bradykinin in SAH mice, in addition, notable increase in capillary blood perfusion for control mice and less robust effects in SAH mice. This suggests that bradykinin may play a role in mediating astrocytic response and microcirculation postSAH, but larger numbers of treatment animals and quantitative assessment of calcium signaling are needed. Further investigation of microcirculatory failure could lead to increased knowledge of the pathophysiological mechanism of vasospasm and brain ischemia after SAH, and may lead to clinical therapeutic interventions

## References

1. Agulhon C, Petravicz J, McMullen AB, Sweger EJ, Minton SK, Taves SR, Casper KB, Fiacco TA, McCarthy KD. What is the role of astrocyte calcium in neurophysiology? *Neuron*. 2008 Sep 25;59(6):932-46.
2. Austinat M, Braeuninger S, Pesquero JB, Brede M, Bader M, Stoll G, Renné T, Kleinschnitz C. Blockade of bradykinin receptor B1 but not bradykinin receptor B2 provides protection from cerebral infarction and brain edema. *Stroke*. 2009 Jan;40(1):285-93. Epub 200
3. Fiacco TA, Agulhon C, Taves SR, Petravicz J, Casper KB, Dong X, Chen J, McCarthy KD. Selective Stimulation of Astrocyte Calcium In Situ Does Not Affect Neuronal. Excitatory Synaptic Activity. *Neuron*. 2007 May 24;54(4):611-26.
4. Gröger M, Lebesgue D, Pruneau D, Relton J, Kim SW, Nussberger J, Plesnila N. Release of bradykinin and expression of kinin B2 receptors in the brain: role for cell death and brain edema formation after focal cerebral ischemia in mice. *J Cereb Blood Flow Metab*. 2005 Aug;25(8):978-89.
5. Macdonald RL, Pluta RM, Zhang JH. Cerebral vasospasm after subarachnoid hemorrhage: the emerging revolution. *Nat Clin Pract Neurol*. 2007 May;3(5):256-63.
6. Sehba, FA, Bederson, JB. Mechanisms of Acute Brain Injury After Subarachnoid Hemorrhage. *Neurological research* 2006 Jun 28(4):381-98,
7. Takano T, Tian GF, Peng W, Lou N, Libionka W, Han X, Nedergaard M. Astrocyte-mediated control of cerebral blood flow. *Nat Neurosci*, 2006. 9(2): p. 260-7
8. Trabold R, Erös C, Zweckberger K, Relton J, Beck H, Nussberger J, Müller-Esterl W, Bader M, Whalley E, Plesnila N. The role of bradykinin B(1) and B(2) receptors for secondary brain damage after traumatic brain injury in mice. *J Cereb Blood Flow Metab*. 2010 Jan;30(1):130-9. Epub 2009 Sep 23.
9. Vates GE, Nottebohm F. Feedback circuitry within a song-learning pathway. *Proc Natl Acad Sci (USA)* 1996;92:5139-5143.

# Basic Science & Clinical Research

**Benjamin A. Plog, MS2**

**Preceptor:**

**Dr. G. Edward Vates, M.D., Ph.D.**

**Assistant Professor, Department of Neurosurgery University of Rochester Medical Center**

## **SAH induced changes in microglia and the impact on capillary function**

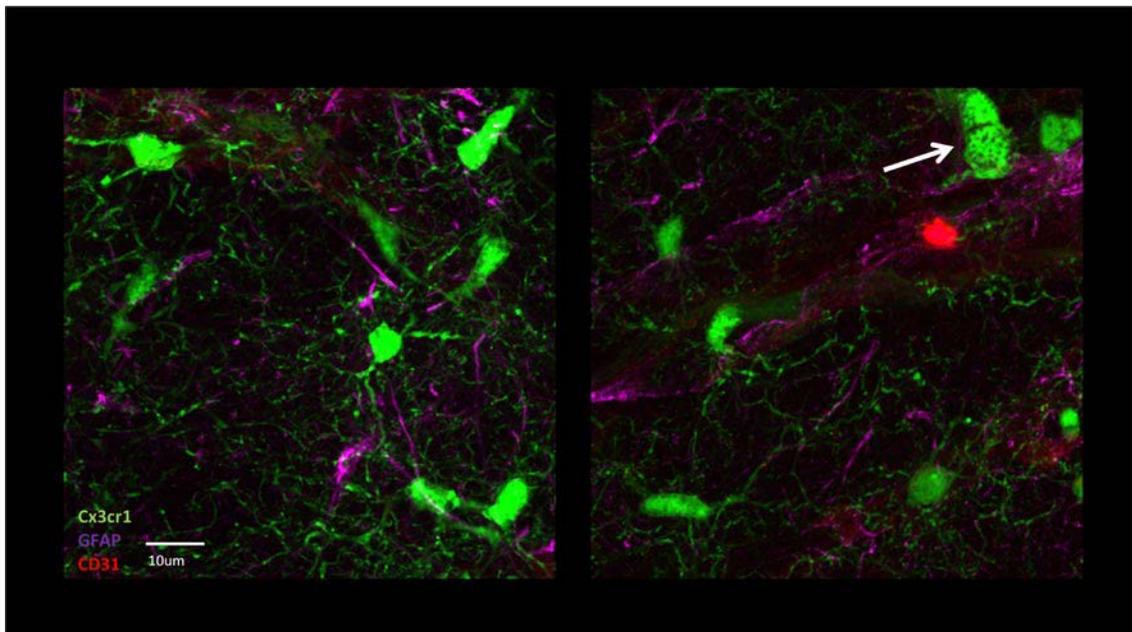
**Introduction:** Subarachnoid hemorrhage (SAH) is a devastating neurologic event that causes poor neurologic outcomes in patients for a variety of reasons. Cerebral vasospasm is a common consequence of SAH, and can cause cerebral ischemia and infarction [1]. Many patients with vasospasm, however, do not necessarily develop strokes, and many patients with ischemia-related neurologic deficits do not demonstrate vasospasm [1, 4, 5]. This has led to a reinvigorated search for other mediators of neurologic injury after SAH.

**Background:** Recent work has suggested that SAH causes significant changes in capillary function independent of vasospasm, which can then lead to cerebral infarction and poor patient outcomes [1, 2, 3]. Work from this laboratory has shown that SAH leads to capillary failure, brain hypoxia, and neuronal injury and death [6]. Using *in vivo* 2-photon laser scanning microscopy, our laboratory has developed novel assays for looking at capillary blood flow, and have shown that SAH causes changes in capillary blood flow that are not related to vasospasm. However, the biologic mechanisms by which SAH induces changes in the capillaries remain poorly defined. Microglia are the resident inflammatory cells in the brain. There is some evidence that SAH can cause activation of microglia [7], but the time course and degree of microglial activation after SAH remains poorly described, in part because the quantification of microglial activation has depended on immunohistochemically techniques that are prone of artifacts.

**Objective:** To demonstrate SAH causes activation of microglia within 48 hours, using novel transgenic mice expressing green fluorescent protein under the *cx3cr1* promoter.

**Methods:** We used a transgenic mouse model that expresses eGFP under the control of the endogenous *cx3cr1* locus; in these mice, microglia selectively express eGFP and are visible with confocal microscopy. We performed either SAH or SHAM in age and sex matched mice, using an autologous blood injection model of SAH, and then waited either 6 or 48 hours to perform routine immunohistochemistry for CD 31 (to label endothelial cells) and GFAP (to label astrocytes). Using confocal microscopy, we examined SAH-induced changes in microglial morphology, which was quantified using a stereological system created in our lab. The signal generated by each microglia, after noise had been subtracted, could be used to compute the area of each of these microglia in a single plane. By adding up the areas over every plane of imaging a regional volume for each microglia could be generated.

**Results & Discussion:** Mean microglial volume in SAH mice, when compared to SHAM mice, was significantly reduced at 48 hours (10531.481 +/- 1422.465 vs. 17038.500 +/- 3144.091,  $p = 0.035$ ). Further, at the 6-hour time point the same relationship between SAH and SHAM microglial volume was identified (19981.867 +/- 1928.497 vs. 27484.476 +/- 5587.957,  $p = 0.108$ ), although the reduction of cell volume was not statistically significant at 6 h. The reduced microglial volume seen in SAH mice when compared to SHAM is in accordance with the biology of microglia. When microglia are quiescent they have many thin, ramified processes that survey a wide local environment looking for injury-mediating agents. However, when activated (i.e. following SAH) they retract their processes and assume a more amoeboid morphology, ideal for phagocytosing and neutralizing potentially injurious substances. Consequently, it would be expected that silent microglia would occupy a much larger regional volume than microglia that are activated and have withdrawn their processes from the surrounding environment.



Microglia at 48 hours following SHAM (left) and SAH (right). Green signal corresponds to eGFP under the endogenous cx3cr1 promoter in microglia, purple signal corresponds to GFAP labeling for astrocytes, and red signal indicates CD 31 labeling for endothelial cells. White arrow demonstrates amoeboid microglial morphology corresponding to an activated state following SAH. Of particular interest here is the perivascular location of activated microglia, leading to the question do macrophages cross the blood brain barrier in response to CNS insult, or do microglia migrate towards capillaries and post-capillary venules following injury?

**Conclusion:** Subarachnoid hemorrhage causes activation of microglia within 48 hours as observed by reduced regional volume in comparison to SHAM microglia. What remains to be determined is if activated microglia, while retracting certain processes, specifically extend other processes toward capillaries and post-capillary venules. Future work using *in vivo* analysis with transgenic mice will determine if activated microglia extend processes specifically toward endothelial cells, and whether capillaries that are contacted by microglia are more likely to have reduced or absent transit of RBCs, suggesting a link between microglial activation and failure of the microvasculature after SAH.

#### References:

1. Macdonald, R.L., Pluta, R.M. & Zhang, J.H. Cerebral vasospasm after subarachnoid hemorrhage: the emerging revolution. *Nature clinical practice neurology* **3**, 256-263 (2007).
2. Ferguson, S. & Macdonald, R.L. Predictors of cerebral infarction in patients with aneurysmal subarachnoid hemorrhage. *Neurosurgery* **60**, 658-667; discussion 667 (2007).
3. Rosengart, A.J., Schultheiss, K.E., Tolentino, J. & Macdonald, R.L. Prognostic factors for outcome in patients with aneurysmal subarachnoid hemorrhage. *Stroke* **38**, 2315-2321 (2007).
4. Hansen-Schwartz, J., Vajkoczy, P., Macdonald, R.L., Pluta, R.M. & Zhang, J.H. Cerebral vasospasm: looking beyond vasoconstriction. *Trends in pharmacological sciences* **28**, 252-256 (2007).
5. Stein, S.C., Levine, J.M., Nagpal, S. & LeRoux, P.D. Vasospasm as the sole cause of cerebral ischemia: how strong is the evidence? *Neurosurgical focus* **21**, E2 (2006).
6. Vates, G.E., McConnell, E., Kang, H., Takano, T., & Nedergaard, M. Brain injury after subarachnoid hemorrhage can be reversed by capillary-specific therapy. Under submission, (2010).
7. Kitai, R., Hand, Y., Ishida, M., Nakagawa, T., Tsuchida, A., & Kubota, T. Activation of microglia after experimental subarachnoid hemorrhage in rats. Macdonald, R. Loch, comp. Cerebral Vasospasm: Advances in Research and Treatment. New York: Thieme, 2005.

## Basic Science & Clinical Research

**Jason Reminick, MS2**  
**Benjamin George**

**Preceptors:**  
**Nicholas Scoglio**  
**URMC**  
**Department of Neurology**

**Ray Dorsey, MD, MBA**  
**Associate Professor of Neurology, Johns Hopkins University**  
**Director, The Johns Hopkins Parkinson's Disease and Movement Disorders Center**

### **Establishing a Telemedicine Network for Nursing Home Care for Parkinson Disease**

**Introduction:** Telemedicine is the use of electronic communication technology to exchange medical information over some geographic distance between patient and physician to provide healthcare and improve patients' health status. To date, telemedicine has been shown to be clinically effective in treatment of a variety of diseases and conditions including acute pediatric care, stroke and epilepsy. While telemedicine provides an appropriate medium in which to administer a full Parkinson disease (PD) examination, use of this process is limited. Currently, ~40% of individuals with PD will eventually require nursing home or assisted living care, while 5.1-6.8% of all individuals in nursing homes have PD. However, many of these patients, while necessitating a high level of care and disease management, often lack access to neurologists, especially those with subspecialties in conditions such as PD. When evaluated by neurologists, less than half of these individuals are judged to be receiving optimal treatment. Although patients are at times transported out of the nursing home for doctors' appointments, such practices are often limited due to distance, travel and staffing costs. Telemedicine may bridge this distance gap to provide subspecialty care directly into the nursing home.

#### **Objective:**

- 1) To evaluate access to neurological care over the previous year for individuals residing in six nursing homes situated throughout upstate, New York (Avon, Conesus, Hornell, Newark, Seneca, and The Shore Winds in Rochester) in the ROHM Network of the Homes (a chain of 12 nursing homes in upstate, New York and one in Florida).**
- 2) To assess baseline characteristics for a longitudinal telemedicine study that will be conducted over the coming year.**

**Methods:** Nine residents with Parkinson and/or other movement disorders in three of the six nursing homes (Avon, Seneca, and Conesus) were enrolled in the study and were assessed for clinical characteristics at baseline (in-person) using the Unified Parkinson Disease Rating Scale (UPDRS), Montreal Cognitive Assessment (MoCA), and Minimum Data Set—a comprehensive assessment instrument required by Medicare and Medicaid for residents in certified nursing homes (data was provided by the nursing homes on behalf of the participants for which it was available). A survey of access to specialty care over the previous year was also conducted. No medication changes were made at this initial assessment.

**Results:** To date, assessments have been performed on nine residents (n=9, male = 1, female =8) in three of the six nursing homes within the telemedicine study. The mean age of the study participants was 80. In terms of clinical assessment, there was a mean UPDRS motor score (n=8) of 48.8 (range: 38-69) and mean

MoCA of 14.4/30 (range: 4-25). Minimum Data Set (n=8) revealed an average requirement of two or more person assists in bed mobility, transfer, and toilet use for those examined. Three study participants had sustained a fall in the past 180 days, one resulting in a hip fracture. 5/9 patients reported being treated by an internist or family practitioner for the care of their Parkinson disease. 2/9 reported receiving care from a general neurologist and 2/9 were receiving only in-facility care. No patients were currently being treated by a specialist or subspecialist and only one individual reported traveling in the past five years (~70 miles) to see a movement disorder specialist.

**Conclusion:** Individuals residing in the three nursing homes have significant disability as a result of their Parkinson disease, while having limited access to specialty neurological care due to distance from provider and mobility issues. Telemedicine may serve as an effective means to bridge this gap and provide the necessary care directly into the nursing home, although further study is needed. We are currently in the process of continuing to enroll patients and will begin the telemedicine leg of the study in the coming months. Additionally, a financial modeling study is being performed in parallel to assess the cost-effectiveness of telemedicine in collaboration with the Simon Graduate School of Business Administration. We expect both studies to be completed within a year.

# Basic Science & Clinical Research

Lindsay Rubenstein, MS2

**Preceptor:**

**Karl A. Illig, M.D. Professor & Chief  
Division of Vascular Surgery  
University of Rochester Medical Center**

## **Evaluation of Longitudinal Professional Outcomes with Respect to Performance on an Endovascular Simulation Task**

**Introduction:**

The use of simulator technology to teach endovascular procedures is emerging as an exciting and promising development in the surgical field. In 2003, an article in the *British Journal of Surgery* referred to surgical simulation as “a good idea whose time has come,” and foreshadowed that the technique will revolutionize medical education.<sup>1</sup>

Aside from its merits as a training aide, simulator technology can also be used as a so-called “rehearsal tool,” enabling surgeons to prepare for a specific procedure by using an individual patient’s actual anatomy in a virtual practice run. It is, therefore, not surprising that simulator technology is being lauded as having the potential to enhance surgical proficiency and to foster advancements in patient safety.

With such vast developments in the field of endovascular simulation, it is becoming increasingly important to understand how this tool will fit into various levels of medical education. This is particularly important with respect to the field of vascular surgery, which is progressively shifting from traditional fellowship training toward integrated five-year residency programs that students will enter right out of medical school.

Prior studies have assessed the ability of endovascular simulation tasks to improve the technical performance and continued interest level of preclinical medical students in vascular surgery,<sup>2</sup> but to our knowledge this study is the first of its kind to evaluate longitudinal outcomes, specifically with respect to residency choices.

**Background:**

A 2006 study at the University of Rochester Medical Center (URMC) entitled *Simulator Assessment of Innate Endovascular Aptitude versus Empirically Correct Performance* sought to further clarify the potential of use of simulator technology in teaching endovascular surgical techniques.<sup>3</sup> Performance of 26 medical students on an endovascular simulator task was measured with respect to time scores (calculated based on three consecutive simulator tasks) and subjects’ Modified Reznick Scale values (an average “performance score” derived from separate graded critiques by two attending surgeons). This project, along with the post-testing assessment model put forth by Lee, et al. (2009),<sup>2</sup> served as the basis for our current research.

**Objectives:**

The aim of this study was to develop a comprehensive questionnaire that could be used to follow-up with former subjects in order to determine if performance on endovascular simulator tasks correlates with later involvement or success in the surgical field.

**Methods:**

Subjects included the 26 participants who were medical students at the time of the original study. Initial contact was made by the primary investigator of that project, in collaboration with a current medical

student researcher. The SAFUS (Simulator Assessment Follow-Up Study) Questionnaire, which had been developed as a result of this collaboration, was administered either electronically or through telephone interview by student researchers. Data collection is ongoing, and all results below should be viewed as preliminary.

### **Results:**

One subject was excluded from data analysis due to failure to pursue a residency program upon completion of medical school. A second subject, currently an MD/PhD candidate, will be excluded until officially matched into a residency program. A third subject was excluded post-testing for choosing to drop out of the trial after being unable to complete the first simulator task; this subject later went on to pursue a medical specialty. The remaining subjects (n=23), were fairly evenly split between medical (n=12) and surgical (n=11) residency specialties.

As hypothesized, medical students who later went on to surgical specialties had faster completion times, with a mean of 359 seconds compared to a mean of 519 seconds for the medical specialty group. Interestingly, performance score data was fairly similar between the two groups with surgical and medical specialties having average scores of 11.1 and 10.7, respectively. Additional analyses to determine if these differences are significant, and also to examine other factors addressed in the SAFUS Questionnaire, are pending.

### **Conclusions:**

Preliminary results suggest that medical students who chose to pursue surgical residencies displayed, on average, slightly superior performance on endovascular surgery simulation tasks while in medical school. Further analysis of SAFUS Questionnaire data such as the factors most important in cultivating specialty interest and the influence of simulator exposure on specialty choice is necessary to appreciate fully the results of this study. These findings have the potential to provide valuable information pertaining to the development and implementation of surgical simulation in the assessment and recruitment of medical students for surgical residency programs, particularly in the field of vascular surgery.

### **References:**

1. Champion HR, Gallagher AG. Surgical simulation- a good idea whose time has come. *British J Surgery* 2003; 90(7): 767-768.
2. Lee JT, Qiu M, Teshome M, Raghavan SS, Tedesco MM, Dalman RL. The utility of endovascular simulation to improve technical performance and stimulate continued interest of preclinical medical students in vascular surgery. *J Surg Educ* 2009; 66(6): 367-373.
3. Hislop SJ, Hsu JH, Narins CR, Gillespie BT, Jain RA, Schippert DW, Almudevar AL, Illig KA. Simulator assessment of innate endovascular aptitude versus empirically correct performance. *J Vasc Surg* 2006; 43(1): 47-55.
4. Tsang JS, Naughton PA, Leong S, Hill AD, Kelly CJ, Leahy AL. Virtual reality simulation in endovascular surgical training. *Surgeon* 2008; 6(4): 214-220.
5. Cates CU, Patel AD, Nicholson WJ. Use of virtual reality simulation for mission rehearsal for carotid stenting. *JAMA* 2007; 297(3): 265-266.

## Basic Science & Clinical Research

Dan Schatz, MS2

Preceptors: Paul Allen, PhD

Gary Paige, M.D./PhD

Department of Neurobiology and Anatomy University of Rochester Medical Center

### **Deficits in Auditory and Vestibular Function in Episodic Ataxia Type-1: A Study of Physiology and Phenotypic Presentation.**

**Introduction:** Episodic Ataxia type-1 (EA-1) is a channelopathy caused by a mutation in the KCNA1 gene that presents in patients with deficits in motor control as evident by tremors, fasciculations, seizures and loss of coordination. Targeted deletion of the homologous Kcna1 mouse gene results in profound deficits in auditory spatial discrimination behavior. The effects of KCNA1 mutation on the spatial hearing of EA-1 patients is currently unknown.

**Objective:** To determine the effect of the KCNA1 mutation present in EA-1 patients on auditory spatial localization.

**Background:** Smooth and coordinated movement within the environment demands the integration of multiple sensory systems including the auditory system. The auditory pathway uses interaural timing and intensity differences to construct a map of the environment requiring the precise function of many neurobiological mechanisms. One such is the Kv1.1 protein, a Shaker-type DTX-sensitive low-threshold voltage gated potassium channel subunit. Kv1.1 is highly expressed in the auditory brainstem of mice (Grigg et al. 2000)<sup>1</sup>. Targeted deletion of the Kcna1 gene, which codes for Kv1.1 in the mouse (Smart et al. 1998)<sup>2</sup> has been used to assess the role of Kv1.1 channel subunits in hearing; in vivo (Kopp-Scheinflug et al. 2003)<sup>3</sup> in vitro (Gittelmaan and Tempel, 2006)<sup>4</sup> and behaviorally (Allen et al. 2003)<sup>5</sup>. Kcna1 knockout mice have abnormal stimulus coding in their binaural brainstem nuclei, and behaviorally they exhibit deficits in sound localization. This lead us to hypothesize that auditory deficits will be present in human EA-1 patients who present with a variety of point mutations in the KCNA1 gene (Browne et al. 1994)<sup>6</sup>.

**Methods:** Utilizing the subject database of the CINCH collaboration, three patients with EA-1 were identified for this study, and age-matched normal subjects were used for comparison. After an initial interview subjects were screened using the clinical neurological exam, audiograms, hearing-in-noise testing, visual acuity, video-oculography and nystagmography for signs of neurological, ophthalmic, auditory, and vestibular pathology. Auditory localization experiments were conducted in a dark sound-attenuated room with a black screen covering a speaker two meters away from the subject. A robotic arm moves the speaker to 80 different precise locations without the subject's knowledge and repeated for four different frequency bands (250-500 Hz, 1000-1250 Hz, 1250-1575 Hz and 1500-1890 Hz). Subjects localized the target by joystick pointing. Additional auditory testing was conducted under headphones using adaptive psychoacoustics at multiple different frequency bands (500-750 Hz, 750-1000 Hz, 1000-1250 Hz and 1250-1500 Hz). Finally, a sound localization questionnaire was developed and administered.

**Results:** All three EA-1 patients had age-appropriate auditory thresholds. Interaural timing difference thresholds as tested by headphones was normal for all three EA-1 patients at 500-750 Hz. However, one patient had a notably elevated threshold for the 1000-1250 Hz band and all three patients showed elevated thresholds for the 1250-1500 Hz band. Despite normal accuracy of free field sound localization in the

250-500 Hz band results were notable for an abnormally large number of accuracy errors in the 1000-1250 Hz band in one subject while all three subjects had a markedly increased number of accuracy errors in the 1250-1500 and 1500-1890 Hz bands. Precision in the free field sound localization was age appropriate for two of the three patients with the third having unusually high precision errors for both the 1250-1500 Hz and 1500-1890 Hz bands.

**Conclusion:** EA-1 patients have normal auditory spatial acuity at frequencies below 1000Hz. However at higher frequencies, both free field measurements and headphone tasks reveal abnormal lateralization and localizations. These abnormalities were seen in precision measurements (in 1/3 patients) and systematic localization errors at higher frequencies (all three patients). Future work will involve more detailed measurements with an increased number of EA-1 patients.

## References

- 1 Grigg, J. J., Brew, H. M., & Temple, B. L. (2000). Differential expression of voltage-gated potassium channel genes in auditory nuclei of the mouse brainstem. *Hearing Research*, 140:77-80.
- 2 Smart, S.L., Lopantsev, V., Zhang, C.L., Robbins, C. A., Wang, H., Chiu, S. Y., Schwartzkroin, P. A., Messing, A., & Tempel, B. L. (1998). Deletion of the Kv1.1 potassium channel causes epilepsy in mice. *Neuron*, 20:809-819.
- 3 Kopp-Scheinflug, C., Fuchs, K., Lippe, W. R., Tempel, B. L., & Rubasmen, R. (2003) Decreased temporal precision of auditory signaling in KCNA1-null mice: An electrophysiological study in vivo. *Journal of Neuroscience*, 23:9199-9207.
- 4 Gittelman, J.X., & Tempel, B. L. (2006). Kv1.1-containing channels are critical for temporal precision during spike initiation. *Journal of Neurophysiology*, 96:1203-1214.
- 5 Allen, P.D., Bell, J., Dargani, N., Moore, C. A., Tyler, C.M., & Ison, J.R. (2003). KCNA1 knockout mice have a profound deficit in discriminating sound source location. *Society for Neuroscience Abstracts*, 29:#183.181.
- 6 Browne, D.L., Gancher, S.T., Nutt, J.G., Brunt, E. R. P., Smith, E. A., Kramer, P., & Litt, M. (1994). Episodic ataxia/myokymia syndrome is associated with point mutations in the human potassium channel gene, KCNA1. *Nature Genetics*, 8:136-140.

# Basic Science & Clinical Research

**Jesse Schenendorf, MS2**

**Preceptor:**

**Jonathan Weinsaft, M.D.**

**Assistant Professor of Medicine Greenberg Division of Cardiology**

**Weill Medical College of Cornell University Cardiac MR/CT Imaging Program**

Introduction:

Approximately one million Americans sustain acute myocardial infarction (AMI) annually, with prevalence of AMI likely to increase in the context of rising rates of predisposing risk factors such as diabetes mellitus and hyperlipidemia. (1) Mitral regurgitation (MR) is a known consequence of AMI that can contribute to impairment of cardiac function and heart failure symptoms. Fortunately, effective medical and surgical therapies for MR exist. However if not identified early, MR can result in irreversible cardiac dysfunction, which increases clinical risk and downstream medical costs. (2-4) Early identification of patients at risk for progressive MR is important for timely implementation of corrective therapies. Current methods to predict MR using cardiac structure as longitudinal predictors of post-AMI MR, including cardiac chamber size, contractility, and infarct size are inadequate. (5-8) Identification of indices that accurately predict MR progression and long-term severity is of substantial importance in the care and management of AMI patients.

Background:

Papillary muscle infarction (PMI) can occur in association with an AMI and serve as an alternative cause for the development of MR. The correlation between PMI and MR is well established in the context of papillary muscle rupture. (9-11) It is also possible that lesser degrees of papillary muscle necrosis can result in MR which progresses with time. Studies have shown that PMI can occur in the absence of rupture. (12,13) However, to date the impact of isolated PMI and its ability to predict MR is not known. Clinical studies of the correlation between PMI and MR have not been possible as prior to recent advances in imaging technology; the available modalities were not capable of accurately identifying PMI.

Delayed enhancement MRI (DE-MRI) provides a highly accurate technique to identify myocyte necrosis. DE-MRI has been shown to provide non-invasive assessment of infarct morphology and size that closely correlates with histopathologic infarct size in both the acute ( $r=0.99$ ) and chronic ( $r=0.97$ ) MI. (14, 15) DE-MRI has also been shown to be capable of identifying PMI. Recent advances in MRI technology, including 3D MRI, may provide further improvement in detection of PMI over conventional 2D imaging. Thus, DE-MRI provides a novel, non-invasive method to study incidence, imaging characteristics, and predictors of PMI following AMI.

Objective:

To identify incidence and structural predictors of PMI following AMI.

Methods:

We will study incidence and predictors of PMI among consecutive subjects with AMI enrolled in a prospective imaging registry at Weill Cornell. This patient population has been (and will continue to be accrued) during prospective recruitment (2-5 days post AMI) at Weill Cornell. In accordance with the existing imaging protocol for this registry, all subjects undergo cardiac MRI 20-40 days following AMI. Comprehensive demographic characteristics (including risk factors for CAD) and AMI treatment results (including angiographic findings, enzymatic infarct size, and therapeutic regimen) are collected. MRI data have been quantitatively analyzed for cardiac chamber size, contractile function, and left ventricular wall infarction. For the proposed study, comprehensive analysis will be performed to identify and characterize PMI using both 2D and 3D DE-MRI. The ability to detect PMI infarct and agreement between 2D and 3D methods will be analyzed. Comprehensive

analyses will be performed to identify correlates of PMI by 2D and/or 3D DE-MRI. Clinical and imaging findings including, infarct distribution, transmural, and size will be compared between subjects. Variables that differ significantly between subjects with and without PMI will be used as predictors in a logistic regression model (forward stepwise regression) with presence or absence of PMI as the dependent variable. Echo and clinical variables will be tested in separate multivariate models in order to develop imaging-specific and clinical risk profiles for PMI.

#### Results:

Results are not currently available.

#### Conclusions:

The results of this proposed study will provide important insights into incidence and predictors of PMI following AMI. Future studies will address the prognostic importance of PMI as a longitudinal predictor of post-AMI mitral regurgitation.

#### Sources:

- 1) Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics--2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2009;119:480-6.
- 2) Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *Jama* 2001;285:2370-5.
- 3) Wolf PA, Dawber TR, Thomas HE, Jr., Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. *Neurology* 1978;28:973-7.
- 4) Wolf PA, Mitchell JB, Baker CS, et al. Impact of atrial fibrillation on mortality, stroke, and medical costs. *Arch Intern Med* 1998;158:229-34.
- 5) Lund GK, Stork A, Muellerleile K, et al. Prediction of left ventricular remodeling and analysis of infarct resorption in patients with reperfused myocardial infarcts by using contrast-enhanced MR imaging. *Radiology* 2007;245:95-102.
- 6) Hombach V, Grebe O, Merkle N, et al. Sequelae of acute myocardial infarction regarding cardiac structure and function and their prognostic significance as assessed by magnetic resonance imaging. *Eur Heart J* 2005; 26:549-57.
- 7) Choi KM, Kim RJ, Gubernikoff G, et al. Transmural extent of acute myocardial infarction predicts long-term improvement in contractile function. *Circulation* 2001; 104:1101-7.
- 8) Rubenstein JC, Ortiz JT, Wu E, et al. The use of periinfarct contrast-enhanced cardiac magnetic resonance imaging for the prediction of late postmyocardial infarction ventricular dysfunction. *Am Heart J* 2008; 156:498-505.
- 9) Vlodayer Z, Edwards JE. Rupture of ventricular septum or papillary muscle complicating myocardial infarction. *Circulation* 1977;55:815-22.
- 10) Wei JY, Hutchins GM, Bulkley BH. Papillary muscle rupture in fatal acute myocardial infarction: a potentially treatable form of cardiogenic shock. *Ann Intern Med* 1979;90:149-52.
- 11) Hider CF, Taylor DE, Wade JD. The effect of papillary muscle damage on atrioventricular valve function in the left heart. *Q J Exp Physiol Cogn Med Sci* 1965;50:15-22.
- 12) Mittal AK, Langston M, Jr., Cohn KE, et al. Combined papillary muscle and left ventricular wall dysfunction as a cause of mitral regurgitation. An experimental study. *Circulation* 1971;44:174-80
- 13) Tsakiris AG, Rastelli GC, Amorim Dde S, et al. Effect of experimental papillary muscle damage on mitral valve closure in intact anesthetized dogs. *Mayo Clin Proc* 1970;45:275- 85.
- 14) Kim RJ, Fieno DS, Parrish TB, et al. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. *Circulation* 1999;100:1992-2002.
- 15) Wagner A, Mahrholdt H, Holly TA, et al. Contrast-enhanced MRI and routine single photon emission computed tomography (SPECT) perfusion imaging for detection of subendocardial myocardial infarcts: an imaging study. *Lancet* 2003;361:374-9.

# Basic Science & Clinical Research

Ian Schreiner, MS2

**Preceptor:**

**Manish Shah, M.D., Associate Professor Department of Emergency Medicine  
University of Rochester Medical Center**

**A Pilot Study to Assess the Feasibility and Acceptability of Validating Depression and Cognitive Impairment Screening Measures in the Emergency Department**

**Introduction:** This study was conducted to assess the feasibility of a planned R01 funded study to be conducted by Dr. Manish Shah. Although multiple screening tools for both depression and cognitive impairment have been developed and validated in primary care and other settings, few have been validated in the Emergency Department setting. In addition to feasibility, this study evaluated the acceptability of several measures from the participants' perspective.

**Objectives:** (1) Assess the feasibility of enrolling emergency department (ED) patients and evaluating them for depression and cognitive impairment in preparation of a larger ED-based validation study of these measures. (2) Evaluate the acceptability of our research methods, as perceived by the subject.

**Background:** Depression is listed by the World Health Organization as one of the most burdensome diseases<sup>1</sup> and up to 10% of the older adult population suffers from major depression<sup>2,3,4</sup>. Older adults who are hospitalized for depression typically have had symptoms for many months before admission and most are admitted through the emergency department<sup>5,6,7</sup>. The complications of depression are enumerable and include worse outcomes after stroke, myocardial infarction and coronary artery bypass grafting, prolonged recovery periods and even death<sup>8,9,10,11</sup>. Despite all this, it is estimated that less than one-half of the depressed older adults are diagnosed and treated in the primary care setting<sup>12,13</sup>. A screening measure validated for the older adult ED population could provide the information a primary care physician needs to treat patients adequately.

The need for dementia screening is also great. Due to the aging of the American population, it is estimated that the number of older adults suffering from dementia will triple by the year 2050<sup>14</sup>. Like depression, primary care physicians fail to diagnose dementia about half of the time<sup>15,16,17,18</sup>. This can delay much needed behavioral treatment (in the case of Alzheimer's disease) or even a cure (in the case of reversible dementias such as hypothyroidism and vitamin B12 deficiency). Untreated symptoms cause care-giver burnout and increased early admission to nursing homes<sup>19,20</sup>. A valid screening tool for dementia in the ED could be used to flag patients for early intervention and early treatment.

Mild Cognitive Impairment (MCI) is considered an early warning sign for dementia and is defined as an objective memory deficit which does not interfere with activities of daily living<sup>21</sup>. MCI is sometimes associated with deficits in executive, language and visuospatial functioning though individual findings can be variable<sup>22,23,24</sup>. Though MCI can be stable for years, up to 64% of those diagnosed with MCI convert to dementia within two years<sup>25</sup>. MCI diagnosis is also correlated with a decline in quality of life and increased healthcare costs<sup>26,27,28</sup>.

**Methods:** This study enrolled a sample of community-dwelling older adults (age $\geq$ 60) cared for at the University of Rochester-Strong Memorial Hospital (URMC) ED and discharged home from the ED. Informed consent was obtained and an interview was conducted to collect demographic information, previous medical history, and social history. The interview also included the Patient Health

Questionnaire- 9 (PHQ-9) and Six Item Screener (SIS), two instruments that are proposed for ED-based screening for depression and cognitive impairment, respectively<sup>29,30,31,32,33</sup>. The Structured Clinical Interview for the DSM-IV (SCID) is considered the gold standard for depression diagnosis<sup>34</sup> and was performed by an experienced and trained psychiatry student. The Geriatric Depression Scale-15 (GDS-15) and the Hamilton Rating Scale for Depression (Hamilton) were obtained as additional comparison measures for depression. Because anxiety and delirium are often comorbid with depression and can confound results, Generalized Anxiety Disorder-7 (GAD-7) and Confusion Assessment Method for the ICU (CAM-ICU) were used to assess anxiety and delirium, respectively.

Feasibility data was collected on length of interview, number of interruptions, and data points lost due to early discharge or other interruptions. Participants were also asked open ended questions to determine what they liked and disliked about the study as well as their reasons for participating.

**Results:** The participants were of mixed ethnic backgrounds (White n=25 [73.5%], Black n=6 [17.7%], Other/unknown n=3 [8.8%]) and had median age of 70 (IQR 64,80). The median interview length was 68 minutes with between zero and six interruptions (median=1). A variety of reasons for participation were reported including an altruistic desire to help (n=17, 50%), boredom or a desire to kill time (n=8, 23.5%), and a special interest in the topic (n=7, 20.6%). Reported dislikes/annoyances included no dislikes (n=18, 52.9%), the questions on depression (n=6, 17.6%) and the questions on memory (n=2, 5.9%). Reported likes included general enjoyment in participation (n=11, 32.4%) and talking with the research assistant (n=5, 14.7%). Eight participants (23.5%) were scored depressed on the PHQ-9, nine on GDS-15 (26.5%), seventeen on the Hamilton (50%) and ten on SCID (29.4%). Five participants scored positive for anxiety on GAD-7 (14.7%) and none were found to be delirious by CAM-ICU. MCI was found in four participants by SIS (11.8%) and seventeen by the MoCA (50%).

**Conclusion:** The overwhelming majority of those who consented to participate completed the study. Although some participants reported discomfort with some of the content of the questions, there were no serious objections. In conclusion, it is feasible to perform these measures in an ED setting.

#### References:

1. Ani C, Bazargan M, Hindman D, et al. Depression symptomatology and diagnosis: discordance between patients and physicians in primary care settings. *BMC Family Practice*. 2008;19:1. doi:10.1186/1471-2296-9-1.
2. Lyness JM, Caine ED, King DA et al. Psychiatric disorders in older primary care patients. *J Gen Intern Med*. 1999; 14:249-254.
3. Lyness JM, King DA, et al. The importance of subsyndromal depression in older primary care patients: prevalence and associated functional disability. *J Am Geriatr Soc*. 1999; 47:647-652.
4. Koenig HG, George LK, Peterson BL, Pieper CF. Depression in medically ill hospitalized older adults: Prevalence, characteristics, and course of symptoms according to six diagnostic schemes. *Am J Psychiatry*. 1997; 154: 1376-1379.
5. Baldwin RC, Jolley DJ. The prognosis of depression in old age. *Br J Psych*. 1986; 149:574-583.
6. Koenig HG. Depression outcome in inpatients with congestive heart failure. *Arch Intern Med*. 2006; 166: 991-996.
7. Pennix WJH, Guralnik JM, Ferrucci L, et al. Depressive symptoms and physical decline in community dwelling older persons. *JAMA*. 1998; 279:1720-1726.
8. Devanand DP, Sano M, Tang MX, et al. Depressed mood and the incidence of Alzheimer's Disease in the elderly living in the community. *Archives of General Psychiatry*. 1996; 53:175-182.
9. Jiang W, Alexander J, Christopher E, et al. Relationship of depression to increased risk of mortality and rehospitalization in patients with congestive heart failure. *Arch Intern Med*. 2001;161:1849-1856.
10. Whooley MA, de Jonge P, Vittinghoff E, et al. Depressive symptoms, health behaviors, and risk of cardiovascular events in patients with coronary heart disease. *JAMA*. 2008; 300:2379-2388.
11. Romanelli J, Fauerbach J, Buch D, et al. The significance of depression in older patients after myocardial infarction. *J Am Geriatr Soc*. 2002; 50:817-822.

12. Unutzer J, Katon W, Callahan CM, et al. Depression in a sample of 1801 depressed older adults in primary care. *J Am Geriatr Soc.* 2003; 51: 505-514.
13. Blazer D. Depression in the elderly. *N Engl J Med.* 1989 320 164-66
14. Herbert LE, Scherr PA, Bienias JL, et al. Alzheimer's disease in the US population: Prevalence estimates using the 2000 census. *Arch Neurol.* 2003; 60:1119-1122.
15. Callahan CM, Hendrie HC, Tierney WM. Documentation and evaluation of cognitive impairment in elderly primary care patients. *Ann Intern Med.* 1995; 122: 422-429.
16. Boise L, Neal BM, Kaye J. Dementia assessment in primary care: Results from a study in three managed care systems. *J Gerontol A Biol Sci Med Sci.* 2004; 59: M621-M626.
17. Bush C, Kozak J, Elmslie. Screening for cognitive impairment in the elderly. *Can Fam Physician.* 1996; 43:1763-1768.
18. Boustani M, Callahan CM, Unverzagt FW, et al. Implementing a screening and diagnosis program for dementia in primary care. *J Gen Intern Med.* 2005; 20:572-577.
19. Ballard C, Neill D, O'Brien J, et al. Anxiety, depression, and psychosis in vascular dementia. *J Affect Disorders.* 2000; 59:97-106.
20. Steele C, Rovner B, Chase GA, et al. Psychiatric symptoms and nursing home placement of patients with Alzheimer's disease. *Am J Psychiatry.* 1990; 147: 1049-1051.
21. Petersen RC, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. *Arch Neurol.* 2001;58:1985-1992.
22. Graham JE, Rockwood K, Beattie BL, et al. Prevalence and severity of cognitive impairment with and without dementia in an elderly population. *Lancet.* 1997;349:1793-1796.
23. Weintraub, S. and Mesulam, M.M., 1993. Four neuropsychological profiles in dementia. In: Boller, F. and Spinnler, H., Editors, 1993. *Handbook of neuropsychology vol. 8*, Elsevier, Amsterdam, pp. 253-282.
24. Mapstone M, Steffenella T, and Duffy CJ. A visuospatial variant of Mild Cognitive Impairment: Getting lost between aging and AD. *Neurology.* 2003; 60:802-808.
25. Geslania DM, Tierneya MC, Herrmann N, Szalaic JP. Mild Cognitive Impairment: An Operational Definition and Its Conversion Rate to Alzheimer's Disease. *Dementia and Geriatric Cognitive Disorders.* 2005;19:383-389.
26. Plassman BL, Langa KM, Fisher GG, et al. Prevalence of cognitive impairment without dementia in the United States. *Ann Intern Med.* 2008; 148:427-434.
27. Gauthier S, Reisberg B, Zaudig M, et al. Mild cognitive impairment. *Lancet.* 2006; 367: 1262-70.
28. Lysetsos CG, Lopez O, Jones B, et al. Prevalence of neuropsychiatric symptoms in dementia an mild cognitive impairment: results from the Cardiovascular Health Study. *JAMA.* 2002;288:1475-1483.
29. Lerner EB, Fernandez AR, Shah MN. Do EMS providers think they should participate in disease prevention? *Prehospital Emergency Care.* 2009; 13: 64-70. NIHMS 104677.
30. Shah MN, Clarkson L, Lerner EB, Fairbanks RJ, McCann R, Schneider SM. An emergency medical services program to promote the health of older adults. *Journal of the American Geriatric Society.* 2006; 54: 956-962.
31. Shah MN, Lerner EB, Chiumento S, Davis EA. An evaluation of paramedics' ability to screen older adults during emergency responses. *Prehospital Emergency Care.* 2004; 8: 298-303.
32. Shah MN, Richardson T, Swanson P, Findlay-Lester R, Pilato A, Karuza J, Katz P, Conwell Y. Screening older adults in the ED for depression and cognitive impairment: stability of symptoms after two weeks. *Acad Emerg Med.* 2009; 16: S93.
33. Shah MN, Karuza J, Rueckmann E, et al. Reliability and validity of prehospital case finding for depression and cognitive impairment. *J Am Geriatr Soc.* 2009; 57: 697-702. NIHMS 80660
34. Ventura J, Liberman RP, Green FM, et al. Training and quality assurance with the Structured Clinical Interview for DSM-IV. *Psychiatry Research.* 1998; 79: 163-173.

## Basic Science & Clinical Research

Aqsa Shakoor, MS2

**Preceptor: David Gillespie, M.D.**  
**Department of Vascular Surgery**  
**University of Rochester Medical Center**

### **MMP-2 and MMP-9 Expression is Increased in C5 and C6 Dermal Fibroblasts Compared to C2 in a Model of Constant Cellular Stretch**

**Background:** Chronic venous insufficiency (CVI) affects up to 2.5 million patients per year in the United States and imbalances in the homeostasis of extracellular matrix (ECM) is considered to be a hallmark of chronic venous ulceration. The delicate balance between ECM synthesis and degradation determines the level of ECM deposition in wounds and is mediated by the activity of matrix metalloproteinases (MMP) secreted from dermal fibroblasts. In an effort to investigate if MMP alterations occur as part of the progression of CVI, we examined MMP-2 and MMP-9 activity in dermal fibroblasts derived from patients with advanced CVI. Furthermore, we attempted to determine if there were any differences in MMP activity in fibroblasts in response to mechanical stretch.

**Methods:** Commercially available adult fibroblasts and dermal biopsies obtained from adult patients with CVI (CEAP 2, 4, 5 or 6) were used in this study. In order to mimic the increased stretch to which dermal fibroblasts are exposed to in patients with CVI, adult fibroblasts were cultured on collagen coated flexplates, and subjected to constant equibiaxial elongation (21%) for 1, 3 or 5 days using a Flexercell® strain unit. Culture media was collected and MMP-2 and MMP-9 activity was determined by gelatin zymography. Thigh and ankle biopsies were taken from patients diagnosed with C2, C4, C5, or C6 stage of CVI and dermal fibroblast cultures were established and media was collected for analysis of MMP-2 and MMP-9 activity.

**Results:** When compared to static fibroblasts, 1, 3, and 5 day constantly stretched fibroblasts showed an increase in active MMP-2 and pro-MMP-9 secretion, and 1 day active MMP-9. Pro- MMP-9 secretion was observed to be decreased in ankle (diseased) tissue when compared to thigh (healthy) tissue in C2 and C4 patients but increased in C5 and C6 patients. C6 patients had significantly increased pro MMP-9 secretion ( $p < 0.05$ ). Active MMP-9 was also observed to be increased in C5 patients in the thigh compared to the ankle. There were no observed alterations in dermal fibroblast secretion of pro- or active MMP-2 secretion from ankle compared to thigh tissue of C2, C4, C5, or C6 patients.

**Conclusion:** Our data shows a trend of increased pro- and active MMP-2 and pro- MMP-9 expression in stretched fibroblasts compared to static control fibroblasts. This may be indicative of increased MMP activity resulting in increased tissue turnover and an inability for sufficient wound healing to be sustained. Also, MMP-9 expression appears to be down-regulated at C2 and C4 disease states compared to healthy tissue, but up-regulated at C5 and C6 states. These results suggest that alterations in MMP secretion by dermal fibroblasts may play a role in the development of CVI. Elucidating the role of MMPs in non-healing wounds has tremendous potential to help treat CVI and alleviate the burden of this disease in high risk patients such as those with diabetes

## Basic Science & Clinical Research

**Puja Sood, MS2**

**Preceptor: Robert E. Goldstein, M.D. Professor, Department of Medicine  
Uniformed Services University of the Health Sciences**

### **Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy Mortality Review**

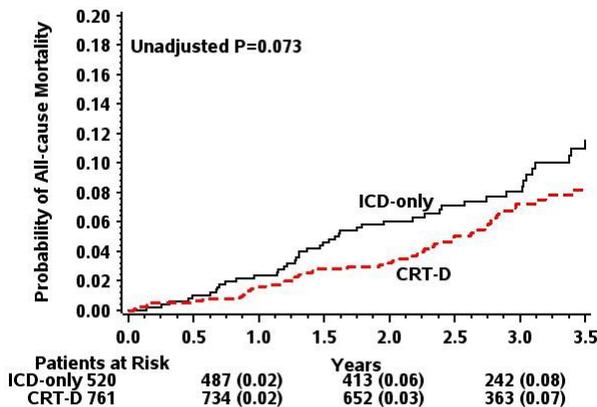
*Introduction:* Patients who suffer from cardiac disease causing reduced left ventricular function have a high risk of symptomatic heart failure, arrhythmia, and early death. Eligible patients who present such warning signs receive an implantable cardioverter-defibrillator (ICD) that is able to deliver life-saving counter shocks from within the patient during an episode of potentially lethal ventricular fibrillation (Moss et al.). While proving beneficial for many patients by prolonging lives, the ICD does not remove all sources of elevated risk. In fact, studies have shown patients who have ischemic heart disease and are treated with ICDs are more likely to suffer from subsequent heart failure events (Goldenberg et al.) Recently, cardiac resynchronization therapy (CRT) using biventricular pacing has reversed mechanical dysfunction and improved symptoms in patients with heart failure associated with left ventricular dyssynchrony. To see if combined therapy of ICD with CRT (CRT-D) would reduce the occurrence of heart failure events in patients compared to ICD-only, Moss et al. conducted a new study, the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT). The conclusion of the study laid a strong foundation for the claim that using CRT-ICD therapy in a prophylactic manner will reduce the possibility of heart-failure events or death in patients with ischemic or nonischemic heart disease who may be asymptomatic but have a wide QRS complex (Moss et al.). However, the long-term effects on mortality remain uncertain.

*Objective:* To review cause of death in patients in the above study and note variations, determine cause-specific death rates, identify factors associated with each cause of death in ICD and ICD- CRT patient groups, and to define baseline characteristics and changes in ventricular function after one year of management with ICD or ICD-CRT and relate these to patient outcomes.

*Methods:* A list of specific variables of interest was compiled and a specific data collection form was designed to record values of these variables for each patient, in each of the MADIT-CRT subsets (CRT-D vs. ICD-only). The variables observed included status of implant, gender, QRS duration at baseline, EF value at baseline, device interrogation results, age at death, time between implantation and death, history of diabetes mellitus, history of atrial fibrillation, history of sleep apnea, left bundle branch block (LBBB), clinical status/function at time of death, presence of symptoms including hypotension, fatigue, shortness of breath, and edema, factors regarding the death (including site, cause, mechanism, ischemia, and contributing factors) as reviewed by the Mortality Endpoint Review Committee, and a summary of the medications of each patient. Case report forms and (blinded) narrative summaries from the Mortality Endpoint Review Committee of the MADIT-CRT patients who died from the beginning of the trial at December 22, 2004 through December 31, 2009 were scrutinized to determine which patients died from progressive heart failure, which from arrhythmia, and which from other causes. Clinical information and statistical support was provided by the Data Coordinating Center for MADIT-CRT study located at the University of Rochester. Statistical tests were used to determine the significance of the difference in characteristics between those who died by treatment assignment. A Kaplan-Meier survival analyses were performed, stratified by diabetes status for patients randomized to ICD and CRT-D, showing risk of all-cause mortality and risk of cardiac death. The log-rank statistic was used for determination of statistical significance. Additional analyses are pending.

**Results:** Among those who died, there was a higher percentage of females in the ICD-only treated patients than in the CRT-D treated patients (26% vs. 10%, respectively;  $p=0.01$ ). Survival analysis in the overall study population showed no difference between the two treatment groups for risk of death ( $p=0.49$ ), or risk of cardiac death ( $p=0.12$ ). 77% of the ICD-only patients and 58% of the CRT-D patients had LBBB ( $p=0.02$ ). Among patients with LBBB, CRT-D therapy was associated with a meaningful trend to an overall lower death rate ( $p=0.073$ ) when compared to patients receiving ICD-only therapy (Fig.).

**Conclusion:** Among patients with LBBB, CRT-D therapy was associated with a somewhat lower death rate when compared to patients receiving ICD-only therapy. A longer follow-up of the patients enrolled in MADIT-CRT is needed to determine if CRT-D therapy significantly reduces mortality.



**References:**

- Goldenberg I, Moss AJ, Hall WJ, et al. “Causes and consequences of heart failure after prophylactic implantation of a defibrillator in the Multicenter Automatic Defibrillator Implantation Trial II.” *Circulation* 2006; 113:2810-7.
- Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C. “Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms.” *Journal of the American College of Cardiology*. 2008; 52:1834-43
- Moss AJ, Hall WJ, Cannom DS, et al. “Cardiac-Resynchronization Therapy for the Prevention of Heart-Failure Events.” *New England Journal of Medicine*. 2009 Oct 1; 361(14):1329-38.

# Basic Science & Clinical Research

Imran Uraizee, MS2

**Preceptor:**

**Burns C. Blaxall, PhD, FAHA Associate Professor**

**Department of Pharmacology and Physiology**

**Department of Medicine**

**University of Rochester Medical Center Aab Cardiovascular Research Institute**

## **Exploring a role for the Extracellular Matrix Protein Fibronectin in Cardiac Remodeling and Heart Failure**

**Introduction:**

Heart failure (HF) results from a wide range of acute and chronic insults, including coronary artery disease and hypertension, and remains a leading cause of death worldwide despite recent therapeutic advances<sup>2,4,8,9</sup>. A majority of HF cases stem from ischemic events, specifically myocardial infarction (MI). MIs are becoming an increasing cause for concern for several reasons. In the United States alone, the estimated incidence of MI is approximately 600,000 new and 320,000 recurrent cases per year<sup>10</sup>. MI leads to pathologic cardiac remodeling where areas of initial infarct are replaced with matrix-rich scar tissue and can adversely affect heart function<sup>1</sup>. Ischemic injury causes an acute loss of cardiomyocytes, fibroblast proliferation, extracellular matrix (ECM) deposition, recruitment of inflammatory cells, scar formation, and infarct expansion. In particular, extensive structural and ECM remodeling in the infarct, border zone, and remote myocardium, are major components of pathologic cardiac remodeling post-MI. However, cardiac remodeling remains poorly understood. Previous data shows that the ECM protein fibronectin (FN) plays an important role in regulating ECM remodeling.

**Objective:**

To explore the role of FN in cardiac remodeling and heart failure by determining: 1) the ability of cardiomyocytes to polymerize fibronectin and 2) if inhibition of FN polymerization following MI reduces pathologic cardiac remodeling and progression of heart failure.

**Background:**

A soluble, secreted protein that is deposited into the ECM via a cell-dependent process, FN regulates deposition of other ECM proteins, including Type I collagen, and may be linked to the progression of heart failure<sup>12,14</sup>. Additionally, FN can promote cellular proliferation, hypertrophy, migration, and contractility<sup>6,7,11,13,14,15</sup>. FN expression tends to be upregulated in animal models of HF as well as humans with both MI and dilated cardiomyopathy etiologies of HF<sup>3,5</sup>. Preliminary data has shown that *in vivo* inhibition of FN by the peptide pUR4 in mice improves heart function and decreases excess FN deposition following MI. Still, there is little knowledge regarding the specific role of FN in the heart and in pathologic cardiac remodeling. Inhibiting FN deposition may be a novel therapeutic paradigm for MI and a viable strategy for improving heart function.

**Methods:**

Isolated neonatal rat cardiomyocytes (NRVMs) were incubated overnight at 37°C in DMEM culturing medium with 10% FN-depleted neonatal calf serum (NCS), followed by an additional overnight incubation in serum free culturing media with or without exogenous FN. Cells were fixed on the third day and then triple-stained using two separate fluorescent antibody stains for  $\alpha$ -actinin (protein

specifically expressed in cardiomyocytes) and FN along with a DAPI nuclear stain. Stains were visualized using fluorescent microscopy and compared to control NRVMs that were immersed in DMEM culture media with 10% NCS followed by the same staining procedures.

12 C57BL/6J mice ranging from 8-10 weeks old underwent baseline echocardiography following by left anterior descending (LAD) coronary artery ligation. S-T elevation and left ventricular blanching were

observed to confirm induction of MI. 7 mice were administered daily intraperitoneal injections of pUR4, an inhibitor of FN polymerization, for 7 days beginning with the day of surgery, and the remaining 5 mice received III-11-C, a control peptide, over the same time course. Mice were scheduled for echocardiography at 2 weeks and 4 weeks post-MI followed by sacrifice for cardiac histology.

### **Results:**

Fluorescent microscopy of triple-stained plates revealed variable cardiac fibroblast (CF) contamination in wells with experimental and control NRVMs. Fibronectin stained inconsistently and auto-fluorescence also interfered with visualization. No significant difference in FN polymerization by NRVMs was discernible between experimental and control conditions.

All 7 pUR4 mice expired within one-week post-LAD ligation, and only 3 mice from III-11-C control group survived to 4 weeks. Echocardiography was performed on these 3 mice only at 4 weeks and revealed substantially lowered ejection fractions and massive heart failure.

### **Conclusions:**

Determination of the ability of cardiomyocytes to polymerize FN remains a challenge because of inability to obtain a pure isolation of NRVMs devoid of CFs, which produce substantial amounts of FN. Additionally, auto-fluorescence posed some difficulty to visualizing fluorescent antibody stains. Further experimentation with novel NRVM isolation techniques and alternative cell culture techniques may help provide more optimal conditions.

All 12 mice received large MIs due to very proximal ligations of the LAD coronary artery. Survival and reproducibility of MI size and functional outcome remain the key challenges in this procedure. Repeated practice efforts should minimize the variability and improve both survival and reproducible outcomes. In particular, more distal ligations in future trials may ensure onset of MI with improved survival. Establishing the model will lay the foundation for proceeding with our proposed studies in this murine MI model.

### Literature Cited

1. Brown RD, Ambler SK, Mitchell MD, Long CS. The cardiac fibroblast: therapeutic target in myocardial remodeling and failure. *Annu. Rev. Pharmacol. Toxicol.* 2005;45:657-687.
2. Chien KR, Olson EN. Converging pathways and principles in heart development and disease: CV@CSH. *Cell.* 2002;110(2):153-162.
3. Dobaczewski M, Bujak M, Zymek P, Ren G, Entman ML, Frangogiannis NG. Extracellular matrix remodeling in canine and mouse myocardial infarcts. *Cell Tissue Res.* 2006;324(3):475-488.
4. Frey N, Olson EN. Cardiac hypertrophy: the good, the bad, and the ugly. *Annu. Rev. Physiol.* 2003;65:45-79.
5. Heling A, Zimmermann R, Kostin S, Maeno Y, Hein S, Devaux B, Bauer E, Klovekorn WP, Schlepfer M, Schaper W, Schaper J. Increased expression of cytoskeletal, linkage, and extracellular proteins in failing human myocardium. *Circ. Res.* 2000;86(8):846-853.

6. Hocking DC, Sottile J, Langenbach KJ. Stimulation of integrin-mediated cell contractility by fibronectin polymerization. *J. Biol. Chem.* 2000;275:10673-10682.
7. Hocking DC, Chang CH. Fibronectin matrix polymerization regulates small airway epithelial cell migration. *Am. J. Physiol.* 2003;285(1):L169-179.
8. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW, Antman EM, Smith SC, Jr., Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation.* 2005;112(12):e154-235.
9. Jessup M, Brozena S. Heart failure. *N Engl J. Med.* 2003;348(20):2007-2018.
10. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, Ford E, Furie K, Go A, Greenlund K, Haase N, Hailpern S, Ho M, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott M, Meigs J, Mozaffarian D, Nichol G, O'Donnell C, Roger V, Rosamond W, Sacco R, Sorlie P, Stafford R, Steinberger J, Thom T, Wasserthiel-Smoller S, Wong N, Wylie-Rosett J, Hong Y. Heart Disease and Stroke Statistics--2009 Update. A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation.* 2008.
11. Sechler JL, Schwarzbauer JE. Control of cell cycle progression by fibronectin matrix architecture. *J. Biol. Chem.* 1998;273:25533-25536.
12. Sottile J, Hocking DC. Fibronectin polymerization regulates the composition and stability of extracellular matrix fibrils and cell-matrix adhesions. *Mol. Biol. Cell.* 2002;13:3546-3559.
13. Sottile J, Hocking DC, Swiatek P. Fibronectin matrix assembly enhances adhesion-dependent cell growth. *J. Cell Sci.* 1998;111:2933-2943.
14. Sottile J, Shi F, Rublyevska I, Chiang HY, Lust J, Chandler J. Fibronectin-dependent collagen I deposition modulates the cell response to fibronectin. *Am. J. Physiol. Cell Physiol.* 2007;293:C1934-1946.
15. Zhou X, Rowe RG, Hiraoka N, George JP, Wirtz D, Mosher DF, Virtanen I, Chernousov MA, Weiss SJ. Fibronectin fibrillogenesis regulates three-dimensional neovessel formation. *Genes Dev.* 2008;22(9):1231-1243.

# Basic Science & Clinical Research

Vijay Vanchinathan, MS2

**Preceptor:**

**Charles J. Lowenstein, M.D. Chief, Division of Cardiology**

**Professor, Department of Medicine**

**Director, Aab Cardiovascular Research Institute University of Rochester Medical Center**

## **Effects of the platelet granule compounds PPI, NAP-2, and GTP on in vitro endothelial cell activation**

**Introduction:** Platelets are anuclear cells derived from bone marrow megakaryocytes, and are primarily responsible for hemostasis after injury to the vasculature.<sup>1</sup> During platelet activation, exocytosis of dense, alpha, and lysosomal granules release many distinct molecules, which may interact with endothelial cells lining the blood vessels to promote thrombosis.<sup>1,2</sup> Certain granule compounds, however, activate the endothelium to promote pro-inflammatory and immune-related changes<sup>3</sup> that may underlie the pathology of cardiovascular diseases.

**Objective:** To determine whether the platelet granule compounds pyrophosphate (PPI), neutrophil-activating protein-2 (NAP-2), and guanosine triphosphate (GTP) activate human umbilical vein endothelial cells (HUVECs) to synthesize or release vascular cell adhesion molecule-1 (VCAM-1), monocyte chemoattractant protein I (MCP-1), von Willebrand factor (vWF), and endothelin-1 (ET-1).

**Background:** Platelet granule contents can stimulate endothelial cells to release mediators of thrombosis and inflammation like vWF and VCAM-1. Müller et al recently showed that platelet polyphosphates help drive inflammatory pathways by activating the plasma coagulation factor XII<sup>4</sup>. Seye et al found that the nucleotides ATP and UTP induce VCAM-1 expression in coronary artery endothelial cells<sup>5</sup>. Other classic inflammatory platelet proteins include beta-thromboglobulin and platelet factor 4, which are the precursor and derivative products of NAP-2, respectively<sup>1,2,6</sup>. In vitro studies have shown that NAP-2 not only dose-dependently increases neutrophil binding to HUVECs, but that it also increases their transendothelial migration<sup>6</sup>.

**Methods:** HUVECs were grown as a monolayer in 12-well and 6-well plates, as well as 25 and 75 cm<sup>2</sup> flasks, using complete media supplied by Lifeline Cell Technology (Oceanside, CA). PPI was isolated and then diluted to a concentration of 10 µM in our laboratory; recombinant NAP-2 was purchased from PeproTech (Rocky Hill, NJ); GTP was purchased as an aqueous solution from USB (Cleveland, Ohio). Confluent cells were treated with PPI, NAP-2, or GTP for 45 minutes, 6 hours, or 16 hours at concentrations ranging from 1 ng/mL to 1 µg/mL. Cells treated with nothing served as the negative control, and cells treated with either TNF-α or thrombin as the positive control. After exposure, the conditioned cell media was collected, centrifuged, and examined by ELISA for the presence of MCP-1, vWF, and ET-1. MCP-1 and ET-1 ELISA kits were purchased from R&D Systems, Inc. (Minneapolis, MN); vWF ELISA kits were purchased from American Diagnostica Inc. (Stamford, CT). Treated cells were lysed, sonicated, and centrifuged, and the resulting supernatant was tested for the membrane-bound VCAM-1 by Western blotting.

**Results:** As compared to the controls, cells treated with PPI, NAP-2, and GTP did not show increased expression of either VCAM-1 or MCP-1. Furthermore, NAP-2 did not increase endothelial cell production

of vWF and ET-1.

**Discussion:** Previous studies have shown that platelet nucleotides and phosphates can induce inflammatory changes, which suggests that comparable platelet compounds, such as PPI and GTP, may play similar roles in the body. While neither was shown to elicit endothelial cell activation in this project, they cannot yet be excluded from having a part in the complex transformation endothelial cells undergo during thrombosis and inflammation. More research is needed to determine what function, if any, they have in the interaction between platelets and the vasculature.

As a strong chemoattractant for neutrophils, NAP-2 is believed to influence the inflammatory process in endothelial cells. Though we did not find any evidence to support this, other studies found after our project had started do imply that this may indeed be true. Smith et al demonstrated that NAP-2 was elevated in patients with both stable and unstable angina, and that NAP-2 increased levels of E-selectin, VCAM-1, MCP-1, and IL-8 in vitro<sup>7</sup>. The effects of NAP-2 need to be verified and better defined within the broad context of vascular inflammation and thrombosis.

### References:

1. Steinhubl SR, Moliterno DJ. The role of the platelet in the pathogenesis of atherothrombosis. *Am J Cardiovasc Drugs* 2005;5(6):399-406.
2. Rendu F, Brohard-Bohn B. The platelet release reaction: granules' constituents, secretion and functions. *Platelets* 2001;12:261-273.
3. Semple JW, Freedman J. Platelets and innate immunity. *Cell Mol Life Sci* 2010;67:499- 511.
4. Müller F, Mutch NJ, Schenk WA et al. Platelet polyphosphates are proinflammatory and procoagulant mediators in vivo. *Cell* 2009;139:1143-1156.
5. Seye CI, Yu N, Jain R et al. The P2Y<sub>2</sub> receptor mediates UTP-induced vascular cell adhesion molecule-1 in coronary artery endothelial cells. *J Biol Chem* 2003;278(27):24960-24965.
6. Gleissner CA, von Hundelshausen P, Ley K. Platelet chemokines in vascular disease. *Arterioscler Thromb Vasc Biol* 2008;28:1920-1927.
7. Smith C, Damäs JK, Otterdal K et al. Increased levels of neutrophil-activating peptide-2 in acute coronary syndromes: possible role of platelet-mediated vascular inflammation. *J Am Coll Cardiol* 2006;48(8):1591-1599.

# Basic Science & Clinical Research

Neal Weisbrod, MS2

**Preceptor:**

**Mark B. Taubman, M.D.**

**Dean, School of Medicine and Dentistry University Vice President for Health Sciences University of Rochester**

**The Role of Phosphatases in Dexamethasone Mediated Knockdown of MCP-1 mRNA**

**Introduction:** Inflammation is a central process in the development and progression of atherosclerosis. The chemokine MCP-1 is important for guiding monocytes/macrophages to the arterial wall to mediate the early stages of atherosclerosis. These cells may then become foam cells in the subendothelial space and lead to formation of a fatty streak, the core of an atherosclerotic lesion.<sup>1</sup> Glucocorticoids such as dexamethasone (Dex) regulate MCP-1 mRNA stability and are sometimes utilized in treatment of atherosclerosis for their anti-inflammatory effects.<sup>2</sup> However, these drugs often incur significant side effects. A more detailed understanding of the mechanism by which Dex destabilizes MCP-1 mRNA may lead to the design of pharmacological agents capable of inhibiting vascular inflammation without as many side effects.

**Objective:** To determine whether tyrosine phosphatases or serine/threonine phosphatases such as PP1, PP2A, and PP2B are involved in the Dex mediated knockdown of MCP-1 mRNA.

**Background:** Thus far the Taubman lab has accumulated evidence that the Glucocorticoid Receptor (GR) through which Dex acts forms a complex with Y-box binding protein-1 (YB-1). YB-1 appears to have endonuclease activity, which supports its role in Dex mediated MCP-1 mRNA knockdown. In order to investigate the exact mechanism of this signaling, we treated smooth muscle cells with inhibitors of various classes of signaling molecules, such as kinases, intracellular calcium, and phosphatases. The first inhibitor that was found to block the Dex mediated knockdown of MCP-1 mRNA was Calyculin A, which primarily targets PP1, PP2A, and PP2B.

**Methods:** Rat smooth muscle cells (SMCs) were cultured in Dulbecco's Modified Eagle's Medium (DMEM) with 10% heat inactivated fetal calf serum. At 70-80% confluence in 100mm dish, the cells were treated for 15 minutes with inhibitor in DMEM at a concentration generally between 2x and 10x the IC<sub>50</sub>: 10-100 $\mu$ M sodium orthovanadate, 2-10nM calyculin A, 15-60 $\mu$ M dephostatin, 5-10 $\mu$ M NSC 87877. Two cell dishes were used for each inhibitor and each concentration, and after 15 minutes of incubation with inhibitor, dexamethasone was added to one of the plates to a final concentration of 3.3 $\mu$ M. Cells were then incubated for 2 hours, at which point the RNA was harvested and purified using QIAGEN QIAshredder and mRNeasy Mini Kit. RTPCR was performed on the RNA using primers specific for MCP-1 or GAPDH and the products were evaluated using gel electrophoresis.

**Results:** RTPCR demonstrated attenuation of the Dex mediated knockdown of MCP-1 mRNA by 50 $\mu$ M sodium orthovanadate and 10nM calyculin A. MCP-1 mRNA levels were similar to control levels for 10 $\mu$ M sodium orthovanadate, 2nM calyculin A, 5 $\mu$ M NSC87877, and 10 $\mu$ M NSC87877. The results of trials with dephostatin were inconclusive due to lack of reproducibility.

**Conclusions:** The ability of sodium orthovanadate to attenuate Dex mediated knockdown of MCP-1 mRNA suggests that a tyrosine phosphatase is involved in Dex signaling, as sodium orthovanadate is a non-selective inhibitor of protein tyrosine phosphatases (PTPs). However, the ability of calyculin A to

rescue MCP-1 mRNA from Dex mediated knockdown suggests that a serine/threonine phosphatase is involved in Dex signaling, as calyculin A primarily targets PP1, PP2A, and PP2B. Two possible hypotheses to explain these findings include the presence of a mixed-type phosphatase which can be inhibited by tyrosine as well as serine/threonine phosphatase inhibitors, as well as the possibility that the toxicity of calyculin A is inducing other cellular changes responsible for the observed effect. Further investigation using more specific and, ideally, less toxic inhibitors of PTPs and serine/threonine phosphatases is necessary to further define the signaling pathway.

## References

- 1 Niu J, Kolattukudy PE. Role of MCP-1 in cardiovascular disease: molecular mechanisms and clinical implications. *Clin Sci (Lond)*. 2009 Jul 2;117(3):95-109.
- 2 Dhawan L, Liu B, Blaxall BC, Taubman MB. A novel role for the glucocorticoid receptor in the regulation of monocyte chemoattractant protein-1 mRNA stability. *J Biol Chem*. 2007;282:10146-10152.

## Basic Science & Clinical Research

Claire Zhang, MS2

**Preceptor:**

**Loralei Thornburg, MD Maternal Fetal Medicine  
Assistant Professor in Obstetrics and Gynecology  
University of Rochester Medical Center**

**Correlation of adnexal mass gynecologic ultrasound findings with surgical pathology**

Lisa Gray MD, Claire Zhang BS, J. Christopher Glantz MD MPH, Loralei L. Thornburg MD

**Objective:** To evaluate the accuracy of ultrasound (US) in predicting adnexal mass pathology by correlating sonographic results with surgical pathology.

**Study Design:** Retrospective analysis of medical records of all patients from 1996 through 2010 with US-diagnosed adnexal masses who subsequently underwent surgery within 6 months in Rochester. Accuracy and correct laterality of US diagnoses were described for benign and malignant masses. Suspicion for malignancy is defined as any of the following listed in the description: size over 10cm, complex, solid, excrescences, septated, or suspicion for malignancy.

**Results:** Of 443 patients with adnexal mass on gynecologic ultrasound, 178 (40%) underwent surgery with complete records available for 152. Specific US diagnoses was given in 90 patients (59%), with the remainder descriptive only. At least one US diagnosis was correct in 69/90 patients (77%). Laterality for pathologic findings was correctly identified in 129/152 patients (85%). The most frequent US diagnosis (32) was teratoma, which was correct in 26 (81% positive predictive value), and was confirmed present at surgery in 43 patients (overall sensitivity 60%). Of the 25 patients with malignant pathology, 20 were flagged as suspicious by US diagnosis or description (sensitivity of 80%). Of 127 patients with benign pathology, 63 had US suspicion for malignancy, for a specificity of US of 50%.

**Conclusions:** Ultrasound is a widely available method for evaluating adnexal masses. Although accuracy of teratoma diagnosis, laterality for adnexal masses and sensitivity for detection of malignancy were all high, the specificity of ultrasound for all gynecological diagnoses was limited.

# Community Health Research

**Stephanie Charles, MS2**

**Preceptor:**

**Adrienne Morgan, M.S.**

**Senior Director for the Center for Advocacy, Community Health, Education and Diversity  
University of Rochester Medical Center**

## **Health education in minority youth: Evaluating the effect of health instruction on the knowledge of school health topics.**

**Introduction:** Minority teens are at greater risk than non-minority teens for contracting HIV and STDS. They are also more likely to engage in risky behavior such as underage drinking and smoking which can put them at risk for future health concerns such as heart and lung disease<sup>5</sup>. In addition, obesity and hypertension are on the rise in such populations due to unhealthy eating habits, financial difficulties as well as lack of knowledge of proper nutrition<sup>4</sup>. Due to the prevalence of such issues, it is important to ensure that teens receive instruction on these topics in order to make informed decisions concerning their health.

**Objective:** To ascertain the level of understanding of health topics in minority high school students measured through testing performance before and after instruction.

**Background:** Each year, 8 million cases of STDs occur in people under 25 years of age. Sexually active adolescents have higher rates of STD acquisition than any other age group. In addition, many young adults diagnosed with acquired immunodeficiency syndrome (AIDS) contracted the human immunodeficiency virus (HIV) as teens<sup>5</sup>. Although the average age of sexual introduction nationwide among teens is 16, among inner city youths the average is 13 years of age. Consequently, younger adolescents are more likely to engage in impulsive sexual behavior and are less likely to use contraception which increases risk for pregnancy and STD's. Also, teens that use drugs or alcohol are more likely to be sexually active at earlier ages, possibly due to the dis-inhibiting effects of these substances on adolescents' decisions to delay intercourse<sup>1</sup>. According to the US department of health and human services, African American and Mexican American adolescents ages 12-19 were more likely to be overweight, at 21 percent and 23 percent respectively, than non-Hispanic White adolescents (14 percent)<sup>4</sup>. The reasons for these differences include that poorer families could experience greater instability in the home, worse nutritional management, or may demonstrate accepting attitudes toward obesity. Overweight adolescents are 10 times more likely to become obese adults than their lean peers as well as suffer the medical consequences of such conditions such as Type II diabetes and cardiovascular problems including cardiovascular disease and cancer<sup>3</sup>. However, physical concerns are not the only issue. Teens who suffer from early sexual exposure in addition to substance abuse and obesity tend to have lower self esteem and suffer from depression<sup>1</sup>. Since adolescence represents a pivotal time in the development of attitudes and behaviors that can have life altering consequences, it is important to inform teenagers about health issues in hopes of influencing future decision making.

**Methods:** Participants included four male and seven female Hispanic and African American high school students ranging in age from 14-18, enrolled in Fordham University's Upward Bound Summer program. Those enrolled in the Upward Bound program were automatically assigned to the health course pending signed consent from parents/guardians. Lecture materials included power points and handouts made from Soujourner House's Health lifestyles course as well as information from the following websites: Family

Doctor.org, CDC.gov, Mayo clinic.org, Utah education Network.org, Women web.cam, Kids health.org, Pathmicro.med. Visual education was provided through the film Philadelphia. On the first day of instruction a 45 point multiple choice and fill in the blank examination was given to students to access baseline knowledge. Six topics were represented including: Nutrition and diet (9points), STD's (6 points), Obesity and hypertension (8 points), HIV (6 Points), Substance abuse (7 points) and Relationships including Domestic Violence and Sexual assault (6 points). Bonus points were worth 3 points. Instruction was presented on the aforementioned topics, for 2 and ½ hours three days a week for six weeks. During class time, power points were presented and written papers on topics were assigned. Students were also allowed to work in groups and pairs for certain activities. On the final day of class, the same test was given in order to track any changes in test score, which was indicative of the level of understanding ascertained by the students throughout the course.

**Results:** Test means were used to evaluate the effectiveness of instruction. The test was scored out of 45 points and each question was worth one point overall. Changes in test scores from before to after instruction were assessed using paired t-tests. Overall, all of the students showed significant improvement  $p < .011$ . The average score for the pretest was 21.4 and the average score for the post test was 34. Out of the six topics presented, two were found to have had insignificant effects in terms of expanding knowledge base in students,  $p > .01$ . The other four topics examined including Obesity and hypertension, Relations, HIV, and Substance Abuse showed statistically significant improvement through instruction  $p < .01$ .

	Maximum Points	Pre-Test Mean	Post Test Mean	Mean of paired differences	student t test
Topic 1. Nutrition and Diet	9	4.5	4.8	0.81	>.01
Topic 2. STD's	6	2.3	3.4	0.78	>.01
Topic 3. Obesity and Hypertension	8	4.4	7.2	4.58	<.01
Topic4. Relations	6	3	5.6	6.63	<.01
Topic5. HIV	7	3.6	6	4.53	<.01
Topic 6. Substance Abuse	6	3.3	4.8	3.27	<.01
Bonus	3	0.27	2.2	6.7	<.01
Maximum points	45	21.4	34	8.7	<.01

**Conclusion:** Overall these results show that instruction was beneficial to students. Higher post- test scores over pretest scores proved that the information effectively reached its target audience. Hopefully in the future, with informed decision making students will lower their risks of detrimental end points such as STDs, HIV, and substance abuse as well as obesity and hypertension.

### References:

1. Bachanas, P.J., Morris, M.K., Lewis-Gess, J.K., Sarett-Cuasay, E.J., Flores, A.L, Sirl, K.S., & Sawyer, M.K (2002). Psychological Adjustment, Substance Use, HIV Knowledge, and Risky Sexual Behavior in At-Risk Minority Females: Developmental Differences During Adolescence. *Journal of Pediatric Psychology*, 27(4), 373-284.
2. Creswell, J.W. (2007). *Qualitative inquiry & research design: choosing among five approaches* (2<sup>nd</sup> ed.) Thousand Oaks, CA: Sage Publication.
3. Germann, J.N., Kirschenbaum, D.S., Rich, B.H. & O'Koon, J.C. (2006). Long-term Evaluation of disciplinary Treatment of Morbid Obesity in Low- income Minority Adolescents: La Rabida Children's Hospital's FitMatters Program. *Journal of Adolescent Health*, 39(4.) 553-561.
4. Mizra, N.M., Kadow, K., Palmer, M., Solano, H., Rosche, C. & nmYanovski, J.A. (2004). Prevalence of Overweight among Inner City Hispanic Children Adolescents. *Obesity Research*, 12, 1298- 1310.
5. S.F., Arons, G.A., Sedlar, G.R., & Brown, S.A. (2001). Adolescent substance abuse and sexual risk-taking behavior. *Journal of Adolescent Health*, 28(3,) 181- 189.

# Community Health Research

**Elizabeth Koch, MS2**

**Olivia Widger, MS2**

## **UR Well Summer Internship**

The primary objective for our summer with UR Well was to improve current operations at both the St. Joseph's and Asbury clinics. In the past, summer projects were designed to expand services offered by the UR Well clinics. However, we recognized several organizational needs and decided to devote our summer to perfecting the services already offered by UR Well. With the assistance of the UR Well Co-Directors, we were able to identify four specific goals for the summer:

1. *Create more structure within the Asbury clinic in order to better manage the greater patient load.*
2. *Establish a standard training process for all Administrative Coordinators and Front Desk volunteers.*
3. *Strengthen relations with the St. Joseph's Neighborhood Center staff.*
4. *Improve relations with preceptors.*

### ***Create more structure within the Asbury clinic in order to better manage the greater patient load.***

As the Asbury clinic has expanded its services, a need has arisen for more streamlined operations. The most important aspect of this was figuring out the best way to efficiently manage a much heavier patient load each night. To accomplish this, we worked with the Clinical Coordinators to establish time limits for acute visits and for physical exams. We also began to triage patients upon arrival – by getting a description of their chief complaint, we are able to better assess the type of services they will need, and thus serve them in a more efficient and timely fashion. Another result of our increased patient load is a high demand for school and work physicals. We found that we needed an official physical form to give to patients who needed documentation of a physical exam. For this purpose, we created a physical exam form modeled after those used for instruction at the medical school. This serves a dual purpose – it gives the patient an official record of his/her visit, and it saves time for the health teams by providing them with a standardized format for the physical exam.

### ***Establish a standard training process for all Administrative Coordinators and Front Desk volunteers.***

Perhaps the most important aspect of our work to create more structure within the Asbury clinic was creating a standard training process for all other Administrative Coordinators and incoming Front Desk volunteers. In the past, there had been no consistent training, and as a result, patients were treated differently and given different information from night to night. To solve this problem, we created highly detailed training modules for both St. Joseph's and Asbury that have been distributed to each second-year Administrative Coordinator and each first-year Front Desk volunteer. In addition, each returning Administrative Coordinator was trained by one of us to ensure that from this point out, each clinic night operates with the same policies and practices.

More recently, we have personally interviewed and selected incoming first-year students to work at the Front Desk. We have met with them as a group, and will continue to hold regular meetings for all people involved in the administrative aspect of UR Well to ensure that we remain consistent in the way we operate each clinic night. Not only have we stressed the importance of consistency, we have also increased the accountability that each Administrative Coordinator has in making sure that photocopies are made if we are running low on physical exams, and other important details that before were passed on to the next week's volunteer. This will improve the quality of service we provide to our patients.

### ***Strengthen relations with the St. Joseph's Neighborhood Center staff.***

An additional goal of the summer was to improve relations with St. Joseph's Neighborhood Center staff. Since many of the second-years did not feel that they were adequately trained to run St. Joseph's, many mistakes were made on clinic nights in regards to billing and appointment scheduling. Throughout the summer, we strived to learn the proper way to run St. Joseph's. We now have a good knowledge of how to respectfully use their space and resources, which we have been able to pass along to all other administrative volunteers via the training modules. We also were available to troubleshoot with St. Joseph's staff regarding any issues that came up. For example, we worked closely with the staff to come up with a better scheduling system to avoid late clinic nights. By the end of the summer, UR Well's relationship with staff at St. Joseph's had improved greatly.

***Improve relations with preceptors.***

We are lucky to have such a large group of volunteer physicians that dedicate their time to us every Tuesday and Thursday night. Going into this summer, we felt that we should be doing more to welcome each new preceptor to the clinic, and introduce them to our mission and provide guidance for what they should expect on their first clinic night. To address this, we made a preceptor welcome packet that will be sent to each new preceptor before their first clinic night. In this packet we have included a description of the mission of URWell, as well as a brief history of both St. Joseph's Neighborhood Center and URWell at Asbury. In addition, we included an overview of how each clinic runs on a typical night, and what sorts of services we can provide at each location. This will help the preceptor be better prepared for the type of exams and equipment he/she will be working with. Lastly, we included descriptions of the partnerships we have made within the medical community that can be utilized should a patient need a service that we cannot perform. We believe that this packet will make the new preceptor feel at ease before his/her arrival to the clinic, and most importantly it will help them make the most of the services we can provide for our patients.

***Beyond our summer with UR Well –***

Currently, we are working on several projects that expand on our summer work. First of all, we are working to train second-year Administrative Coordinators in several clinical skills. Originally, simple clinical procedures such as blood draws and TB placements were included in the job description of the Administrative Coordinator in order to allow the health teams to continue seeing patients. Due to the lack of training, we have been unable to perform these procedures. Not only has this affected the efficiency of the clinic nights, it has also deprived Administrative Coordinators from the chance to be involved in the clinical aspect of UR Well. We are now working with the staff at St. Joseph's to organize a training session to learn these clinical procedures and more. Additionally, we are pushing our fellow volunteers to be agents of change within UR Well. This fall, we will be asking each Administrative Coordinator to complete a UR Well improvement project. This will provide an opportunity to implement many of the suggestions made in the strategic plan, created in the spring by the former UR Well director.

This is an exciting time for UR Well – a time for improvement, change, and expansion. We are pleased to be part of UR Well at such a critical point in its development. It is our goal to continue to increase the efficiency of the clinic nights and expand our services in order to achieve our ultimate goal of providing the uninsured and underinsured population of Rochester with affordable, high- quality healthcare.

# Community Health Research

**Bo Hoon Lee, MS2**

**Preceptor:**

**Caroline Magyar, Ph.D., Susan Strahosky, M.D. Associate Professor, Assistant Professor  
Department of Pediatrics**

## **Assessing Community Need for After-School Supports for Families Affected By Autism**

**Objectives:** (1) To ascertain the need for after-school child-care supports for families caring for children with autism, and (2) To ascertain the role that medical students can play in the development and/or provision of after-school family supports to complement medical training in the development of a pediatric medical home for children with autism.

**Introduction:** The Division of Neurodevelopmental and Behavioral Pediatrics, Strong Center for Developmental Disability, and the Rochester Regional Center for Autism Spectrum Disorders (RRCASD), Department of Pediatrics, University of Rochester School of Medicine, has a long history of linking university functions to community activities. The NDBP and its center's form the largest autism center in the state. RRCASD maintains an extensive database of community agencies and an extensive list-serve of parents/caregivers, community providers, and individuals with ASD.

**Background:** Autism spectrum disorders (ASD) are a group of biologically based neurodevelopmental disorders marked by significant qualitative impairments and limitations in three major domains: socialization, communication, and behavior (stereotyped interests and activities). There has been an apparent three- to ten-fold increase in the prevalence of ASD in the U.S. over the past twenty years and affects a staggering number of American families (Waterhouse, 2008). Taking care of a child with an ASD can be emotionally, physically, and financially burdensome. While many informational resources for families exist through national, state and regional organizations, there continues to be a dearth of services at the local level, particularly after-school family support services (OMRDD, 2009). There is a recognized need for more program development and staff training to assist existing agencies in developing and providing ASD specific services that meet local family support needs, and for developing new services that tie university-based functions to community-based needs.

**Methods:** There were two data collection phases in this study: (1) an environmental scan of the existing community infrastructure for after-school family support services, through web-based review of the developmental and human service organizations listed in the RRCASD database (2) examination of parent opinion about the need for a specific after-school child-care service being proposed (Night-Off Program).

**Results:** Regional density map of available services pinpointing locations of current agency services and locations of current agency services specific to after-school child-care revealed a disproportionate lack of the latter. Parent/Caregiver feedback indicated that 76.9% responded that they would use the new service provided by medical students while 17.9% responded that they would not. Descriptive responses illustrated that hesitation to use the program included distance from Rochester, having multiple children and age (older than pediatric age range). Responders who were already using respite or child-care services through other agencies were equally enthusiastic about Night-Off and the additional socialization opportunities that it would provide for their children.

**Conclusion:** There is a definite deficit in local affordable child-care options available to families caring for children with autism and a paralleled need for such services. The proposed program is as follows: the

Night-Off Program will offer a free in-home after-school childcare service for families with children within the pediatric age-range and who meet the eligibility criteria. It will bring medical students into the autism community to provide occasional childcare services. Training and education will be in the form of lectures and discussions presented by qualified health professionals, including specialists and experienced medical doctors. Once adequate training has been completed, students will go in pairs to families' homes 1-2 times a month during the late-afternoon/evening hours. Night-Off will be a volunteer-based service structured and developed to increase awareness among medical students and service the autism community and its childcare needs, appropriate to the capacity of the program.

### **References:**

- Bromly, J., Hare, D.J., Davison, K., Emerson, E. Mothers supporting children with autistic spectrum disorders: social support, mental health status and satisfaction with services (2004). *Autism* 8: 409-423.
- Lee, L., Harrington, R.A., Louie, B.B., Newshaffer, C.J. (2008). Children with autism: quality of life and parental concerns. *J Autism Dev Disord* 38: 1147-1160.
- Montes, G., Halterman, J.S. Child care problems and employment among families with preschool-aged children with autism in the United States (2008). *Pediatrics* 122: e202-e208 New York State, Office of Mental Retardation and Developmental Disabilities (2009). *Interagency Task Force on Autism*. Albany, NY. Available on-line:[http://www.omr.state.ny.us/autism/hp\\_autism\\_interagency.jsp](http://www.omr.state.ny.us/autism/hp_autism_interagency.jsp)
- Pervasive Developmental Disorders. In: American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR®). American Psychiatric Association, Washington, DC 2000. p. 70.
- Smith, L.E., Hong, J., Seltzer, M.M., Greenburg, J., Almeida, D.M., Bishop, S.L. Daily experiences among mothers of adolescents and adults with autism spectrum disorder (2010). *J Autism Dev Disord* 40:167-178
- Waterhouse, L. Autism overflows: increasing prevalence and proliferating theories (2008). *Neuropsychol Rev* 18: 273-286
- Williams, J.G., Higgins, J.P., Brayne, C.E. (2006). Systemic review of prevalence studies of autism spectrum disorders, *Arch Dis Child* 91(1): 8-15.

# Community Health Research

Mark Sullivan, MS2

## **Preceptors:**

**Dr. Edmund D. Pellegrino,**  
Emeritus Professor of Medicine and Medical Ethics,  
Kennedy Institute of Ethics

**Dr. Jane Greenlaw,**  
Director and Associate Professor, Center for Ethics, Humanities, & Palliative Care,  
University of Rochester School of Medicine & Dentistry

## **Virtue Ethics In The Education Of Life-Long Learners**

### **Introduction:**

In the Fall/Winter 2009 *Rochester Medicine* publication, Dr. Brad Berk discusses his vision of a more “compassionate caregiving”. At the same time, he brings to light the daily challenges that physicians must face when trying to preserve the physician-patient relationship in the hospital environment. The article calls for solutions that legitimize compassionate caregiving in the workplace and that provide educational opportunities for students to develop the necessary dispositions for its practice.

### **Background:**

On the dawn of 100th year anniversary of the Flexner report, medical educators across the country are discussing how to prepare students for the practice of medicine in the next century. Many of the changes in medical education have been a response to changes in the organizational structure of the medical institution, to the current state of the economy, and to the postulated diseases that will manifest themselves in the future patient population. Despite these significant changes, some educators have suggested that what is essential to advancing medical education is a continued focus on the character traits or attitudes that are necessary to providing care for patients. This is evident in comments made by patients about the importance of bedside manner, in themes of commencement addresses, and in the emergence of hospital models directed towards patient-centered care. Limited attention, however, has been afforded to an examination of virtue ethics and how learning ethics at the bedside can be useful in developing the necessary characteristics aimed at preserving the physician-patient relationship.

### **Methodology:**

- Define virtue ethics.
- Present the philosophical basis of virtue ethics in the health professions.
- Propose a model for a bioethics interest group that would provide interested medical students with an opportunity to further explore issues of professionalism and the physician-patient relationship with faculty at the University of Rochester School of Medicine & Dentistry.

### **References:**

- Aristotle, and D. P. Chase. *Nicomachean Ethics*. Mineola, NY: Dover Publications, 1998.
- Peabody, FW. The care of the medical patient. *JAMA* 1927;88: 877-82.
- Pellegrino, ED. Professionalism, profession and the virtues of the good physician. *Mt Sinai J Med* 2002;69(6):378-84.
- Pellegrino, ED, Thomasma DC. The virtues of medical practice. New York: Oxford UP, 1993.
- Sielger, M. A legacy of osler: teaching clinical ethics at the bedside. *JAMA* 1978;239(10):951-6.
- Spike, J, Greenlaw, J. Ethics consultation: high ideals or unrealistic expectations. *Ann Intern Med* 2000;133(1):55-7.
- Wentzel, M. The comeback. *Rochester Medicine* Fall/Winter 2009; 4-9.

# Community Health Research

**Sarah Waldman, MS2**

**Preceptor:**

**Adrienne Morgan, MS**

**Director CACHED (Center for Advocacy, Community Health, Education and Diversity) University of Rochester School of Medicine and Dentistry**

## **Evaluation of the Advantages and Disadvantages of Partnering with Remote Area Medical to Support the Rochester Weekend of Care**

**Introduction:** In 1985, Remote Area Medical (RAM) was founded by Stan Brock in order to provide medical services to places around the world that do not have access to care or resources. Over the past few decades the non-profit organization has turned its focus on the United States<sup>4</sup>. RAM conducts healthcare weekends in multiple states across the country; bringing dental, vision, and medical care, free of charge, to anyone willing to wait in line. They provide all of the dental and visual equipment necessary for free care in a large mobile clinic setting including, labs that can manufacture glasses within a few hours. With the RAM model in mind, five students from the University of Rochester School of Medicine and Dentistry set out to establish a weekend of care in Rochester. The goal of this summer project was to determine whether working directly with RAM would be necessary and beneficial to creating a sustainable weekend of care for the Rochester community.

**Objectives:** To assess strategies to most effectively organize and execute a community health weekend in Monroe County, including an assessment of potential relationships with community partners and Remote Area Medical (RAM).

**Background:** According to the National Health Interview Survey (NHIS), in 2008, approximately 14.7% of the population under age 65, or 40.7 million individuals living in the United States, is either uninsured or underinsured<sup>1</sup>. The data for Monroe County is strikingly similar to the national average with 10% of individuals under the age of 65 lacking insurance coverage in the year 2000<sup>3</sup>. While this data is 10 years old, recent signs such as the economic recession, suggest that the numbers are stable if not elevated. Additionally, Rochester has seen an increase in the utilization of free clinics and resources within the last few years. St. Joseph's Neighborhood Center, a free clinic run by students from the University of Rochester School of Medicine and Dentistry, experienced a 70% increase in the last quarter of the 2008 fiscal year<sup>2</sup>. Currently, the St. Joseph's clinic services 3,500 patients annually, with 22,000 patient encounters. While clinics such as St. Joe's help to fill a gap for the poor working, there are long waiting periods; patients often wait several weeks before they can be seen at the clinic. In an effort to address care for the uninsured and underinsured of Monroe County, a group of medical students began a Community Health Improvement Clerkship (CHIC project) to establish a weekend for the local community that would provide free medical, dental, and vision care to patients. After assessing the need in the community and connecting with local organizations, the medical students contacted RAM in hopes that they would be able to ensure the portable dental equipment and mobile visual units needed to institute the weekend of care. While they began to formulate a relationship with RAM, details of how the two organizations would work together were not concrete. Further information about RAM and its projects needed to be obtained.

**Methods:** The primary goal of this project was to attend an established RAM event with the intent of determining how to best provide the dental and vision care and whether RAM was a necessary partner in offering such services. On the weekend of July 23, 2010 to July 25, 2010, three medical students from the

class of 2013 traveled to Wise County Virginia to observe a RAM event at the Wise County Fairgrounds. The students participated in volunteer activities, interviewed volunteers, spoke with patients, and discussed strategies with leaders of each division of care. Paperwork, photos, and contact information were collected. Meetings were held with Jean Jolly, the Rochester contact with RAM, and Stan Brock, the founder of RAM.

**Results:** Initially, RAM appeared to be a successful organization that would afford the medical students the opportunity to easily provide dental and vision resources at the weekend of care. Upon further evaluation at the event in Wise County Virginia, it became more apparent that forming a partnership with RAM would not be in the best interest of the project. This decision was based on four main observations of the RAM organization:

- 1) *RAM holds no insurance:* All events organized with the help of RAM are publicized as RAM events. The organization controls the press and media but takes on no liability for the events. They have no insurance policies and if an unfortunate circumstance were to arise, RAM would hold the individual practitioners responsible.
- 2) *There is no certainty RAM will attend the event:* Over the course of the weekend in Wise County, references were made to at least three other RAM events that had been suddenly cancelled within weeks of the scheduled clinics. In these cases, money had been raised, volunteers had been recruited, and advertisements had even been purchased. The relationship with RAM may be a risky investment with no contract or firm commitment that they must attend.
- 3) *Following discussions with the leaders of RAM it became clear that our event was a means for political ambitions:* In each state that RAM has entered they have attempted to change the laws to allow physicians licensed in outside states to practice at the event. Currently, in New York, there is no temporary license to practice and only those who hold New York licenses can practice. This information made it even more apparent that RAM might not attend our weekend of care since outside practitioners could not participate and RAM has hopes of changing the legislature.
- 4) *Long term partners of the RAM hinted at terminating their relationship with the organization:* The UVA health system has been a main contributor to the success of the event in Wise County. Over the past 10 years they developed a strong medical service division for the event using their own hospital supplies, employees, and funding. After a long relationship with RAM, UVA may be separating from the event and establishing its own weekend of care. In a telling sign, the UVA re-triaged every patient sent to them from the main RAM triage center.

**Conclusions:** While it will require more work upfront and services may need to be more focused, it is clear that in order to successfully put on a safe and effective clinic, the weekend of care is more sustainable without the assistance of Remote Area Medical.

#### **References:**

1. NHIS - National Health Interview Survey Homepage. <http://www.cdc.gov/nchs/nhis.htm>. Updated 2009. Accessed August 5, 2009, September 12, 2009, October 14, 2009.
2. St. Joseph's Neighborhood Center - <http://www.sjncenter.org/index.php>. Updated 2009. Accessed August 22, 2009, September 12, 2009, October 14, 2009, September 27, 2010.
3. <http://www.harrisi.org/news/allnewsbydate.asp?NewsID=238>. Updated 2009. Accessed August 5, 2009, September 12, 2009, October 14 2009, September 27, 2010.
4. Remote Area Medical - <http://www.ramusa.org/about/mission.htm>. Updated 2010. Updated 2010. Accessed September 27, 2010.

# Community Health Research

Emilie Wasserman, MS2

**Preceptor:**

**Sarah Betstadt, M.D., M.P.H. Department of Obstetrics and Gynecology  
University of Rochester Medical Center**

## **Community Outreach: A Summer in Abortion Care & Reproductive Health**

**Introduction:** As an undergraduate, I enrolled in Gender Studies courses alongside my premedical requirements because I was inspired by the work of Planned Parenthood, GLBT health centers, and ACT UP, which addressed gender-based inequities in healthcare. As a member of URMC's chapter of Medical Students for Choice (MSFC) during my first year of medical school, I became acquainted with the barriers to reproductive freedom for women in the United States, which include physician shortages, procedural cost. There is also a prevailing social stigma, which is assigned both to patients who receive abortion services and providers of abortion services.<sup>i</sup> Because reproductive health represents the intersection between my undergraduate work and my passion for medicine, I spent the summer of 2010 doing a Community Outreach Project in abortion care and reproductive health.

**Objective:** Provide hands-on support for Planned Parenthood in Rochester and the Termination of Pregnancy Clinic at Strong Memorial Hospital while gaining exposure to and knowledge about reproductive health.

**Background:** In 2005, 85% of counties in the United States lacked an abortion provider, leaving 35% of American women without access to a local provider.<sup>ii</sup> According to Dr. Carol Joffe, who has been writing about abortion in the US for the last four decades "The lack of routine training in the most relevant specialty, Obstetrics and Gynecology, is the main reason for the shortage of abortion providers."<sup>iii</sup> The Kenneth J. Ryan Residency Training Program and Family Planning Fellowships, which provide funding to institutions for the purpose of increasing abortion content in medical education, have successfully trained more than 170 fellows at 49 distinct residency programs, demonstrating the potential of medical education to heal the provider shortage.<sup>iv</sup>

**Externship Design:** My Summer Community Outreach Project had three core components: clinical exposure to reproductive healthcare, community advocacy and preparation for student leadership.

I spent approximately 35 hours each week participating in patient care, including time at ambulatory, clinic and operating room settings. My procedure log from the summer included: Intrauterine device insertion, Implanon placement, cervical dilation, laminaria insertion, pap smears, paracervical block, pelvic exams, STI testing, dilation and evacuation, dilation and suction, and trans abdominal and vaginal ultrasound. I learned to take a thorough obstetrical history, counsel patients on contraceptive options and perform pregnancy options counseling.

Community advocacy took the form of 30 hours of training to become a Rape Crisis Counselor at Planned Parenthood, followed by 24 hours of being on-call each month for the hotline over the summer. Rape Crisis counselors are trained in the legal, social and psychological issues surrounding sexual assault and are certified to serve as advocates for victims of sexual assault.

To prepare for my MSFC leadership role for the 2010-11 academic year, I read *Dispatches From the Abortion Wars* by Carol Joffe and *This Common Secret* by Susan Wickland to increase my historical understanding of abortion in the United States. I also prepared a thirty-minute presentation entitled "Anti- Abortion Arguments by Self-identified Feminists and Advocates for Women in Germany and the United States," which I delivered to my preceptors.

**Conclusion:** My Summer Community Outreach Project in Abortion Care & Reproductive Health increased my understanding of women's health and family planning through a biopsychosocial approach. Procedural training was complemented by counseling and history taking experience. This period of focused exposure to family planning provided an essential supplement to my medical education, which I hope others will pursue.

---

<sup>i</sup> Joffe, Carol. *Dispatches from the Abortion Wars*; Beacon-Hill: Boston, 2009.

<sup>ii</sup> Jones RK et al. Abortion in the United States: Incidence and Access, 2005, *Perspectives on Sexual and Reproductive Health*, 2008, 40(1):6–16.

<sup>iii</sup> Joffe, Carol. *Dispatches from the Abortion Wars*; Beacon-Hill: Boston, 2009.

<sup>iv</sup> Bazelon, Emily. The New Abortion Providers, *New York Times Magazine*, July 18 2010, pp .

# International Medicine Research

Michael Barnes, MS2

**Preceptor:**

**Michael Keefer, MD Department of Infectious Disease  
University of Rochester Medical Center**

## Grassroot Soccer

*Considering how the universal language of football<sup>D</sup> is harnessed to fight HIV/AIDS in South Africa*

**Introduction:**

At the end of 2008 it is estimated around 31.3 million adults and 2.1 million children were living with the human immunodeficiency virus (HIV). During 2008, 2.7 million people became infected with HIV and 2 million died from AIDS. Although this opportunistic virus has spread across the globe, approximately 2/3 of individuals living with HIV reside in Sub-Saharan Africa, reflecting how the HIV/AIDS epidemic has truly taken root within the developing world<sup>1</sup>.

Tremendous resources have been directed towards preventive initiatives in the global fight against HIV. With the potential for long-term benefits inherent in early interventions, at-risk youth have naturally become an ideal target for such efforts. Although HIV infection in people aged 15-24 is declining in many countries, a significant number of young people continue to be infected each year. Approximately half of the people who acquire HIV become infected before they turn 25<sup>1</sup> and AIDS is the second most common cause of death among 20-24 year olds<sup>2</sup>.

There is substantial literature demonstrating how HIV interventions can successfully promote the adoption of protective sexual behaviors among adolescents<sup>4,5,6</sup>. School-based health education programs represent the most common approach to reach youth, however the success of such initiatives has been mixed, if evaluated at all. Along with failing to reach children not in school, fear of community disapproval, reluctance to discuss sex or HIV, curriculum overload and preference for doctrinaire instructions have been demonstrated limitations to the effectiveness of using regular curriculum teachers<sup>7,8</sup>. Indeed, these factors were found to represent barriers to successful HIV prevention interventions for youth worldwide<sup>9</sup>. Given the popularity of football in Sub-Saharan Africa and South Africa's hosting the World Cup in 2010, a number of organizations have developed alternatives to the traditional school curriculum HIV/AIDS education in South Africa.

In the third of a longitudinal series of stocktaking reports on Children and AIDS published in 2008, UNICEF, UNAIDS, WHO & UNFPA suggest national HIV and AIDS strategic plans need to have a strong focus on prevention, advocating specific plans taking into account assessments of risk, vulnerability and disparities among young people both in and out of school<sup>3</sup>. Ultimately, this report cites a lack of data as "a major constraint on responding appropriately to young people's need for information on how to prevent HIV".

**Objectives:**

- (1) To explore parallels and differences between various organizations harnessing the power of soccer in at-risk adolescent HIV/AIDS education across the geography of South Africa and during the 2010 World Cup.

**Variables** ... history, endeavor, philosophy, approach & ambition

- (2) To examine the degree to which strategic plan recommendations from the 2008 stocktaking report on Children and AIDS published by UNICEF, UNAIDS, WHO & UNFPA are realized on and around the pitch in South Africa during the summer of 2010.

**Variables** ... outcome monitoring, subpopulations served

<sup>D</sup> football = soccer here

**Background:**

Grassroot Soccer, a registered 501(c)3 charitable organization harnessing the universal language of football and the energy surrounding the world cup for education of at-risk adolescents in the global fight against HIV, has demonstrated exponential growth since conception in 2002. This group's fundamentally research driven and innovative model, as well as the evidence-based preventive care it makes possible, illuminates GRS as an obvious informative model for future health education and prevention throughout the developing world.

Given recent insights into mechanisms of HIV transmission down generations, Skillz Street is a new curriculum that specifically targets adolescent girls with activities-based HIV Prevention curriculum endeavoring to build knowledge, skills and self-efficacy to prevent HIV, while simultaneously challenging the underlying social norms, particularly gender norms, fueling the epidemic. The study is ongoing, encompasses 2400 graduates and is being conducted in Cape Town, Port Elizabeth and Soweto.

During the 2010 World Cup in South Africa, GRS conducted 41 Skillz Holiday Programs in 7 of 9 South African provinces in collaboration with implementing partners and corporate sponsors. Reaching approximately 4,100 youth with a balance of soccer, HIV prevention and life skills activities, these programs also provided meals and a constructive, healthy environment for youth during the extended World Cup school holiday throughout South Africa. Campers were recruited through the public school system and the curriculum they are engaging focuses on building life skills through key curricular topics including making healthy decisions, avoiding risks, building support networks, reducing stigma and discrimination, increasing knowledge about testing and treatment, addressing gender issues, and assessing values.

**Methods:**

This research project has three facets, was conducted across 6 locations and 3 organizations employing soccer in at-risk adolescent HIV/AIDS education in the townships of Soweto (Johannesburg), Khayelitsha (Cape Town), Umlazi (Durban), New Brighton and Motherwell (Port Elizabeth). The first facet includes 16 focused interviews conducted with coaches, administrators & founders to explore each site and organizations history, endeavor, philosophy, approach & ambition. The second arm of this study entails observation of these various initiatives for further exploration of differences and parallels across groups and geography. Finally, to further understand the role of monitoring and evaluation in Grassroot Soccer's curriculum development and meteoric success, many hours were spent assisting with pre and post survey outcomes measurement for an exciting new curriculum, Skillz Street.

**Results:**

- (1) Each site and the three organizations examined in this study are, intuitively, both markedly alike and remarkably different. The most striking commonality being the degree to which success hinges upon charismatic coaches and staff familiar and empowered by a culturally savvy, engaging curriculum. Common challenges include turnover and training of personnel, cultural gender norms, stigma, misinformation and community integration. A final commonality of interest is how both GRS and Whizz Kids are integrating into the South African school system curriculum.

The degree and nature by which football is *actually* incorporated into the curriculum is markedly different between GRS & Whizz Kids, the two major organizations in the field, reflecting a fundamental spectrum in the use of sport for development. For instance, soccer often manifests as a metaphor or takes the back seat in GRS curriculum. The third organization involved in this project, CTC10 is markedly different in its sole focus on one site and one community in Khayelitsha township outside Cape Town, illustrating tremendous success with community integration. Indeed, the degree of effort as well as success in community integration varied across sites and organizations, with success reflecting both effort as well as inclusion of community members in design and implementation. Furthermore, the role monitoring and evaluation played varied across groups, with the fundamental role evidence plays in the GRS business model clearly setting the gold

standard. Lastly, the emphasis on cultivating peer educators by GRS represents a particularly powerful mechanism for the dissemination of health information<sup>10,11</sup>.

- (2) The degree to which strategic plan recommendations for outcome monitoring and targeted subpopulations from the 2008 stocktaking report on Children and AIDS published by UNICEF, UNAIDS, WHO & UNFPA are realized on and around the pitch in South Africa during the summer of 2010 remain quite variable across organization. As mentioned, GRS sets the standard for outcome monitoring. Due to the focus on schools for recruitment, children who are not in school remain underserved by these preventive health education initiatives.

### **Conclusions:**

As demonstrated this summer in South Africa, the universal language of football and the groundswell surrounding the world cup have tremendous potential for health education, providing the essential catalyst for an attentive audience. As we endeavor to harness and realize this potential, there is an opportunity for GRS, WhizzKids and CTC10 to inform each others work through relative expertise in fundraising, monitoring and evaluation, integration into the public school system and community integration.

Internal and externally implemented monitoring and evaluation offer a rigorous mechanism by which we can continually improve our efforts and efficiency in preventive health education, as illustrated by the GRS model. In light of their exponential growth and underlying success in fundraising, it would appear such measures may become increasingly important for fundraising and grant writing in this field as well.

Children not in school remain particularly vulnerable due to the difficulty in accessing this particularly exposed population. Bridging this educational void will be essential in ongoing efforts to educate young generations of South Africans about HIV/AIDS.

### **References:**

1. UNAIDS (2009, November), 'AIDS epidemic update'
2. Patton G et al (2009, 12th September), 'Global patterns of mortality in young people: a systematic analysis of population health data' *The Lancet* 374(9693).
3. UNICEF, UNAIDS, WHO & UNFPA (2008), 'Children & AIDS, 3rd Stocktaking Report'
  4. Kim et al. (1997). Effectiveness of the 40 adolescent AIDS-risk reduction interventions: A quantitative review. *Journal of Adolescent Health*. 20(3), 204-215.
  5. Mullen et al. (2002). Meta-analysis of the effects of behavioral HIV prevention interventions on the sexual behavior of sexually experienced adolescents in controlled studies in the United States. *Journal of Acquired Immune Deficiency Syndrome*, 30, 94-105.
  6. Peersman & Levy (1998) Focus and effectiveness of HIV-prevention efforts for young people. *AIDS*, 12(SA), S191-S196.
  7. Kinsman et al. (2001). Evaluation of a comprehensive school-based AIDS education programme in rural Masaka, Uganda. *Health Education Research*, 16(1) 85-100.
  8. Visser, M. (1996) Evaluation of the first AIDS Kit, the AIDS and lifestyle education programme for teenagers. *South African Journal of Psychology*, 26(2), 103-113.
  9. Applegate, M. (1998). AIDS education for adolescents: A review of the literature. *Journal of HIV/AIDS Prevention and Education*, 2(1), 5-29.
  10. Clark et al. (2006) An Adolescent-targeted HIV Prevention Project Using African Professional Soccer Players as Role Models and Educators in Bulawayo, Zimbabwe. *Aids & Behavior*. 10:S77-S83
  11. [www.grassrootsoccer.org](http://www.grassrootsoccer.org)

# International Medicine Research

**Matthew Brockway, MS2**

**Howard Lin, MS2**

**Preceptors:**

**Douglas Stockman, MD Department of Family Medicine, Highland Family Medicine**

**Joseph Lanning**

**Malawi Immersion Seminar Director University of Georgia**

## **Understanding Local Perceptions of Relevant Diseases in Rural Malawi**

**Background:** In light of the numerous health disparities in the world, populations in Africa are among those generally considered to have the poorest overall health. In Sub-Saharan Africa alone, measures of health outcomes are staggering. According to 2008 statistics, the mortality rate for infants is 88.5 per 1,000 live births. Furthermore, life expectancy at birth is only 51.5 years. Within the African continent, some countries are facing larger health disparities than others. One severely affected country is Malawi. In 2007, this country's infant mortality rate was 110 per 1,000; the life expectancy at birth was 50 years (World Bank). Before one can address these health disparities and develop methods of intervention, one has to develop a better understanding of the causes for these health disparities. This entails understanding local perception of relevant diseases and the impact these disease have on everyday life. Illness is culturally shaped in the sense that how we perceive, experience, and cope with disease is based on our explanations of sickness, explanations specific to the social positions we occupy and systems of meaning we employ (Kleinman).

**Objective:** The purpose of this project was to develop a better understanding of local perceptions of relevant diseases specific to rural Malawi.

**Methods:** Four focus group discussions were conducted to conclude which diseases were most relevant within the local rural area. From the results of the focus group discussions, questionnaires were created with regard to 10 relevant diseases. Within the questionnaire, the diseases were presented with the same terminology expressed by the participants from the focus groups. The questions addressed ranking the frequency and severity of each disease, methods of treatment for each disease, whether the disease could be caused by witchcraft or not, and if the disease was found to have higher incidence in certain months within the year. Surveys were given to 44 individuals varying in age and sex from 8 local surrounding villages to assess the local perceptions of each of the diseases.

**Results:** Results from the focus group discussions suggested that 10 locally relevant diseases include cholera, diarrhea, emotional problems (depression and madness), HIV/AIDS, leprosy, malaria, malnutrition (kwashiorkor and marasmus), sexually transmitted infections (syphilis and gonorrhea), tuberculosis, regular cough, and vomiting. Of the diseases listed, HIV/AIDS was considered the most severe disease by 33 out of 44 participants and malaria was considered to be the most frequent disease by 25 out of 44 participants. When participants were asked to qualify decisions of HIV/AIDS being the most severe disease, a common theme that reoccurred was that HIV/AIDS is the most severe because there is no cure for it. Despite many participants acknowledging that treatments are available to prolong the life of an individual with HIV and that many people die each year from other diseases such as cholera and malaria, many were still insistent that the lack of a cure qualified HIV/AIDS to be the most severe.

**Conclusion:** A questionnaire survey addressing the severity and frequency of 10 relevant diseases, administered to 44 local participants within a rural area in Malawi, indicates that HIV/AIDS is perceived to be the most severe disease within the area and that malaria is perceived to be the most frequent disease within the area. Qualifications of responses suggest that HIV/AIDS is perceived to be the most severe disease do to the fact that there is no cure for the disease. Addressing other cultural factors that pertain to how individuals perceive the severity of a particular disease may help in better understanding the local perceptions of diseases relevant to rural Malawi.

### **References:**

Kleinman, Arthur M.D. "Culture, Illness, and Care." *Annals of Internal Medicine*. 88.2. (1978): 251-258.

World Bank Group (2008). *The World Bank, Africa, Data and Statistics*. Website, updated 2010. Retrieved January 2010, from <http://www.unmillenniumproject.org/>

World Health Organization (2009). *World Health Statistics 2009*. PDF article accessed online. p. 14, 22, 40, 42. Retrieved January 2010, from [http://www.who.int/whosis/whostat/EN\\_WHS09\\_Full.pdf](http://www.who.int/whosis/whostat/EN_WHS09_Full.pdf)

World Health Organization (2004). *Newborn health: Policy and planning framework*. Retrieved January 2009, from Healthy Newborn Partnership. Website: [http://www.healthynewborns.org/files/595\\_HNP\\_FW\\_Draft\\_2\\_05.pdf](http://www.healthynewborns.org/files/595_HNP_FW_Draft_2_05.pdf)

# International Medicine Research

**Peter Capucilli, MS2**

**Brendan McCleary, MS2**

**Michael Prucha, MS2**

**Preceptor:**

**Percy Mayta Tristan, MD, MPH - National Institute of Health of Peru**

## **Factors Influencing Specialty Choice among Medical Students in Peru**

**Introduction/Background:** In an effort to elicit the factors involved in medical students' decisions to pursue individual fields of medicine, we conducted a survey study at four geographically diverse medical schools in Peru. We chose to conduct our study in Peru based on data surrounding its great shortage of physicians. While the US medical system is not currently in such a distressed state, it is plausible to infer that the effects of a significant shortage in physicians, particularly primary care physicians, might be well observed in a country such as Peru.

**Objective:** To analyze the importance of the factors that influence Peruvian medical students in making choices about their future medical specialties and emigration.

**Background:** Peru shows a lack of access to physicians of many specialties in underserved and rural areas. Despite the fact that Peru currently has 24 medical schools and graduates hundreds of physicians per year, lack of access to physicians continues to be a problem in some regions (ASPEFAM, 2010). Peru has experienced a decrease in the number of new doctors choosing primary care fields from 40.4% choosing a primary care field in 2000, to 35.3% making the same choice in 2004, a 5.1% decrease in only 4 years (ASPEFAM, 2005). While several studies in the US have investigated the factors behind choice of medical specialties in medical students, insufficient attention has been given to these phenomena in Latin America.

**Methods:** All participants were active medical students, candidates for the "Physician-Surgeon" degree (equivalent to MD in the US). The original, two-sided survey tool entitled, "Selection of a Medical Specialty Choice among Medical Students," was administered to first, fifth, and sixth year students at four medical schools in Peru to examine both incoming medical students without clinical exposure (first years) and students in the later years of education with experience in a clinical setting (fifth and sixth years). The survey included questions regarding demographics, emigration intention, as well as a four-point forced-choice ranking of factors that influence students' choice of medical specialties. Students rated each factor as Extremely Important, Very Important, Less Important, or Not Important in their consideration and decision to pursue their intended specialty. Surveys were administered to students during their scheduled lecture hour, and were given fifteen minutes to complete the questions. A verbal consent statement was read in Spanish explaining the purpose of the survey, possible harms and benefits, as well as the confidentiality of data.

**Results:** A total of n=617 surveys were included in the multivariate  $\chi^2$  analysis performed using STATA 9.1 for Windows. Medical specialties were grouped into four areas of practice including, medicine specialties, surgical specialties, non-patient specialties, and general medicine specialties. Influencing factors were separated into two categories, specifically "demographic factors" and "career factors." Each factor within the major categories was evaluated for statistically significant influence on students' choice of medical specialty, according to the importance rankings for each factor.

"Demographic factors" found to be statistically significant in influencing career choice were year in

school ( $p=0.002$ ) and being older or younger than 22 years of age ( $p=0.001$ ). Civil status, gender, university attended, hometown, and emigration intention had no significant influence on students' choice of medical specialty. "Career factors" that significantly influenced medical students' choice of specialty included the following: high salary ( $p<0.001$ ), flexible schedule ( $p=0.011$ ), number of hours worked per week ( $p=0.038$ ), interaction with patients ( $p=0.030$ ), ability to help the underserved ( $p=0.034$ ), and debt. "Career factors" that had no significant effect on students' choice of medical specialty were years of residency, access to technology, specialty prestige, family opinion, difficulty in obtaining a residency position, and ability to practice medicine near family.

**Analysis/Conclusions:** The results of our study suggest that both demographic and career factors have significant impacts on choices medical student make when choosing a medical specialty. Among the demographic factors, year in school had a statistically significant influence on specialties that students chose. While first-year students with no clinical experience were most likely to choose "medicine" specialties, sixth-year students were most likely to choose "surgical" specialties and "non-patient" specialties, and fifth-year students were most likely to choose "general" specialties." The age of the students also had a statistically significant effect, with a difference for students older or younger than 22 years of age. Students older than 22 more often reported interest in "surgical" specialties while younger students reported interest in pursuing careers as "medicine" specialties. These data may indicate that exposure to clinical care as well as education throughout medical training might have an impact on the specialties students choose to pursue. Students' interests seem to change as they are exposed to a broader field of medicine through the years of medical education and clinical training.

Several "career factors" significantly influenced medical students' specialty choices. These results suggest important trends regarding the most influential factors for students in choosing one of the four major areas of medical practice. Common to all four specialty areas was the importance of interaction with patients. Those entering fields that are intimately involved in patient care such as general medicine, surgical medicine and medicine specialties presumably hold patient interaction as important. Conversely, those who have indicated interest in non-patient specialties might also have rated patient interaction as an important influencing factor for the opposite reason (ie. They do not want much patient contact). We also found that opportunity to work with the underserved was important to all four specialty areas, but was particularly important to medicine, general medicine, and surgical specialties. All three groups indicated at least 50% of the time that this is a "very important" factor in their decision. A third point to note from the data is that only those interested in surgical specialties chose high salary as an important influence in their specialty choice. This data is consistent with the fact that surgeons in Peru are among some of the highest paid specialists. Furthermore, surgical specialties indicated that flexibility of schedule was less important, suggesting that they might be willing to sacrifice schedule flexibility for higher wages. Students choosing non-patient specialties, in contrast, rated flexibility of schedule as an important factor in their decision, indicating that these positions, not involved directly in patient care, offer the physician a more flexible schedule.

It is important to note that debt was rated as the least important factor in a separate ranking of factors, likely because few students borrow money for medical education in Peru. While our data show that many students choose to go into a General Medicine type specialty, it is important to note that these physicians do *not* represent Primary Care as we know it in the US. In Peru, those who practice in the clinics are generally non-specialized MDs. Thus, the General Medicine practitioners represent a different subset of specialties, and not Primary Care.

Medical students of the future will continue to exercise their free will in choosing a medical profession. However, we hope that our research might assist governments, professional organizations and other decision-making bodies in their ability to influence the distribution of medical specialties. We hope that such a redistribution of the medical workforce, both in geography and of specialties, will help to extend physician services to underserved populations. Additionally, the results of this study may assist medical educators and advisors who work intimately with medical students through critical career decision

## References

- Asociación Peruana de Facultades de Medicina (ASPEFAM) 2010, [www.aspefam.org.pe/miembros.htm](http://www.aspefam.org.pe/miembros.htm)
- Asociación Peruana de Facultades de Medicina (ASPEFAM) 2005, [www.aspefam.org.pe/Curso/tallerespecialistas/ponencia4.pps](http://www.aspefam.org.pe/Curso/tallerespecialistas/ponencia4.pps)
- Bodenheimer, Thomas. Primary Care -- Will It Survive?. *N Engl J Med* 2006 355: 861-864
- Borges et al., Influences on specialty choice for students entering person-oriented and technique-oriented specialties. *Medical Teacher*. 31( 2009), 1086-1088.
- Cahill, et al. (2009). Should I Stay or Should I Go?: The Factors Influencing Physician Migration in Peru. Poster Presentation. University of Rochester School of Medicine and Dentistry.
- Donnon, T., Woloschuk, W., and Myhre, D. Issues related to medical students' engagement in integrated rural placements: an exploratory factor analysis. *Canadian Journal of Rural Medicine* 2009; 14 (3).
- Dorsey ER, Jajoura D, Rutecki GW. 2005. The influence of controllable lifestyle and sex on specialty choices of graduating U.S. medical students, 1996–2003. *Acad Med* 80: 791–796.
- Hauer et al. Factors associated with medical students' career choices regarding internal medicine. *JAMA*. 300(10) (2008):1154-1164.
- Howard S. Teitelbaum, DO, PhD, MPH, Nat Ehrlich, PhD, and Lisa Travis, MS. Factors Affecting Specialty Choice Among Osteopathic Medical Students. *Academic Medicine*, Vol. 84, No. 6 / June 2009
- Jumpa M, et al., The role of regulation in influencing income-generating activities among public sector doctors in Peru. *Hum Resour Health*. 2007 Feb 26;5:5.
- Mayta-Tristán, et al. Low wages and brain drain: an alert from Peru, *Lancet*. 2008 May 10; 371(9624): 1577
- McGaha, AL, Schmittling, GT, DeVilbiss, AD, Pugno, PA. Entry of US Medical School Graduates Into Family Medicine Residencies: 2008–2009 and 3-year Summary. Vol. 41, No. 8, 555-566.
- Ministerio de Salud del Perú (MINSa) 2007, <http://www.minsa.gob.pe/portada/estadistica.htm>
- Ministerio de Salud del Perú (MINSa) 2009, <http://www.minsa.gob.pe/servicios/serums/2009/default.asp> [Pan-American Health Organization 2008, http://new.paho.org/per/index.php?option=com\\_content&task=blogcategory&id=811&Itemid=557](http://new.paho.org/per/index.php?option=com_content&task=blogcategory&id=811&Itemid=557)
- Rabadán et. al. Changes in the knowledge of and attitudes toward family medicine after completing a primary care course. *Medical Student Education*. 42(1) (2009): 35-40.
- Schwartz, R.W., Jarecky, R.K, Strodel, W.E., Haley, J.V., Young, A.B. and Griffen, W.O., Jr. Controllable Lifestyle: A New Factor in Career Choice by Medical Students. *Acad. Med.* 64(1989): 606- 609
- Schwartz, R. W., et al. Career Change: In Quest of a Controllable Lifestyle. *K. Surg. Res.* 47(1989); 189- 192
- Schwartz, R. W., et al. The Controllable Factor and Students' Attitudes About Specialty Selection. *Acad. Med.* 65 (3) (1990): 207-210
- Stagg, P., Greenhill, J., Worley, P.S. A new model to understand the career choice and practice location decisions of medical graduates. *Rural and Remote Health*. 9: 1245. (Online), 2009.
- World Health Organization Data 1999, <http://www.who.int/countries/per/en>

# International Medicine Research

**Jennifer Choudri, MS2**  
**Michael Nitzberg, MS2**  
**Sarah Porter, MS2**

**Preceptors:**

**Dawn DeWitt MD, MSc, FACP, FRACP**  
**Professor of Rural Medical Education**

**Chair of Rural Health Academic Centre and Clinical Dean Melbourne Medical School, University of Melbourne**

**Ben Canny MBBS, PhD Professor of Physiology**

**Deputy Dean (MBBS) & Head of Program (Central MBBS) Vice President of Academic Board**

**Chair of Monash University Human Research Ethics Committee Faculty of Medicine Nursing and Health Sciences, Monash University**

**Anne Nofziger, MD**

**Assistant Professor of Family Medicine**

**University of Rochester School of Medicine and Dentistry**

## **Graduate-entry vs. Undergraduate-entry Programs in Australia: Student Decision-making, Coping and Burnout**

**Introduction:** Australia currently has a mix of undergraduate- (entry direct from high school) and graduate-entry medical schools. Most new programs and several older medical schools are moving to graduate entry despite lengthening training times. There is much debate and limited research to support this change. Prior research has shown no difference between the two types of students in their ability to obtain medical degrees, research outcomes, or career positions.<sup>1</sup> However, differences have been shown in students' confidence, ability to collaborate, and levels of anxiety present when transitioning to clinical years.<sup>2</sup> While there is limited information regarding motivation, burnout, and empathy<sup>1,3</sup>, no studies have included data on alcohol use in Australian medical students. Data on these factors may inform the debate regarding coping and success in undergraduate versus graduate programs.

**Objective:** To quantify differences in empathy, burnout, alcohol use, and motivation for attending medical school between undergraduate-entry and graduate-entry Australian medical students.

**Methods:** Paper surveys were completed by 640 first and second year medical students from four universities in Victoria and New South Wales, Australia. The survey was designed to answer questions about student motivation to enter medical school, how well students handle the workload and lifestyle, and alcohol consumption habits. The Copenhagen Burnout Inventory<sup>4</sup> was used to assess the level of burnout in each group. The Interpersonal Reactivity Index was used to assess empathetic concern and personal distress in response to extreme distress of others.<sup>5,6</sup> Alcohol consumption and abuse were assessed by the AUDIT survey.<sup>7</sup> Graduate- or undergraduate-entry, as well as basic demographics, were assessed by student self-report through survey items.

**Results:** Undergraduate-entry students were found to have significantly greater empathetic concern ( $20.8 \pm 0.3$  vs.  $19.7 \pm 0.2$ ,  $p=0.001$ ) and personal distress in response to extreme distress of others ( $10.1 \pm 0.3$

vs.  $9.0 \pm 0.2$ ,  $p=0.003$ ) than their graduate-entry counterparts. Undergraduate-entry students scored lower on the AUDIT alcohol abuse scale than the graduate-entry students ( $4.1 \pm 0.4$  vs.  $5.8 \pm 0.2$ ,  $p<0.001$ ). There was no significant difference in level of burnout between the two groups ( $49.3 \pm 1.2$  vs.  $48.3 \pm 0.9$ ,  $p=0.457$ ). There were no significant differences between the groups in their motivations to attend medical school ( $6.1$ ,  $df=4$ ,  $p> 0.05$ ). Students strongly prefer the course style they are currently studying ( $394$ ,  $df=4$ ,  $p< 0.001$ ).

**Conclusion:** Undergraduate-entry students tend to be more empathetic and less at risk for alcohol abuse during the first two years of medical school than graduate-entry students. From these findings, it appears that undergraduate-entry students are more capable of handling the stresses associated with medical school. We recommend that further research be conducted before abolishing undergraduate-entry medical programs.

### References:

1. Rolfe I, Ringland C, Pearson, S. Graduate entry to medical school? Testing some assumptions. *Medical Education*. 2004;38:778-786.
2. Dean S, Barratt A, Hendry G, Lyon P. Preparedness for hospital practice among graduates of a problem-based, graduate-entry medical program. *Medical Journal of Australia*. 2003;178:163-166.
3. Newton B, et al. Is there a hardening of the heart during medical school? *Academic Medicine*. 2008;83(3):244-249.
4. Borritz M, et al. Burnout among employees in human service work: Design and baseline findings of the PUMA study. *Scandinavian Journal of Public Health*. 2006;34(1):49-58.
5. Davis, MH. A multidimensional approach to individual differences in empathy. *JSAS Catalog of Selected Documents in Psychology*. 1980;10:85.
6. Davis, MH. Measuring individual differences in empathy: Evidence for a multidimensional approach. *Journal of Personality and Social Psychology*. 1983;44:113-126.
7. Saunders, JB, et. al. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption-II. *Addiction*. 1993;88:791-801.

# International Medicine Research

**Leana Doherty, MS2**  
**Nicole Tetreault, MS2**

**Preceptors:**

**Cynthia Angel, M.D.**

**Department of Obstetrics and Gynecology University of Rochester Medical Center**

**C. Luis Vasquez, M.D. Yantalo Peru Foundation**

**Participation of Women in Cervical Cancer Screening in Yantalo, Peru INTRODUCTION:** Cervical cancer rates are among the highest in the world in South America and current screening efforts have not been effective in reducing high incidence and mortality rates (1). In South America, incidence rates of cervical cancer are higher than 25 per 100,000 while that in most developed countries are less than 10 per 100,000. In Peru, cervical cancer is one of the leading causes of cancer deaths in women (3). For cervical cancer, screening participation compliance is crucial for detecting early changes in cervical epithelium. Conventional cytology (Pap smear), liquid based cytology, HPV testing and visual screening with acetic acid or Lugol's iodine can detect changes in the cervix years before it develops into invasive cancer (2). For early detection and management of invasive cancer, public education and awareness on the signs and symptoms is critical. These signs include: intermenstrual bleeding, post-coital bleeding, heavier menstrual flows, excessive purulent discharge, recurrent backache and lower abdominal pain. In 2000-2003, a study conducted in San Martin, Peru demonstrated that the presence of and contact with health services played a role in increasing the participation in screening of women not previously screened or not screened in the past five years (5).

**OBJECTIVE:** To assess the number of women screened in Yantalo, Peru, given the availability of screening provided by the easily accessible local government clinic, as well as whether or not women continue getting screening. The study also aimed to understand the reasons why certain women have not obtained screening, as well as identify potential sub-populations with risk factors that are not being screened to help target such populations for future education programs.

**METHODS:** This study was conducted in the northern Peruvian Amazon town of Yantalo, Peru, located in the Province of Moyombamba in the San Martin Region. Surveys were read to participants in Spanish. During the first two weeks of study, participants were given the option of coming to the town hall during announced hours. After that period, information was collected in the participants' homes. After the interview, all participants were given an informational handout to educate them about cervical cancer. The survey was comprised of 27 questions, several of which were adopted from the World Health Organization health survey from 2002 as well as a similar previous study (7, 1). In addition to demographics, information collected included: health care seeking behavior such as organization membership, where people go when they are sick, and where they obtain their health information. Health care behavior was obtained by asking about quantity of fruits and vegetables eaten, amount of physical activity, smoking status, if they are currently sexually active, use of birth control, and use of protection. Specific information about cervical cancer included what they knew about cervical cancer, if they have obtained a test for cervical cancer or Pap smear, if they have had a vaginal exam and when, where they obtained the test, how many times they have obtained the test, if anyone in their family had cervical cancer, if they have heard of the Human Papilloma Virus, and if they would be willing to obtain a vaccine for Human Papilloma Virus. If they had not had the test, they were asked if they have heard about the tests for cervical cancer and if they had, why they had not obtained it previously.

**RESULTS:** We aimed to survey the 378 women over 18 years old living within the District of Yantalo, among 38 blocks, according to the door-to-door census study conducted by a staff member of the Yantalo Foundation. We were able to survey 334 of those women (88%). When asked if they had ever received a pelvic exam, 40.5% of women never had, while 1.2% were unsure of they had. Out of those women that had received a pelvic exam, 36.2% had obtained it in the last 3 years, 5.8% had obtained it within the last 4-5 years, and 16.3% had obtained it more that 5 years ago. Out of all women surveyed, 49.4% of women responded that they had received a test for cervical cancer (PAP smear), and 17.2% of women claimed that they had never heard about cervical cancer testing. For those that had received a PAP smear, 45.9% have only had 1 in their lifetime, 27.6% have had 2, 16.5% have had 3, 4.7% have had 4, 2.4% have had 5, 2.9% have had more than 5 or were screened annually. When asked if they had a family member who suffered from cervical cancer, 16.9% of women have had. Of all women surveyed, 70.3% of women have never heard of the Human Papilloma Virus, although 83.4% of them would be willing to be vaccinated against it. Also, 64.8% of women claimed they were sexually active, but 86.5% did not use condoms. All other results are pending statistical analysis.

**CONCLUSIONS:** Only 49.4% of women over 18 are obtaining PAP smears. This number is better than a previously reported 40% in other areas of the country, most likely due to a health care clinic within walking distance; however, this percentage is much to low in a country with such a high prevalence of cervical cancer. Additionally, of those women that have received PAP smears, 45.9% have only received one in their lifetime, and less than 10% have received more than 3 in their lifetime. Therefore, not only should there be an effort to increase women getting PAP smears, but there must be an emphasis on continued screening. Also, given that many women in Yantalo have had family members who have had cervical cancer, education and awareness is imperative. The majority of women have not heard of HPV, and 86.5% of sexually active women do not use condoms, there is a need to educate women on the virus, its transmission, and ways that they can protect themselves against it. Lastly, the majority of women would be willing to be vaccinated against HPV, and thus it may be beneficial in trying to get vaccines into the clinic and administered to women as early as possible.

## REFERENCES

- 1) Winkler J, Bingham A, Coffey P, Handwerker WP. "Women's participation in a cervical cancer screening program in northern Peru." *Health Educ Res.* 23 (2008): 10–24.
- 2) Boyle P, Bernard L. *World Cancer Report*. Lyon, France: IARC Press, 2008.
- 3) Ferlay J, Bray F, Pisani P, and Parkin DM. "GLOBOCAN 2002: Cancer incidence, mortality and prevalence worldwide." IARC CancerBase (5), IARCPress: Lyon, 2004.
- 4) "What are the risk factors for cervical cancer?" American Cancer Society. <[http://www.cancer.org/docroot/CRI/content/CRI\\_2\\_4\\_2X\\_What\\_are\\_the\\_risk\\_factors\\_for\\_cervical\\_cancer\\_8.asp](http://www.cancer.org/docroot/CRI/content/CRI_2_4_2X_What_are_the_risk_factors_for_cervical_cancer_8.asp)>. Last review Sept 14, 2009. Accessed Jan 20, 2010.
- 5) Robles SC, Ferreccio C, Tsu V, Winkler J, Almonte M, Bingham A, Lewis M, Sasieni P. "Assessing participation of women in a cervical cancer screening program in Peru." *Pan Am J Public Health* 25 (2009): 189-195.
- 6) "Yantalo International Clinic." Yantalo Peru Foundation. <[http://www.yantalo.org/clinic/yantalo\\_clinic.html](http://www.yantalo.org/clinic/yantalo_clinic.html)>. Accessed Jan 29, 2010.
- 7) World Health Organization World Health Survey 2002. <<http://www.who.int/healthinfo/survey/whshortindividualc.pdf>>. Accessed January 20, 2010.

# International Medicine Research

Jordan Frey, MS2  
Nakita Natala, MS2  
Camille Rodriguez, MS2

## Preceptor:

Ann M. Dozier, Ph.D. Associate Professor  
Department of Community and Preventive Medicine University of Rochester Medical Center

## Where Should I Give Birth?: The Factors Influencing Delivery Decisions of Mothers in the Amazonian Province of Orellana, Ecuador

### Introduction:

Improving the maternal mortality ratio by three quarters and making pregnancy and childbirth safer for women worldwide have been targets of the United Nation's Millennium Development Goals (MDGs) since 2000. However, these targets have not been met, and every minute at least one woman dies from complications during pregnancy or childbirth. Of the estimated total of 536,000 maternal deaths worldwide in 2005, developing countries account for 99%.

In Ecuador, the maternal mortality ratio remains relatively high at 210 deaths per 100,000 live births in 2005. This figure remains despite the 1998 establishment of the *Law for the Provision of Free Maternity and Child Care*, which guarantees free health care for expecting mothers and infants. In particular, women belonging to Ecuador's large indigenous populations, including Quechua, Shuar, and Huaorani, and who live in poor and rural provinces are more likely to die for reasons related to pregnancy and childbirth and present specific challenges to the provision of maternal care. In fact, in the Amazonian province of Orellana, the maternal mortality rate is considerably higher than the national average at 300 per 100,000 live births—higher than in most countries in the region. What may account for this increased likelihood is that among indigenous women, only 34% give birth at hospitals and about 65% choose to give birth at home.

Convincing evidence has been presented to identify the existence of cultural and economic barriers to maternal health care access for indigenous and impoverished women and families. However, research is still needed to explore who makes the decision of where to get care—the pregnant woman, the male head of household, the community, etc.—and how this influences the decision-making process of women around the time of childbirth. The increased maternal mortality rate in the Amazon region and the large percentage of home births observed in indigenous Ecuadorian populations provides an opportunity to explore an important element of maternal care: the decision of where to give birth.

### Objectives:

1. To identify the personal, familial, economical and societal factors influencing maternal care decisions at the time of child delivery and their importance to mothers in the Orellana province in Ecuador.
2. To identify the barriers of maternal care at the time of child delivery as perceived by health facilitators in the community.
3. To analyze Ecuador's Free Maternity Care Law's impact on the country's maternal mortality ratio.

### Methods:

- a. During daily visits to the Loreto Centro de Salud (Health Center) waiting room, interviews were administered in Spanish to 25 multiple and primiparous mothers between the ages of 18 and 50,

who had given birth vaginally or by cesarean section within the past two years. Each interview was approximately 15-30 minutes in length and were recorded and performed in the presence of a translator to ensure the accuracy of interpreted responses.

- b. Five interviews were also administered in Spanish to health care professions (doctors, nurses, *parteras* [Quechua midwives], health care promoters) around the community and in local clinics.

**Results:**

Between June 16<sup>th</sup> and July 8<sup>th</sup>, 25 mothers and 5 health care workers were interviewed.

All calculations were made with respect to the total number of births and not the individual mothers. Of the women interviewed, 48% gave birth at home for at least one birth, 5.3% in a *partera's* house for at least one birth, and 46.7% in a hospital or health clinic for at least one birth.

Doctors and nurses were used to help plan births by 40% of the women interviewed. Of these women, all of them gave birth in the hospital.

Family members were used to help plan births by 48% of the women interviewed. Of these women, 75% gave birth in the hospital, 50% gave birth at home and 33% gave birth at home and at the hospital for at least one birth.

*Parteras* were used to help plan births by 16% of women interviewed. Of these women, 75% gave birth to at least one child in the hospital and at least one child at home and 25% gave birth at a *partera's* house.

Of the women interviewed, 89% who had above HS education went to the hospital for at least one birth, while 73% with below HS education went to the hospital for at least one birth.

The place and position of birth were compared with the ethnicity of the mother and is presented in the table below (n= the number of births):

		Ethnicity			
		Quechua (n=23)	Castillano (n=4)	Mestiza (n=12)	Other (n=7)
<b>Place of birth:</b>	Home	74%	-	17%	29%
	Hospital	26.1%	100%	83%	71%
<b>Position of birth:</b>	Vertical	63%	-	20%	-
	Horizontal	36%	100%	70%	-
	Other	-	-	10%	-

Five members of the local health care team were interviewed: one local health care promoter, one obstetrician, and three *parteras*. The overwhelming opinion of those interviewed was that majority of local women gave birth in the community, not in health care centers. The local health care leader was able to give a succinct reason for this predilection. In his opinion, local women are not able to relate to the terminology used by doctors and this presumably leads to discomfort and potentially mistrust. One *partera*, who works at the clinic's newly established birthing house, explained that women often come to the health center initially because they know her and have faith in her practices. In light of the fact that women are given the choice of a vertical or horizontal birthing process, the obstetrician explained that the vertical birthing position renders babies prone to falling and being injured as they potentially hit the floor.

**Conclusion:**

Of Quechua births, 74% occurred in a home setting and 63% were done in a vertical position, suggesting that these women prefer a more traditional birthing experience. Meanwhile, 100% of Castillano, non-Indigenous, births occurred in the hospital and horizontal position, indicating a cultural

inclination to more westernized medicine. It also followed that more educated (high school and above) women tended to give birth in the hospital (89%), demonstrating that education may play a role in the decision making process of where to give birth. Given that all the women who used doctors or nurses to help plan their births gave birth in the hospital, prenatal counseling by hospital-associated medical personnel influences where births occur.

The opinions of the five members of the local health care team interviewed provided a singular perspective and insight into how and why mothers make choices relating to their birth experience. An important philosophy of the local health care system is mediating health care between the community and local health care centers. This is symbolized by the practice of stationing *parteras* in the clinic's birthing house along with western medical practitioners. Intermixing traditional and westernized medicine in the context of maternal health can pay dividends for both parties. Another example of intercultural medicine is that women have the option of a horizontal, westernized birthing position or a vertical, traditional Quechua birthing position. It is advantageous in that the option of a traditional birthing process may inspire trust in women as they visit the clinic. Furthermore, the increased supervision given to patients giving birth at the clinic in the vertical position may decrease the likelihood of trauma for patients and their babies.

By increasing the investment in intercultural health, as demonstrated by the stationing of *parteras* in government-funded clinics and the availability of alternative birthing options, safer birthing practices are reaching more women in Ecuador. However, limitations still exist and more far-reaching practices may need to be instituted.

#### **References:**

1. "Goal 5: Improving Maternal Health," United Nations Millennium Development Goals, <http://www.un.org/millenniumgoals/maternal.shtml>
2. "Why do so many women still die in pregnancy and childbirth?" World Health Organization, <http://www.who.int/features/qa/12/en/index.html>
3. "Maternal Mortality in 2005: Estimates developed by WHO, UNICEF, UNFPA and The World Bank," 2007
4. Olfarnes, Trygve, "Providing Maternal Health Care in Ecuador's Amazon Region," United Nations Population Fund News, 1 October 2007, <http://www.unfpa.org/news/news.cfm?ID=1005>

# International Medicine Research

**Conisha Holloman, MS2**  
**Sophia Malary, MS2**  
**Aba Osseo-Asare, MS2**  
**Alliya Qazi, MS2**

**Preceptor:**  
**Gladys Velarde, MD**  
**University of Rochester School of Medicine and Dentistry Department of Cardiology**

## **Yantalo Heart Study: An Assessment of Cardiovascular Risk**

**Background:** Cardiovascular disease is one of the leading causes of death in Peru. Yantalo is located in the northern Amazonian region of Peru with a population of approximately 800. The people of Yantalo represent a population whose health indicators and risk factors are sorely understudied. The nationwide data on Peruvian health may not accurately represent cardiovascular risk factors in Yantalo. The objective of this study is to describe the cardiovascular risk factors as well as the social, demographic and economic characteristics.

**Methods:** Our sample population included 214 females and 126 males over the age of 18. Data collection consisted of written surveys assessing cardiovascular risk and the following biometric analyses: BMI, waist: hip ratio and two blood pressure readings.

**Results:** Survey responses indicated that 72% denied any cardiovascular symptoms (irregular heartbeat, pain or pressure in chest). More than 84% of respondents walked more than the recommended 30 minutes or more a day. The majority of the population did not drink alcohol (80%) or smoke (96%). About 65% of the sample consumed  $\leq 1$  fruit per day and 68% consumed  $\leq 1$  vegetable per day. Of the male participants, 17% had a systolic blood pressure  $\geq 140$ , while only 5% of the female participants fell into this range. The blood pressure values tended to increase with age, with approximately 19% of those over 60 having a systolic blood pressure over 140. The mean BMI for women and men was 25.36 and 24.4, respectively. The mean hip: waist ratio for women and men was .875 and .953, respectively.

**Discussion:** Survey analysis revealed that the most salient risk factor was the low intake of fruits and vegetables in their diet. In the overall sample study, the males tended to have higher blood pressure measurements with more falling in the pre-hypertensive (systolic 121-139) and hypertensive range ( $\geq 140$ ). Nearly 20% of the participants age 60 and over fell into the hypertensive category. On average, women in the population fell into the overweight category with a BMI greater than 25; however, the average BMI for males fell into the normal range. The average hip: waist ratio for women fell above the recommended range of  $\leq .8$  while the average hip: waist ratio for men fell within the recommended range of  $\leq 1.0$ .

**Conclusion:** Future efforts towards promoting the health of the Yantalo population should include educating the population about the importance of a diet rich in fruits and vegetables and maintaining a healthy body weight.

# International Medicine Research

Meghan Kelly, MS2  
Stephen Welle

**Preceptors:**

**Thine Hvid**

**Bente Pedersen**

**Centre for Inflammation and Metabolism**

**Rigshospitalet University of Copenhagen Denmark**

**Bente Klarlund Pedersen, MD, DMSc**

**Professor, Director of Centre of Inflammation and Metabolism Copenhagen, Denmark**

## **Gender Specific Activation of AMP-activated Protein Kinase (AMPK) by Interleukin 6 (IL-6) in Isolated Human Skeletal Muscle Cells**

AMP-activated protein kinase (AMPK) is a metabolic enzyme that regulates cellular energy homeostasis. Its main mechanism of activation is via an elevated cellular AMP:ATP ratio resulting in the upregulation of catabolic processes such as fat oxidation and glycolysis that produce large quantities of ATP, as well as inhibition of processes such as the synthesis of protein, triglycerides and cholesterol that utilize ATP. Previous studies have examined the effect of age on the ability for AMPK to become active using stimuli such as exercise and the AICAR; however these results have been limited to rodent studies. Furthermore, a previous study has suggested that exercise induces AMPK activity in young men, but not young women. Thus, the aim of the present study was to examine the effects of age and gender on AMPK activity in human skeletal muscle. Skeletal muscle biopsies from vastus lateralis were obtained from age-matched men and women ages 18-24 and over 65 (n=9-10). Half of the biopsy was quick frozen and used to analyze protein content and gene expression; the other half used to create primary satellite cell cultures. RNA was isolated from untreated differentiated myotubes to determine whether the age and gender phenotype was maintained within the cell cultures using RT PCR analysis. Concurrently, the cells were treated acutely with IL-6 or AICAR for 30 minutes to determine whether age or gender altered the ability of AMPK activation to occur. Based on previous work by others we have chosen marker genes to represent differences in age and gender (p21, PGC1 $\alpha$  and ER $\alpha$ .) These genes were then examined by RT-PCR in both skeletal muscle biopsies and the primary muscle cell cultures to determine whether cell cultures display similar characteristics seen *in vivo*. We report here that within the skeletal muscle biopsies, gene expression of P21 and PGC1 $\alpha$  were significantly different between young and old subjects, and ER $\alpha$  was significantly different between men and women. There were no differences in basal AMPK activity (as indicated by P- AMPK and P-ACC abundance) in any of the 4 groups. RT-PCR analysis of untreated primary satellite cell cultures indicated that the mRNA content of PGC1 $\alpha$  and P21 do not display the same pattern of expression as seen *in vivo*, however the expression of ER $\alpha$  was significantly different between cells isolated from men and women, suggesting that their "gender identity" remained in cell culture. Finally, treatment of skeletal muscle cells with IL-6 and AICAR resulted in an increase in P-AMPK abundance in cells isolated from men, but not women; a phenomenon that has been observed *in vivo*. These results further indicate that the regulation of AMPK activity is different between men and women. Furthermore, while satellite cells isolated from skeletal muscle biopsies can be used to examine these gender related mechanistic differences in metabolism, this model is unsuitable to examine aging-induced differences on a cellular level.

# International Medicine Research

**Evan Lowy, MS2**

**Preceptor:**

**Christine M. Hay, MD**

**Infectious Disease Fellowship Program Director**

## **Assessment of Agriculture Diversification Initiatives at the Millennium Villages Project in Potou, Senegal**

The Millennium Villages Project (MVP) is led by experts in policy and science at the Earth Institute at Columbia University in collaboration with the United Nations Millennium Project. It aims to meet the Millennium Development Goals (MDGs) set out by the UN at the Millennium Summit in 2000 in a variety of communities throughout sub-Saharan Africa. One of the main sectors of intervention in the MVP is agriculture, with the aim of increasing agricultural production for food security purposes as the initial priority. The project additionally aims to increase the diversity of local diets in order to reduce the prevalence of malnutrition. In rural areas such as Potou, agriculture and public health are closely interrelated, and food security is a constant, pressing concern. Farmers depend on what they grow both for their own diet and for income generation. Anything that interrupts agricultural production will likewise have an effect on public health. This study examines the extent and impact of specific MVP crop and livestock diversification initiatives in the Potou cluster on household and community nutrition, income, and adaptability to shocks, and identifies factors that have contributed to or limited the success of these initiatives.

The MVP cluster in Potou is home to approximately 31,000 people and is located in the Niayes zone of northern Senegal. The area represents the coastal-artisanal fish farming system, where the majority of the inhabitants practice agriculture, livestock production, and fishing. The Potou cluster comprises two distinct ecological regions: the Niayes and the Dieri. In the Niayes zone, farmers have traditionally grown gardening crops such as onion, tomato, cabbage, etc., and practiced fishing where possible. As the soil is not well suited to rainfed crops such as peanuts and millet, they are not grown here. In the Dieri, rainy season crops such as peanuts, millet, cowpea, and sorghum are grown. Livestock, generally cow, goat, and sheep, are raised in both zones. The Niayes region as a whole is both arid and ecologically fragile. Problems encountered by villagers in this area include the increasing threat of desertification, decreasing soil fertility, lack of transportation, malnutrition, and lack of clean water sources.

The central questions of this study are: To what extent have the agriculture diversification initiatives been adopted in the cluster? What factors contribute to or limit the success of these initiatives? What is the impact of the agriculture diversification initiatives on diet diversity, nutrition, food security, and adaptability to shocks? In order to address these questions, 96 surveys were performed in six villages throughout the Potou cluster (the surveys were generated by the MVP agriculture and nutrition coordinators at the Earth Institute at Columbia University).

The initiatives used for the survey were onion, cabbage, tomato, carrot, hot pepper, eggplant, diakhatou (bitter eggplant), watermelon, peanuts, cowpeas, millet, bissap, forage beans, cow artificial insemination, and fishing (includes both fishing and fish transformation/preservation, i.e. salting and drying). Of the farmers surveyed, 23 were women and 73 were men. Although the data from the surveys is still being processed by MVP coordinators at the Earth Institute, there are certain results that can be reported without the final analysis. Of the farmers surveyed, 33% (32/96) are performing activities which they did not do prior to the arrival of MVP in 2006, and 69% (66/96) report that they have increased their agricultural production since MVP began its work in the cluster.

The only truly new initiative introduced by MVP in Potou is cow artificial insemination. This

initiative provides farmers with access to sperm from American and European cow varieties which are able to produce more milk and more meat at younger ages than the local variety. MVP data suggests that the hybrid cows produced by the artificial insemination of local cows should be able to produce 15L of milk a day once mature, whereas local cows produce 3-4L a day at the most; this would theoretically both improve the nutritional content of the local diet and create possibilities for income generation.

Of those surveyed, 11% (11/96) had attempted artificial insemination of one or more of their cows, though not all attempts resulted in successful live births. These 11 farmers were spread across three villages. As this activity is still new in the cluster, it is too soon to tell if the future benefits will outweigh the added cost of inputs for these hybrid cows, as they require extra feed and more substantial shelter. Only 2% (2/96) of farmers surveyed reported any fishing activity (one man as a fisherman and one woman as a fish dryer), although this is not surprising as only one of the villages surveyed was located along the Atlantic coast.

The type of agriculture diversification taking place in the Potou cluster through MVP was not what I had anticipated, in that the diversification has less to do with the introduction of new crops, and more to do with facilitating access to improved seed, improving the timing of such access so that farmers can take advantage of good market prices, reinforcing capacity, and helping to organize farmers. The truth is that farmers in the Niayes region have traditionally been well diversified in their agricultural practices in that they grow two or three crops in addition to whatever the major local crop may be; most also raise some livestock on the side. There were many issues raised during the execution of this survey that will be important to examine in the future. The price of seeds is still a big problem for farmers, as is access to irrigation equipment. The sustainability of many of the interventions taking place in the agriculture sector through the MVP remains unclear. It is clear, however, that without sustainable solutions to the agricultural issues in the cluster, any progress in the realms of nutrition and food security will be short-lived.

# International Medicine Research

Travis O'Brien, MS2

**Preceptor:**

**Andrew Sherman, M.D. Department of Pediatrics  
University of Rochester Medical Center**

## **A Model for Universal Mosquito Net Coverage in Kedougou, Senegal**

Malaria is the fifth leading cause of death due to infectious disease in the world, with an estimated 700,000 to 1,000,000 people dying from the disease during the 2008 calendar year.<sup>1</sup> Tragically, most of those who die of malaria are young children between 6 months and 5 years of age. Ninety-eight percent of these deaths take place in only 35 countries, including the African nation of Senegal.<sup>1</sup> Fortunately, this disease can be prevented by fairly simple and inexpensive measures, such as mosquito nets, protective clothing, and insecticide spraying.<sup>2</sup> Over the last decade, several hundred thousand insecticide-treated mosquito nets (ITN's) have been donated to endemic areas in Africa and Asia in an attempt to decrease the impact of this disease. In areas without previous mosquito net coverage, ITNs can reduce the incidence of malarial episodes by up to 62%.<sup>3</sup> The Global Fund estimates that 130,000 lives of children under 5 were saved by ITN's worldwide between 2003 and 2007.<sup>4</sup>

Several charities have been created in the last decade in an attempt to distribute mosquito nets to parts of the world where malaria is endemic. One such charity, NetLife, was created in 2005 by Dr. Andrew Sherman, a current pediatric resident at the University of Rochester and former Peace Corps volunteer in Senegal.<sup>5</sup> This NGO distributes mosquito nets, with the help of individual donations, throughout the Kedougou region in southwest Senegal. Kedougou has one of the highest incidence rates of malaria in the world, with 90-100% of the population testing positive for previous or current infection.<sup>6</sup> In the summer of 2010, the Senegalese government organized the first universal mosquito net coverage in the nation's history, which began in Kedougou. They still depended upon NGO's to help organize and train distribution teams, as well as provide funding where government resources were inadequate. NetLife, with the help of Peace Corps volunteers, was an integral part of organizing and funding distribution efforts for over 200 distribution sites in the Kedougou region.

In order to assess the short-term success of this first universal coverage, I conducted a survey of 117 households throughout the Kedougou region approximately three weeks following the distributions. In particular, this survey was designed to assess two key differences between this distribution and previous ones led by Netlife. First, to prevent commercial resale of the nets as had been seen in the past, we wrote each person's name and village on every net they received and incinerated all packaging at the end of distribution. These steps served to both decrease resale value and instill a sense of personal ownership. At the beginning of each distribution, we also organized a 20-30 minute presentation in the local language on how to properly install and maintain the nets, as well as an introduction on how malaria is spread and how to protect themselves and others from contracting the illness.

117 households were surveyed from nine different distribution sites in the Kedougou region: 3 districts in the city of Kedougou, 3 large villages (>167 people), and 3 small villages (<167 people). These households endured a total of 217 probable cases of malaria in the past year, with 174 confirmed by blood test. Of 634 distributed nets, 618 (97.5%) were still in their respective households and 587 (92.6%) were correctly hung over sleeping areas. Of 1305 people, 1239 (94.9%) had slept under a mosquito net the previous night, including 95.7% of children under 5 and 100% of pregnant women. Of 706 sleeping areas, 667 (94.5%) were covered with a mosquito net. Each head of household was asked to identify different aspects of malaria transmission that were covered in our presentations the day of distribution. 80.0% of these men knew the three main tenets of mosquito net coverage as advertised by the government: The Whole Family, The Whole Night, and The Whole Year. 94.9% correctly identified mosquitoes as the

vector for transmission, 54.7% described the mode of transmission from one person to another, and 97.2% knew that risk of transmission was greatest after sunset. We then asked the women of the household a series of questions regarding maintenance of the nets, which was also covered in the presentations. 64.9% knew that nets should not be washed more than three times per year, 82.1% knew that nets should not be exposed to sun, 69.2% knew that detergent should not be used to clean nets, and 79.6% knew that bleach should not be used. Products such as detergent and bleach can dissolve the insecticide that is adhered to the nets, rendering them less effective.

Though this survey only provides a short-term assessment of the first universal distributions in Kedougou, the results are encouraging. It appears that the strategy used to prevent resale of the nets was very effective, with nearly all distributed nets still in their respective households and correctly hung over sleeping areas. This may be due to an increased understanding of how malaria is transmitted and how the nets can halt transmission, to which our presentations may have contributed. Nearly every head of household knew that mosquitoes transmit the disease from person to person and that risk is greatest at night, suggesting that these people understand the importance of bed nets in preventing disease. The vast majority of women in these households knew the basics of how to clean and maintain the nets, which bodes well for the long-term utilization and effectiveness of the nets. A longer term follow-up will be needed in the coming months, especially since there is a possibility that villagers will take down nets as the rainy season ends and the risk of contracting malaria decreases.

## References

1. Centers for Disease Control and Prevention, 2010. Malaria Facts. [www.cdc.gov/malaria/about/facts.html](http://www.cdc.gov/malaria/about/facts.html)
2. Eisele TP, Larsen D, Steketee RW. Protective efficacy of interventions for preventing malaria mortality in children in Plasmodium falciparum endemic areas. *Int J Epidemiol.* 2010 Apr;39 Suppl 1:i88-101.
3. Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. Cochrane Database of Systematic Reviews 2004, Issue 2. Art. No.: CD000363. DOI: 10.1002/14651858.CD000363.pub2.
4. Komatsu R, Korenromp EL, Low-Beer D, Watt C, Dye C, Steketee RW, Nahlen BL, Lyerla R, Garcia-Calleja JM, Cutler J, Schwartzlander B. Lives saved by Global Fund-supported HIV/AIDS, tuberculosis and malaria programs: estimation approach and results between 2003 and end-2007. *BMC Infect Dis.* 2010 Apr 30;10(1):109.
5. NetLife, 2009. <http://netlifeafrica.org/default.aspx>
6. I. Kleinschmidt et al. 2001. An empirical malaria distribution map for West Africa. *Tropical Medicine and International Health* 6: 779-786. Topographical data: African Data Sampler, WRI, [http://www.igc.org/wri/sdis/maps/ads/ads\\_id](http://www.igc.org/wri/sdis/maps/ads/ads_id)

# International Medicine Research

**Viral Patel, MS2**

**Thilan Wijesekera, MS2**

**Preceptor:**

**Dr. Luis Vasquez, M.D. Yantalo Foundation**

**Dr. Edward Messing, M.D. Department of Urology  
University of Rochester Medical Center**

## **Evaluating the Risk of Prostate Cancer in Yantalo, Peru: A Longitudinal Study**

**Introduction:** With a population of roughly 1,200 people, Yantalo, Peru is an agriculture-based village in the Altomayo region of Peru whose citizens have been shown to take a traditionally conservative outlook on health practice. Coupled with misconceptions in nutrition, arguable lack of exercise, and limited sexual health awareness, it has been suggested that this population could potentially be at risk for several preventable chronic illnesses<sup>1</sup>. One example is prostate cancer; a slow-growing malignancy that is not only the cancer with the highest incidence in adult males, but also highly treatable with proper preventative screening and early diagnosis<sup>2</sup>. Unfortunately, the two forms of screening, Prostate Specific Antigen (PSA) testing and Digital Rectal Exam (DRE), are potentially cost-prohibitive and uncomfortable, respectively, for Yantalo's impoverished and paternalistic demographic<sup>1</sup>.

**Objective:** We had three primary objectives for our study. Foremost, we wanted to determine if Yantalo had an abnormally high occurrence of the urinary symptoms associated with prostate cancer relative to a comparable Peruvian population or even population in the United States. As a comparison, in a study within the Rochester area of men between the ages of 60-69, 29% had difficulty stopping or starting, 36% had frequent urination, and 4% had pain or burning<sup>3</sup>. Secondly, we aimed to gauge the community-awareness of the symptoms and treatments for prostate cancer, and what might possibly be limiting factors in this health-knowledge. Finally, we wanted to better quantify potential risk factors for malignancy including sexual health, exercise, nutrition, smoking, and alcohol consumption<sup>4</sup>.

**Methods:** Surveys regarding prostate health and awareness were conducted for Yantalo men over the age of 50. Each 18-question survey was translated into Spanish and read to subjects in 15-20 minute sessions in the local town hall or in their residences. Responses were recorded and an information pamphlet regarding prostate anatomy and pathology was provided.

**Results:** In our sample population of 120 males, we were able to obtain data from 108 men with an average age of  $61.2 \pm 8$  years. The majority was unfamiliar with prostate cancer with a minority having limited knowledge of its location and symptoms. On a low/medium/high scale, the population respectively rated their perceived likelihood of developing prostate cancer (82.4%/13.9%/3.8%), understanding of PSA testing (89.8%/8.3%/1.9%), likelihood of receiving PSA testing (90.7%/7.4%/1.9%), understanding of DRE (86.1%/8.3%/5.6%), and likelihood of receiving DRE (87.0%/7.4%/ 5.6%). 25.9% complained of burning with urination; 3.7% had seen blood or discoloration in their urine; 20.4% had difficulty stopping or starting their urination; and 28.7% had more frequent urination than normal. 15.7% had a family history of urinary problems and 7.6% confirmed a family history of prostate cancer. Regarding their exercise, 73.1% described themselves as active, 13.9% as medium and 13.0% as sedentary. Overall, the population's diet consisted largely of rice, fried meat (i.e. chicken, beef, pork, fish), vegetables (i.e. beans, potatoes, yucca), and limited fruits (i.e. oranges and plantains). Concerning their lifestyle, 7.4% reported that they smoked cigarettes and 12.0% consumed

more than one alcoholic drink per week. Pertaining to sexual health, 77.8% were sexually active, 2.8% used protection, and 12.0% had a history of sexually transmitted infection with the most common being gonorrhea.

**Conclusions:** With an expectedly limited knowledge of prostate health and a relatively high national incidence of prostate cancer, our target population showed a lower rate in urinary symptoms such as difficulty starting and stopping, frequency, but a higher rate of pain or burning with urination. While the latter could possibly be attributed to lack of regular health care maintenance (i.e. hygiene and check-ups), the former showed no pressing needs for intervention within the community, especially when coupled with the lack of prostate cancer family history. This might suggest that, although preventative information regarding prostate health could still be employed, it may not necessarily be effective in lowering rates of urinary symptoms.

### References:

1. Lisi, Christopher. "The Influence of Rural Peruvian Amazonian Cultural Paradigms on Access to Healthcare: An Observational Investigation"
2. Penson, David F., Chan, June M., editors. Prostate Cancer. Urologic Diseases in America. US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Washington, DC: US Government Printing Office, 2007; NIH Publication No. 07-5512. p. 78-86.
3. Wei, John T., Calhoun, Elizabeth, Jacobsen, Steven J., editors. Benign Prostatic Hyperplasia. Urologic Diseases in America. US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Washington, DC: US Government Printing Office, 2007; NIH Publication No. 07-5512. p. 51.
4. Klein, Eric A. What's new in Prostate Cancer Screening and Prevention. *Cleveland Clinic Journal of Medicine* 2009; 76: 439-445.

# International Medicine Research

**Brian Pisula, MS2**

**Mary Stokes, MS2**

**Preceptor:**

**Jessie Stone, MD Soft Power Health, Uganda**

## **Malaria Prevention and Awareness in Kyabirwa, Uganda: Survey Analysis**

**Introduction:** An estimated 500 million people suffer from malaria each year, resulting in over one million deaths, mostly children, and mostly affecting poor populations in tropical and subtropical areas (1). While eradication attempts successfully eliminated malaria in the United States by the 1950s, attempts at eradication have failed in Africa, where malaria transmission intensity always exceeded that of the U.S. and where political and economic instability hindered control efforts (2). Furthermore, since the 1980s, mortality from malaria has increased in sub-Saharan Africa, most likely due to the evolution of resistance in the malaria parasite *Plasmodium falciparum* to chloroquine, the primary drug used to fight malaria infection (2,3).

**Objectives:** This study quantitatively assesses the preventative measures used against malaria among those who seek treatment at the Alan Stone Community Clinic in Kyabirwa village, Uganda. The study also qualitatively assesses beliefs about malaria prevention. The purpose of the study is to gain a better understanding of how the community approaches malaria prevention and treatment.

**Background:** The study is based in the village of Kyabirwa, in the Jinja district, in the central-eastern region of Uganda, in East Africa.

In response to very limited medical resources in the rural area of Kyabirwa, Dr. Jessie Stone and local healthcare workers opened the Allan Stone Community Health Clinic in January 2006 to offer healthcare to the area. The clinic now sees approximately 50 patients a day. A primary goal of the clinic is to reduce the local burden of malaria through treatment of the disease, education about the disease, and by providing insecticide treated, quality bed nets for prevention.

A number of factors in sub-Saharan Africa continue to inhibit the eradication of malaria: the tropical climate offers an ideal breeding ground for the mosquito vectors of the *Plasmodium falciparum* parasite; a shortage of facilities, resources and trained personnel to fight the illness increases its virulence in the population; and a lack of infrastructure and commitment from government and communities hinders efforts to control the mosquito population (4). The World Health Organization (WHO) advocates use of an array of methods to fight malaria, including proper medical treatment of affected individuals, control of the mosquito vectors, and personal protection against the mosquito vectors (4,5). For maximal effectiveness, all methods must be applied simultaneously.

Personal protection against the parasite and its vector requires sustained use of insecticide treated bed nets (ITN's), which continues to be one of the most cost-effective interventions against malaria in Africa, and which will not drive the evolution of a more virulent and drug-resistant parasite (6). The WHO's Roll Back Malaria Initiative has set a goal of 80% ITN use by this year, 2010. However, in the 2008 World Malaria Report, the WHO reported that fewer than 20% of surveyed households in Uganda owned an ITN, and even worse, only 10% of pregnant women and children, those most at risk for malaria mortality, slept under a net (5).

Communities that employ the full arsenal of tools against malaria show a significant decline in infection rates and mortality from infection (4). The goal of our research, therefore, is to measure the use of these anti-malarial tools among those diagnosed with malaria.

**Methods:** During the months of June and July of 2010, we verbally administered a survey through a translator to patients at the Allen Stone Community Clinic in Kyabirwa, Uganda. The survey consisted of seven quantitative questions and two qualitative questions regarding malaria prevention and awareness. The responses to the survey questions were recorded during the interview and then entered into an electronic database, using only a numerical, non-identifier, labeling system. The interviews were conducted orally through a translator, as the local language, Lusoga, is a spoken language, not written.

**Results:** 457 patients were surveyed during the study. Of those, 350 had received treatment for malaria: 32 once, 120 two-to-three times, 48 four-to-five times, 153 more than five times, and 10 for an unspecified number of times. 93 respondents reported never receiving treatment for malaria; 13 were unsure if they had been treated. 268 of the 457 respondents reported that they sleep under a bed net; of those, 240 sleep under the net 7 nights per week, 7 five-to-six nights per week, 19 three-to-four nights per week, and two one-to-two nights per week. 184 respondents reported that they do not sleep under a bed net. 401 respondents plan to sleep under a bed net in the future, 20 do not, and 35 were unsure. Those not using a bed net were asked why: 106 reported money as the barrier, 25 reported access, 33 reported discomfort, and 41 reported another unspecified reason. Regarding methods to kill mosquitoes around the home: 87 respondents reported using such methods; 220 reported not. When asked about the most effective method to prevent malaria, 277 cited sleeping under a bed net, 47 medication, 22 spraying to kill mosquitoes, 5 nutrition, 13 another unspecified method, and 87 were unsure. When asked about concern for malaria in their life: 266 reported being very concerned, 89 slightly concerned, 3 neutral, and 99 not at all concerned.

**Conclusion:** The malaria burden is very high in the village of Kyabirwa, Uganda. 76 % of those surveyed had been treated for malaria, 33% more than give times. The community remains very concerned about the impact of malaria in their life. While the 59% who reported sleeping under a bed net to prevent malaria falls short of the WHO goal of 80% bed net usage by 2010, it is well above the 20% figure cited for bed net usage in Uganda (5). This likely reflects the Alan Stone Community Health Clinic's campaign to increase net usage in the surrounding area, through outreach and subsidized net sales. A majority (61%) of survey respondents cited bed net usage as the most effective method to prevent malaria, this correlates with the level of bed net usage in the community and likely reflects the outreach of the clinic as well. Regarding barriers to net usage, 58% of those not currently using a net cited cost. The clinic sells bed nets at a significantly reduced rate, \$1.25, an 80% discount from the cost, and the cost of a clinic visit is more than the cost of the net. As the clinic continues its campaign to raise awareness of malaria transmission and prevention, and to provide high-quality, low-cost insecticide treated bed nets, we anticipate that net usage will continue to increase and the malaria burden will decrease.

## References

1. Greenwood, B. M., et al. Malaria: progress, perils, and prospects for eradication. *J. of Clin. Invest.* 2008; 118(4): 1266-1276.
2. Carter, R. and K. N. Mendis. Evolutionary and historical aspects of the burden of malaria. *Clinical Microbiology Reviews.* 2002; 15(4): 564-594.
3. Nsobya, et al. In vitro sensitivities of *Plasmodium falciparum* to different antimalarial drugs in Uganda. *Antimicrob. Agents Chemother.* 2010 January. doi:10.1128/AAC.01412-09.
4. Okech, et al. Use of integrated malaria management reduces malaria in Kenya. *PLoS ONE.* 2008; 3(12): e4050.
5. World Health Organization. *World Malaria Report 2008.*
6. Korenromp, et al. Monitoring mosquito net coverage for malaria control in Africa: possession vs. use by children under 5 years. *Tropical Medicine and International Health.* 2003 August; 8(8): 1-11.

# Medical Humanities

Ayesha A Khan, MS2

**Preceptor:**

**Stephanie Brown Clark, MA, MD, PhD**  
**Associate Professor, Medical Humanities**  
**Director, Medical Humanities Programs**  
**Center for Ethics, Humanities, and Palliative Care**  
**University of Rochester Medical Center**

## **Muslim Outreach and its Effect on Community Health**

American Muslims have faced much scrutiny and challenges in past decade. The pressures faced by Muslims today are even greater than those felt immediately after 9/11. There is a negative association with being Muslim in the media as seen during President Obama's election and a view that being Muslim is not compatible with being American. This type of pressure results in stress and anxiety. Constant worry of bad perception has been shown to negatively affect health in American Muslims.<sup>1</sup> These difficulties have resulted in a multitude of reactions from American Muslims. Overwhelmingly, being Muslim has begun to mean something more than any religious or cultural affiliation.

There is a movement of American Muslims to change the negative perceptions by making a positive impact in their communities. Many Muslims want to take a more active role in the betterment of society, using the Qur'an to inspire good actions not as Muslims but as humans working towards a better humanity. Muslims are fighting not only for the right to exist in the western society but to show how Muslims can enrich that society.

Inspired from the civil rights movement, many of the second generation Muslims and Muslim converts have begun to focus on uplifting their communities by supporting and fighting alongside the marginalized regardless of religious and ethnic ties. In the hope of creating a better future for the next generation, Muslim organizations fight for social justice at a grass roots level. Following in the footsteps of the Malcolm X and Martin Luther King Jr., activism is an American response to the pressures and marginalization faced by Muslims here today.

Following that logic, young and new Muslims have volunteered alongside their fellow Americans in many efforts. In the past ten years, new organizations have arisen to meet the desires of Muslims who are interested in being collectively and politically involved in social justice efforts. From serving in food kitchens to political organizing and lobbying for the betterment of the greater society, Muslims are actively involved in many efforts. Organizations such as Inner-City Muslim Action Network (IMAN) in Chicago <<http://www.imancentral.org>>, Ta'Leef Collective along with Zaytuna College in San Francisco <<http://taleefcollective.org/>>, and the HUDA clinic in Detroit <<http://hudaclinic.org/>> are setting the future goals of Muslim activism.

I conducted a mini-ethnography with these organizations. This is a process for learning from people about their lives. The mini ethnography focused on the core principles of defining a set of questions, interviewing informants, becoming a participant observer, and analyzing these observations.

## Questions

1. **Demographics and Community-** Can you describe yourself? How do you define community?
2. **Community Involvement-** What does community involvement mean to you?
3. **Muslim Outreach Organization-** How would you describe the mission of this organization? What are the future goals of this organization?
4. **Community and Health-** How does your community affect your health?
5. **Exclusion-** Who feels (would feel) uncomfortable in this community? Why?

The mini-ethnography is presented in a qualitative format outlining my experience at these organizations and interviews with people I met.

IMAN is community center in inner-city south side Chicago that primarily provides for the needs of that underserved community through a free health clinic, job training, public policy lobbying, and green healthy-living seminars. Also a strong component of that organization is an emphasis on arts and culture of American Muslims, with an annual concert features local and international hip-hop performers, spoken word artists, and cultural music shows.

Ta'Leef Collective is a community education outreach program geared at the San Francisco area youth, converts, and those interested in learning more about Islam. Ta'Leef has created outreach programs such as feed the homeless to help reconnect with the community and faith. Ta'Leef holds open houses and discussions at mosques and community centers that are open to anyone interested in learning more about the religion or Muslims. Ta'Leef, an offshoot of Zaytuna College, has access to the leading American Islamic scholars and has a strong educational outreach aspect.

A smaller and newer organization is HUDA clinic, which is primarily a free health clinic. The clinic is run by a small group of local Muslim doctors who wanted to build a sustainable health care option for the underserved and uninsured population of inner-city Detroit. It is adjoined to the Islamic Center of Detroit that also functions as a soup kitchen. It is a growing organization that hopes to continue and provide to the city in many avenues. Overall, the work of Muslim volunteers with the larger community positively influenced their comfort level and acceptance within that community. The activist approach taken by these organizations was reflected in volunteers' optimism of a better future. These organizations need more support and their positive impact should motivate other Muslims to become involved in their greater communities.

## References:

<sup>1</sup> Padela A.I.; Heisler, M. [The association of perceived abuse and discrimination after September 11, 2001, with psychological distress, level of happiness, and health status among Arab Americans.](#) Am J Public Health. 2010 Feb;100(2):284-91. Epub 2009 Dec 17

<sup>1</sup> Esposito, J. L.; Mogahed, D. *Who Speaks for Islam? What a Billion Muslims Really Think*. New York: Gallup Press, 2007.

<sup>1</sup> Ramadan, Tariq. *Western Muslims and the Future of Islam*. Oxford University Press. New York, 2004

<sup>1</sup> Abdo, Geneive. *Mecca and Main Street- Muslim Life in America After 9/11* Oxford University Press. New York. 2006

## Year-Out Research

Calla Brown, CC4  
Bela Denes, CC4

### Preceptors:

Jose Ramiro Cortez Argueta  
Director General, Asociación de Campesinos para el Desarrollo Humano

### The Design Of An Evaluation To Determine The Effect Of A Change In User Fees In Health Care Utilization Behaviors In Rural El Salvador

**Background:** Estancia is a very poor rural community, largely populated by subsistence farmers, in the state of Morazan, in El Salvador. Members of the Estancia community formed the non-governmental organization, *Asociación de Campesinos para el Desarrollo Humano* (CDH), which was officially recognized in 2001, but its staff has a long history of working to improve health in Estancia. CDH's stated mission is "to bring together, strengthen and organize our communities in order to find solutions to the common problems we face, bringing about comprehensive human development"<sup>ix</sup>. CDH operates the local community health center and six early childhood development centers, as well as broader community health and development projects. Prior to January 2010, the clinic asked patients to donate \$1 USD for visits and medicine received, in order to pay staff and continue to stock medications. In January, the pricing scheme changed, and patients were charged a sliding-scale fee of the costs of the medications prescribed and given.

**Objectives:** The main objective of this project was to work with the leadership of the NGO CDH to develop an internal evaluation to determine what effect the pricing change was having on health care utilization behaviors in the community of Estancia.

**Methods:** In order to evaluate the effect of the change in pricing scheme, a survey was developed. The survey was designed to be conducted orally and administered to families within the catchment area of the clinic in Estancia. After designing the survey, the survey was to be tested on a sampling of community members, and a focus group would be held with the staff members of CDH to discuss the survey itself, the initial test-run of the survey, and the general topic of program evaluation.

**Results:** The survey was tested on a sample of 58 community members for language, clarity, and content. These 58 community members were from six different *caseríos*, or small community groups, within Estancia. 67.2% of the respondents were women. 12.5% of the respondents reported cost to be the primary reason why they were not visiting the clinic as much as they had prior to the change in pricing. The results of the staff focus group were qualitative in nature.

**Discussion:** The major result of this study was the development of a methodology that could be used by the organization CDH to evaluate its programming and pricing policy over time. This methodology was developed by international volunteers in conjunction with the local staff of the NGO. This partnership was the main strength of the project. Future work can be done to perform a study using the survey with the power to detect changes in health utilization behavior patterns of the community to determine whether user fees inhibit health care seeking behaviors. Additionally, a study could be performed using the electronic medical record used by CDH to determine whether there has been a change in patient numbers or demographics since the enactment of the new pricing system.

# Year-Out Research

**Sophina M. Calderon, CC4**

**Preceptor(s) Name:**

**Scott McIntosh and Beverly Sirvent**

**Finger Lakes Migrant and Community Health Care Project Sodus Community Health**

## **Community Health Outreach and Case Management in the Finger Lakes Migrant and Community Health Care Project (FLMCHCP)**

**Introduction:** In the migrant community of Sodus, New York, awareness of health care resources and structured individual patient support are essential to achieve an adequate continuity of health care for each migrant individual and family. The majority of migrant families and individuals who actively utilize the resources available to them through the FLMCHCP are people who have a health condition that requires constant attention or are families that are required to keep health information updated for purposes of employment or education. The majority of first-time visits to the clinic include chief complaints of an acute nature and include first prenatal visits of the second or third trimester.

**Objective:** The objective of this Year-Out Community Fellowship was to help increase and sustain utilization rates of FLMCHCP resources among the migrant population of Sodus, NY. The areas of focus were increasing the number of patients seen by in-camp medical teams through community outreach efforts and getting women to receive prenatal care beginning in their first trimesters through individual case management.

**Background:** The Finger Lakes Migrant and Community Health Care Project is a federally funded program that aims to provide affordable health care to migrant farm workers across New York State. Services provided by FLMCHCP include medical and dental attention, medical care provided in camp and housing sites, interpretation services by a multilingual staff, clinic transportation, and provide linkages to important community resources. The Wayne County expansion of the FLMCHCP has incorporated these same protocols into their services for over the past ten years and continues to expand in its outreach efforts and in the quality of services that they provide.

It is fairly well-known among the providers of medical care to migrant patients in the FLMCHCP that patients don't seek medical care for regular health maintenance but tend to present when an acute problem arises or when a chronic problem begins to affect their ability to work. Migrant patients delay in seeking health care for various reasons, including inability to pay for care, not wanting to miss out on a day's worth of wages, misperceptions or lack of knowledge about our services, and fear of immigration authorities, which has become an issue of greater concern recently.

**Methods:** I was placed at the Sodus Community Health extension of the FLMCHCP for the duration of the Year-Out Community Fellowship. I was assigned to an in-camp team which consisted of a nurse practitioner and another outreach worker. Throughout the year, our team visited various camps and returned to the same places on a regular basis due to their changing occupancy by migrant workers. I served on my team as an interpreter for the provider and a health educator teaching occupants of each camp about the importance of preventing and managing diabetes, hypertension, doing HIV testing, and keeping vaccinations updated. Our patient encounter forms are designed for us to ask about various conditions that affect the migrant population, such as, past vaccinations, tuberculosis testing and STD screening. Based on the provider's assessment we distribute medications at a low cost, give vaccinations

and make medical referrals for services at the clinic. Entering these patients' homes and assessing their needs help us to develop a relationship with our patients so that they might be more likely to receive health services if they can see a provider that they can trust.

During most days, I was placed on a case management team that primarily followed the care of migrant prenatal patients through delivery, discharge and postpartum follow-up. While we visit camps, as described above, we also ask women of their reproductive history to find women who are pregnant or could be pregnant. When a woman is confirmed to be pregnant in the clinic by a rapid urine test, the prenatal team is called to take over that woman's care. We gather the information needed to apply for the New York Medicaid PCAP program so that they can participate in appropriate prenatal care beginning in the first trimester. We visit these women in their homes to provide prenatal education and to check their vital signs and assess for any prenatal complications with an in-camp provider. We provide interpreter services at their obstetrical appointments and serve as the primary contact person among their many service providers (ultrasounds, laboratory, obstetrician, PCP, specialists in complicated pregnancies, etc.). If a cesarean is scheduled in advance, we interpret for the patient during her surgery as well. On the day of discharge after delivery, we visit the women in the hospital to fill out birth certificates and interpret the discharge instructions for the nurses.

**Results:** As this season ends at the end of November, our in-camp and prenatal case management data has yet to be compiled.

**Conclusion:** With the consistent outreach and follow-up with patients, whether by phone or personal visits, we have seen patients become more interested in their own care as they are kept more informed. When I go out with the in-camp team to visit patients in their homes, I try to make some connection with each patient and show that I'm interested in their health and their safety. As a person who takes an interest in their culture as much as their health, I ask about their homes and their families. They like to feel that our team is sincerely interested in their overall well-being and that we recognize they are people with loving families and with a complicated history.

The in-camp teams are always so surprised at how honest and persistent I am with the migrant patients, especially the stubborn elderly men who hate to be fussed over. These elderly men remind me very much of my own stubborn grandfather who had several medical problems that required extensive care and follow-up. While these older men are here in the United States without their families, I like to consider myself as their surrogate nagging grand-daughter who has to explain the dangers of not being examined or treated in terms that they can understand. When I step out of my "case manager" shoes, I become a friend of the family who is there to help in any way that I can.

# Year-Out Research

**Kristina Gaud, CC4**

**Preceptor:**

**Ralph Pennino, MD**

**Chief, Plastic Surgery, Rochester General Hospital**

**Founder and President, InterVol**

## **Using Telemedicine to Increase Access to Healthcare in Belize**

**Introduction:** Telemedicine is a powerful medium through which healthcare can be delivered to patients who would otherwise not have access. The following is an account of a 9-month pilot project using telemedicine in Belize. Telemedicine was employed for a variety of uses relating to healthcare, including medical consultations, continuing education for healthcare providers, and providing medical supplies through a medical recycling program.

**Objective:** The project had three main aims: 1) to provide doctors and patients in Belize with specialist consultations with volunteer physicians in Rochester, NY; 2) to provide educational opportunities for doctors, nurses, and students in Belize; and 3) to identify barriers to the use of telemedicine in Belize.

**Background:** Telemedicine is using telecommunication technology for medical diagnosis and health care<sup>1</sup>. Potential benefits of telemedicine are to facilitate communication between physicians and patients<sup>2</sup>, and allow physicians to perform consultations with patients who have poor access to medical care<sup>3</sup>. Other potential benefits include decreasing distances patients have to travel, improving health outcomes and quality of care, and enhancing educational opportunities<sup>4</sup>.

Belize is a country of approximately 300,000 people<sup>5</sup>, but only 259 physicians support this population<sup>6</sup>. Over half of these doctors serve the Belize City area, making access difficult for patients who live in other parts of the country. Additionally, most doctors in Belize are primary care physicians, making access to specialists difficult. Because few doctors are available, telemedicine could potentially bring necessary medical care to hundreds of patients who would otherwise do without, helping correct the shortage of doctors in remote areas such as southern Belize.

### **Methods:**

#### ***Medical consultations***

Healthcare workers and patients at Southern Regional Hospital (SRH) and the surrounding Stann Creek District were educated about telemedicine and informed how to arrange telemedicine consults. Consultations were arranged in-person, by telephone, or e-mail with the researcher, who coordinated appointments with volunteer physicians from Rochester.

#### ***Continuing education for healthcare providers***

Educational sessions via teleconferencing were set up on a weekly basis by this researcher with volunteer faculty at Rochester General Hospital (RGH) and Strong Hospital, for healthcare staff at SRH. Also, doctors and nurses at SRH were invited to participate in weekly Grand Rounds at RGH via teleconferencing. A leadership training course for nurses at SRH was conducted using teleconferencing, for which two two-hour teleconference sessions were held with nursing faculty from Roberts Wesleyan College, Rochester, NY.

#### ***Medical recycling program***

Through teleconferencing, this researcher helped coordinate equipment repair and donation to

SRH. Staff at SRH made an inventory of broken equipment, and a biomedical engineer from Rochester General Hospital assisted in fixing these equipment via teleconference meetings, as well as an in-person trip with InterVol during month 8 of this project.

## **Results:**

### ***Medical Consultations***

Consultations were completed in the following specialties: internal medicine, neurology, dermatology, orthopedic surgery, plastic surgery, neurosurgery, cardiology, obstetrics and gynecology, and nephrology. For one of the patients, a consensus was reached that she would be best benefited by surgical treatment in the United States. For her, telemedicine was used for preoperative consultations, as well as a tool in organizing her trip to the U.S. After preliminary telemedicine meetings, the patient was flown to Rochester to begin surgical treatment there.

### ***Continuing education for healthcare providers***

All the doctors (13 total) at SRH were invited to weekly educational sessions. Attendance averaged 2-3 healthcare workers per session. In post-session interviews, respondents all said that the sessions were helpful, and requested more sessions on various topics. For the nurse leadership course, ten nurses attended. Post-course questionnaires indicated that all of the attendants found the course beneficial, and several requested additional courses for the future. Grand Rounds was attended weekly, with an average attendance of 2-3 healthcare workers per session. In post-session questionnaires, responses were mixed regarding whether the information presented in Rochester Grand Rounds was useful in everyday clinical practice in the low-resource setting of SRH.

### ***Medical recycling program***

The biomedical engineer from InterVol assisted in fixing the following equipment in SRH: anesthesia machine, x-ray machine, suction unit, OR lights, exam lights, a ventilator, air conditioning unit, and OR bed.

**Conclusion:** Telemedicine is a powerful technology that can provide many benefits to Belize and other third world countries. However, it is more than just a technology; it introduces significant changes in the approaches to and organization of healthcare that are difficult to anticipate and manage within a short-term perspective. Therefore, it is important to view this project as a small yet crucial step in a much longer process. The benefits of telemedicine must be kept in sight through the process of implementing the use of telemedicine, which necessarily will require changes in attitudes of what constitutes patient care<sup>7</sup>.

## **References:**

1. Currell R, Urquhart C, Wainwright P, et al. Telemedicine versus face to face patient care: effects on professional practice and health care outcomes. *Cochrane Database of Systematic Reviews* 2000, Issue 2.
2. Balas EA, Jaffrey F, Kuperman GJ, et al. Electronic communication with patients. *Evaluation of distance medicine technology. JAMA* 1997. 278(2):152-9.
3. Bagayoko CO, Muller H, Geissbuhler A. Assessment of Internet-based tele-medicine in Africa (the RAFT project). *Computerized Medical Imaging and Graphics* 2006; 30:40716.
4. Jennett PA, Hall LA, Hailey D, et al. The socio-economic impact of telehealth: a systematic review. *J Telemed Telecare* 2003;9:311-20.
5. Total population estimates and projections. *Statistical Institute of Belize*. Accessed 01/23/10 at 6:03 PM.
6. Belize Basic Health Indicators 2008. Office of the Director of Health Services, The Epidemiology Unit, Ministry of Health, Belize.
7. Gagnon MP, Lamothe L, Mebert M, et al. Telehomecare for vulnerable populations: the evaluation of new models of care. *Telemedicine and e-Health* 2006;12(3):324-31.

# Year-Out Research

**Kathryn M. Kellogg, CC4**

**Preceptor:**

**Rollin J (Terry) Fairbanks, MD, MS, FACEP Department of Emergency Medicine University of Rochester Medical Center**

## **Root Cause Analysis in the Emergency Department: A Comparison Study**

**Objectives:** Efforts to decrease the high rate of preventable adverse events in the ED, where rates have been reported to be particularly high, are continuing. Root Cause Analysis (RCA) is the predominant method used by hospital administrators to investigate adverse events to generate effective and sustained solutions to prevent similar future events. This study is the first to use a system safety engineering approach to examine the types of events that are being investigated by RCA teams, the types of solutions being proposed, and to contrast ED cases with hospital-wide cases.

**Methods:** All RCA reports from 2001 through 2008 were compiled for a 750-bed academic medical center. A qualitative content analysis was conducted to classify the types of events and solutions proposed by the RCA team. Three researchers analyzed the first 50 cases. The remainder were coded by 2 of the researchers, with the third involved for consensus in case of initial disagreement. Descriptive statistics were calculated.

**Results:** 301 RCAs were conducted during the 8-year study period; 26 involved the ED, a rate of 0.4 RCAs per 10,000 patient visits for ED cases, compared to 9.0 for non-ED cases ( $p < 0.01$ ). The most frequent ED event types were: medication error (15%), unexpected pulmonary embolus (11%), unexpected cardiac arrest (11%), procedure complication (8%), retained foreign body (8%), unexpected sepsis (8%), and devastating illness (8%). The most common non-ED event types were: procedure complication (22%), unexpected cardiac arrest (13%), iatrogenic neurologic deficit (12%), unexpected pulmonary embolus (6%), birth complication (5%), and retained foreign body (4%). The remainder of the cases fell into 25 categories, each ranging from 0.4-3%.

56 solutions were proposed in RCAs involving ED cases (mean of 2.2 per case), and 434 solutions were proposed for RCAs in non-ED cases (mean 1.6 per case). For ED cases, the 5 most common solution types proposed were: training (13%), process or workflow change (8%), forms and paperwork changes (8%), information technology structure change (8%), and physical environment change (8%). For non-ED cases the 5 most common solution types proposed were: training (21%), policy reinforcement (12%), process or workflow change (6%), counseling (6%), and forms and paperwork change (5%).

**Discussion:** Event types varied between the ED and rest of the hospital. RCA teams proposed similar solutions for both environments. Training was the most common solution proposed, but has been shown by safety scientists to be less effective than systems-based interventions. Policy reinforcement and counseling were commonly suggested by RCA teams in non-ED settings, but were less commonly recommended in ED RCAs, which tended to suggest more systems-based solutions, such as information technology changes and alterations in forms. The latter are believed to be more sustainable solutions and RCA teams working on non-ED cases may be able to use solutions proposed in ED-based RCAs to improve solutions for all RCA cases.

**Conclusions:** ED RCA rates were significantly lower than non-ED RCA rates. The most common solution types in both areas were those suggested by system safety engineers to be less effective. The effectiveness of the RCA solutions must be studied, and future research to articulate a hierarchical solution typology is recommended.

# Year-Out Research

**Ross Hanson, MS4**  
**India Johnson, MS2**

**Preceptor:**  
**John Markman, M.D. Director**  
**Neuromedicine Pain Management Center**  
**University of Rochester Medical Center**

## **Characterization of Neuropathic Pain in Post Laminectomy Pain Syndromes**

**Introduction:** Low back pain is the third leading indication for surgery in the United States [1, 2]. Despite the growing rates and complexity of surgical treatments, the vast majority of patients are left with residual painful symptoms following these interventions [3, 4]. In a substantial minority, these chronic symptoms are moderate to severe in intensity and cause significant activity limitation. The diagnostic category of post laminectomy pain encompasses a highly prevalent and diverse set of chronic, low back pain syndromes. Roughly 20% of patients experience more severe pain syndromes after surgery, and this is a leading cause of referral for subspecialty pain care [3]. Given the surging prevalence of low back pain and associated growth of complex spine surgery [4], it is important to refine the characterization of these post operative pain syndromes.

**Objective:** To demonstrate the feasibility of adapting DN4 and LEEDS questionnaires to the evaluation of post laminectomy pain syndrome.

**Background:** Although post operative pain syndromes tend to have varied anatomic precipitants and underlying pain mechanisms, patients with more severe back pain are more likely to have a neuropathic component [5]. The presence of a neuropathic mechanism may adversely affect patient outcomes, since this type of pain strongly correlates with decreased quality of life, increased functional impairment, and more severe pain intensity [6]. Consequently, patients with neuropathic pain are more likely to lack response to conventional therapies and endorse greater pain intensity and reduced health related quality of life compared to patients with non-neuropathic pain syndromes. We hypothesized that post laminectomy pain syndromes frequently have a neuropathic component and that patients experiencing this type of pain may be identified using instruments validated in other chronic neuropathic pain conditions.

**Methods:** This was a cross-sectional study with an embedded chart review of patients with chronic pain after spine surgery, designed to examine characteristics of post-laminectomy pain syndrome (PLPS). Eligible patients were between 18 and 85 years of age, spoke English, had previous lumbar laminectomy with or without instrumentation within the past 7 years, and demonstrated persistent pain of greater than 3/10 intensity at the time of initial referral for pain management. Patients were recruited initially by mail with telephone follow-up between October 2009 and January 2010. Of 157 patients identified using IDxAnalyzer and recruited for the study, 43 patients (20 male, 23 female, age range: 28-79 years) were enrolled in the single visit. Subjects completed a panel of self-report measures validated to assess pain and pain-related interference. These included the following: Visual Analog Scale (VAS), Roland-Morris Disability Questionnaire (RMDQ), and Modified Brief Pain Inventory, Short-Form (mBPI-sf). In addition to questionnaires, patients were examined by trained personnel at the time of study visit to complete the following objective measures: Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), and Neuropathic Pain Diagnostic Questionnaire (DN4).

**Results:** In this sample 43 chronic pain patients were evaluated for the presence of neuropathic pain using the validated DN4 cut-off score of 4 or greater [7]. 67.4% were categorized in the  $\geq 4$  neuropathic pain

group (29 patients), and 32.6 % were in the <4 non-neuropathic pain group (14 patients). The same 43 patients were also stratified according to the presence of neuropathic pain using the previously validated LANSS cut-off score of 12 or greater [8]. In this sample of 43 chronic pain patients, 25.6% were categorized in the  $\geq 12$  neuropathic pain group (11 patients), and 74.4 % were in the <12 non-neuropathic pain group (32 patients).

DN4 positive patients scored significantly worse in all pain and disability metrics than those in the DN4 negative category. These included VAS pain intensity (59.7mm vs. 33.3mm,  $p < 0.01$ ), RMDQ (16.3 vs. 10.9,  $p < 0.01$ ), and mBPI-sf (60.9 vs. 33.1,  $p < 0.01$ ). LANSS positive patients also scored significantly worse in the majority of pain and disability metrics than those in the LANSS negative category, although not as markedly as seen with the DN4. LANSS positive patients demonstrated worse pain as demonstrated by VAS (63.5mm vs. 46.9mm,  $p = 0.04$ ). LANSS positive patients also exhibited increased disability as judged by RMDQ (17.9 vs. 13.4,  $p = 0.02$ ) although not by mBPI-sf (63.2 vs. 47.9,  $p = 0.08$ ). Patients with axially-distributed pain predominated (60.5%), though there were no significant differences in pain distribution observed between groups in either neuropathic pain measure (DN4:  $p = 0.76$ , LANSS:  $p = 0.24$ ).

**Conclusion:** The presence of neuropathic pain according to both the DN4 and LANSS was associated with significantly higher pain intensity, increased level of disability, and greater pain-related activity interference. This constellation of findings is concordant with the presence of neuropathic symptoms in other chronic pain syndromes such as post herpetic neuralgia (PHN). Surprisingly, the presence of neuropathic pain was equally distributed among patients with axial predominant syndromes and those with a classic, lateralized radicular distribution of symptoms regardless of the painful region they identified as most bothersome. Neither axial nor radicular-predominant patterns were associated with positive outcomes to the DN4 or LANSS. This finding challenges the historical presumption that axial predominant back pain conforms to the end organ dysfunction model of lumbar back pain. It may be inferred that the mechanism of the underlying pain syndrome may be more valuable with regard to identifying subpopulations of responders to specific treatments than anatomic symptom distribution. Identification of this subpopulation of patients with neuropathic pain offers a foundation for enriched enrollment strategies for clinical trials and enhanced treatment matching in clinical practice for procedures targeting neuropathic pain such as spinal cord stimulation.

#### References:

1. Hart, L.G., R.A. Deyo, and D.C. Cherkin, *Physician office visits for low back pain. Frequency, clinical evaluation, and treatment patterns from a U.S. national survey*. Spine (Phila Pa 1976), 1995. **20**(1): p. 11-9.
2. Taylor, V.M., et al., *Low back pain hospitalization. Recent United States trends and regional variations*. Spine (Phila Pa 1976), 1994. **19**(11): p. 1207-12; discussion 13.
3. Fritzell, P., et al., *2001 Volvo Award Winner in Clinical Studies: Lumbar fusion versus nonsurgical treatment for chronic low back pain: a multicenter randomized controlled trial from the Swedish Lumbar Spine Study Group*. Spine (Phila Pa 1976), 2001. **26**(23): p. 2521-32; discussion 2532-4.
4. Weinstein, J.N., et al., *Surgical vs nonoperative treatment for lumbar disk herniation: the Spine Patient Outcomes Research Trial (SPORT): a randomized trial*. JAMA, 2006. **296**(20): p. 2441- 50.
5. Schmidt, C.O., et al., *Modelling the prevalence and cost of back pain with neuropathic components in the general population*. Eur J Pain, 2009. **13**(10): p. 1030-5.
6. Freynhagen, R., et al., *painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain*. Curr Med Res Opin, 2006. **22**(10): p. 1911-20.
7. Bouhassira, D., et al., *Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4)*. Pain, 2005. **114**(1- 2): p. 29-36.
8. Bennett, M., *The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs*. Pain, 2001. **92**(1-2): p. 147-57.

## Year-Out Research

**Laurel A. Menapace, MS4**

**Preceptors:**

**Derick Peterson, PhD**

**Andrea Berry, MS**

**Department of Biostatistics**

**University of Rochester**

**Tarek Sousou, MD**

**Alok A. Khorana, MD**

**Department of Medicine and Wilmot Cancer Center**

**University of Rochester Medical Center.**

### **Symptomatic and Incidental Thromboses Are Both Associated with Mortality in Pancreatic Cancer**

**Background:** Incidentally diagnosed venous thromboembolism (VTE) is a growing clinical problem. Although pancreatic cancer is well-known to be associated with VTE, contemporary rates of incidental and symptomatic VTE events and their association with mortality are incompletely understood.

**Methods:** We conducted a retrospective cohort study of consecutive pancreatic adenocarcinoma patients seen at the University of Rochester between January 1, 2006 and December 31, 2009. Radiologic reports were reviewed for presence of pulmonary embolism (PE), deep venous thrombosis (DVT), and visceral vein thrombosis. Multiple clinical variables and mortality outcomes were collected. Data were analyzed using a multivariate Cox proportional hazards model.

**Results:** A total of 1151 radiologic exams for 135 patients were included. Forty-seven patients (34.8%) experienced at least one VTE event. There were 12 PEs (n=12 patients, 8.9%), 34 DVTs (n=17 patients, 12.6%), 47 visceral vein (n=31 patients, 22.9%) and 2 arterial (n=2 patients, 1.5%) events. Twenty-one patients (15.5%) experienced more than one event. Incidental events comprised 33.3% (n=4) of PEs, 17.6% (n=6) of DVTs and 100% (n=47) of visceral VTE. Median survival for the study population was 237 (95% CI 199-277) days. Patients with VTE had significantly reduced survival (73 vs. 233 days at 3 months post-diagnosis; 66 vs. 245 days at 6 months post-diagnosis). There was no significant difference between asymptomatic and symptomatic events in terms of conditional median survival at 3 months-, 6 months- or 1 year-post diagnosis. In multivariate analysis, occurrence of either DVT (HR 7.4 95% CI 3.8-14.6, P<0.0001) or visceral asymptomatic events (HR 2.5 95% CI 1.6-3.8, P=0.0001) was significantly associated with mortality along with advanced stage.

**Conclusions:** VTE occurs in over one-third of pancreatic cancer patients, including a significant proportion with incidentally discovered events. Patients with visceral vein events are generally not anticoagulated but these findings suggest a similar association with mortality as symptomatic DVT. Our findings require reconsideration of prognosis and anticoagulation options in pancreatic cancer patients with both incidental and symptomatic VTE.

# Year-Out Research

**Monique Sanchez Castro, MS3**

**Preceptor: Monique Ho, M.D. Assistant Professor  
Department of Obstetrics and Gynecology University of Rochester Medical Center**

## **Vascular growth factors and their key ligands in preeclampsia**

**Introduction:** Preeclampsia affects approximately 6% of all pregnancies, and complications such as placental abruption, thrombocytopenia, disseminated intravascular coagulation, pulmonary edema and aspiration pneumonia continue to cause significant morbidity and mortality, to both mother and fetus (1). The long term goal of continuing research on the pathogenesis of preeclampsia is to identify and treat symptoms early on, before they become harmful to mother and fetus. Screening and early intervention may be improved with increasing knowledge of the genetics and the identification of key proteins.

**Objective:** To determine whether levels of soluble fms-like tyrosine kinase-1 (sFlt-1), placental growth factor (PlGF), and other key vascular analytes are altered in the serum and placentas of women with preeclampsia relative to normotensive, healthy matched controls.

**Background:** Recent advances in the understanding of preeclampsia have focused attention on the genes and subsequent proteins that create an imbalance of vascular factors, therefore leading to altered placental angiogenesis and vasculogenesis, and maternal vascular endothelial cell damage (2). After altered placental trophoblastic invasion, the cycle of hypoxia and oxidative injury leads to the characteristic signs and symptoms of preeclampsia: hypertension, proteinuria and edema (2, 3). In hypoxic conditions, as with preeclampsia, hypoxia induced factor 1 alpha (HIF 1alpha) is no longer degraded by Von Hippel Lindau protein (pVHL), and VEGF (vascular endothelial growth factor) is subsequently up regulated to promote angiogenesis in the hypoxic reaction (4). Therefore, HIF1alpha and pVHL may have important roles that contribute to the pathogenesis of preeclampsia. The proposed mechanism for the disease is that increased sFlt-1 binds VEGF and PlGF, leaving insufficient amounts free for endothelial cell maintenance (5). sFlt-1 is known to be elevated early in preeclampsia, even before onset of clinical symptoms, and may be the key in better understanding this disorder (2, 3, 5). Current research demonstrates that changes in levels of angiogenic factors are important in predicting preeclampsia(6, 7).

**Methods:** Prospective matched case-control study. Six women with preeclampsia and 6 healthy, normotensive women were matched for maternal age, parity, race, gestational age and the presence of labor, and given informed consent. Inclusion criteria for the preeclampsia group were gestational age of 32-42 weeks and preeclampsia (defined as two diastolic BP  $\geq$ 90 mm Hg measured 4 hours – 1 week apart, and either  $\geq$ 300 mg protein on a 24 hour urine sample, two urine dipsticks obtained 4 hrs-1 week apart with  $\geq$ 1+ protein, or a single dipstick measurement of  $\geq$ 2+ protein or a protein/creatinine ratio of  $\geq$ 0.35). Control patients were women between 32-42 weeks gestation without a history of hypertension of any kind. Subjects were excluded if they had received betamethasone, showed evidence of intrauterine growth restriction (IUGR)  $<$ 3%ile, chronic hypertension prior to pregnancy, chorioamnionitis, fetal anomaly, chromosomal abnormality, multiple gestation, pregestational maternal diabetes, or had other evidence of vascular or autoimmune disease. Maternal blood samples were collected prior to delivery and venous cord blood after delivery and separation from the newborn. Serum was removed and frozen at -80°. Within 10 minutes of delivery, the placenta was dissected and the placental samples were placed in RNA preservation medium. Serum levels of sFlt-1 and PlGF were analyzed by enzyme linked immunosorbent assay (ELISA). Membranous VEGFR-1 (Flt-1), pVHL and HIF 1alpha were analyzed by

Western Blot analysis. Basic demographic information and data regarding maternal and newborn morbidities and severity of disease were abstracted from the patient's chart or obtained by interview. Continuous variables including birth weight, gestational age, maternal BMI and weight gain during pregnancy were compared using student's t-test, and categorical variables including fetal sex, 5 minute Apgar score < 7, NICU admission and smoking history by Fisher's exact test.

### **Results:**

The statistical power was calculated to be 15 pairs, therefore, the study remains active in recruitment and sample collection. We are looking for patterns and differences in vascular factors between the preeclampsia and control groups. Our results include:

1. ELISA: sFlt-1 and PlGF
2. Western blot: VEGFR-1, pVHL, HIF 1 alpha
3. Demographic and clinical data comparisons between pairs

### **Conclusion:**

We will continue to recruit in order to fulfill our goal of 15 pairs, however, we expect to find elevated sFlt-1, as well as decreased bound VEGF and PlGF in our preeclampsia group, as previous studies have demonstrated. Analyzing HIF 1 alpha and pVHL along with vascular growth factors in preeclampsia is a fairly novel concept and it is unclear how the direction and magnitude of variation between groups will manifest. If preeclampsia is caused by a deficiency in pVHL, we propose that pVHL will be decreased and HIF 1 alpha elevated in preeclampsia.

### **References**

1. Zhang J, Meikle S, Trumble A. Severe maternal morbidity associated with hypertensive disorders in pregnancy in the United States. *Hypertens Pregnancy*. 2003;22(2):203-12.
2. Bdoeh Y, Karumanchi SA, Sachs BP. Recent advances in understanding of preeclampsia. *Croat Med J*. 2005 Oct;46(5):728-36.
3. Mutter WP, Karumanchi SA. Molecular mechanisms of preeclampsia. *Microvasc Res*. 2008 Jan;75(1):1-8.
4. Tanimoto K, Makino Y, Pereira T, Poellinger L. Mechanism of regulation of the hypoxia-inducible factor-1 alpha by the von Hippel-Lindau tumor suppressor protein. *EMBO J*. 2000 Aug 15;19(16):4298-309.
5. Reddy A, Suri S, Sargent IL, Redman CW, Muttukrishna S. Maternal circulating levels of activin A, inhibin A, sFlt-1 and endoglin at parturition in normal pregnancy and pre-eclampsia. *PLoS One*. 2009;4(2):e4453.
6. Rana S, Karumanchi SA, Levine RJ, Venkatesha S, Rauh-Hain JA, Tamez H, et al. Sequential changes in antiangiogenic factors in early pregnancy and risk of developing preeclampsia. *Hypertension*. 2007 Jul;50(1):137-42.
7. Levine RJ, Lindheimer MD. First-trimester prediction of early preeclampsia: A possibility at last! *Hypertension*. 2009 May;53(5):747-8.
8. Young BC, Levine RJ, Karumanchi SA. Pathogenesis of preeclampsia. *Annu Rev Pathol*. 2010;5:173-92.

# Year-Out Research

Claire Shannon, CC4

**Preceptor:**

**John Goldblatt, M.D.**

**Department of Orthopaedics, Division of Sports Medicine University of Rochester Medical Center**

## **Defining the Unique Serum Proteome of Mild Brain Trauma**

**Background:**

Mild TBI affects 1.2 million Americans per year; yet, there are currently no known treatments or sensitive diagnostics available. A burgeoning topic in brain injury research is the identification of brain specific proteins that cross the blood brain barrier after its integrity is disrupted in the setting of brain trauma.

**Study Objectives:**

A unique study designed to evaluate for the presence of brain-specific proteins in the serum of athletes by comparison of pre and post-concussion blood samples, using the concussion subject as his/her own control. ImPACT testing, an established neurocognitive test, will be used as an objective screen for changes in neurobehavioral performance and to monitor recovery as compared to pre-concussion performance in these individuals.

**Methods:**

177 members of the University of Rochester varsity football, soccer, and basketball teams are presently participating in this study and have provided preseason blood samples and baseline ImPACT testing. Post-injury blood samples and ImPACT testing are collected at predetermined intervals and stored for analysis. The serum from the injured athletes' samples will be assessed for known brain specific proteins, ApoA1 and S100b, using Western Blot and ELISA techniques. When the concussion contingent grows the blood will be tested using proteomic analysis techniques to identify both known and novel proteins unique to brain injury in the serum.

**Results:**

Seven of the 177 participants have suffered concussions to date. The preliminary ImPACT data and serum has been evaluated for 5 of the seven injured subjects to date. In 4 of these 5 concussed subjects, ApoA1 levels (relative optical density) increased immediately after injury, decreasing to pre-injury levels by day 7 in 3 subjects. Visual memory ImPACT scores decreased immediately after injury in 3 of 5 subjects, returning or exceeding pre-injury performance in all subjects by day 7. A greater number of subjects will permit a statistically meaningful correlation of changes in ApoA1 levels to changes in cognitive performance

**Conclusions:**

The ImPACT testing trends show that these athletes have measurable outcome differences. Using concussion subjects as their own controls has promise for identifying proteins unique to brain injury as it theoretically removes confounding data when comparing different individuals due to differences in innate serum proteins.

## Year-Out Research

**Lili Shek, MS4**  
**Otto Thomas, MS4**  
**Scott Simpson, MD**

**URMC Preceptor: Jessie Stone, M.D. Founder**  
**Soft Power Health**

**URMC Preceptor: Michael Keefer, M.D. Professor**  
**Department of Medicine / Infectious Disease University of Rochester Medical Center**

### **Towards a more effective strategy for volunteer HIV-1/AIDS counseling and testing (VCT) in rural Uganda: Foundations for a rural VCT intervention model.**

**Introduction:** Volunteer counseling and testing (VCT) programs have become a cornerstone of HIV prevention and treatment in sub-Saharan Africa, promoting knowledge about one's HIV status, encouraging safe sex, allowing individuals to plan and make informed life decisions based on their HIV status, and providing a cost-effective means of doing all of this. However, VCTs that are designed without respect for specific clinical, educational, cultural, and socioeconomic needs of a community may prove unattractive to participants, resulting in decreased uptake.

**Objective:** The specific aims of this study were, within the Budondo sub-county of eastern Uganda, to describe the characteristics, availability, and usage of current HIV-1 counseling and testing services; to gather an understanding of sexual behavior and HIV-1 knowledge and attitudes toward HIV-1 counseling, testing, and treatment in order to characterize the clinical, educational, cultural, and socioeconomic barriers affecting volunteer counseling and testing (VCT) utilization; and to empower subjects with accurate HIV-1 knowledge.

**Background:** With increased antiretroviral therapy availability in sub-Saharan Africa, VCT programs are now serving as a prime gateway for delivery of treatment.<sup>1-11</sup> However, within some countries such as Uganda the appeal of VCTs to the general population is limited, especially in the rural community, which comprises close to 90% of the population.<sup>12</sup> As of 2006, the Uganda Demographic and Health Survey reported that 80-85% of the surveyed rural population knew where to get an HIV-1 test. In rural districts, only 21% of females and 18% of males were tested and received HIV results.<sup>12</sup> The disconnect between knowledge of HIV-1 testing sites and the uptake of testing, especially in rural areas, is likely due to several factors, among them the method of VCT delivery.<sup>13-17</sup>

**Methods:** After obtaining the approval of chairpersons from both districts and local villages, and holding town meetings regarding this study in order to mobilize the study population, 405 subjects were identified and recruited in their homes to be interviewed, generating a database characterizing local VCT uptake and local demographics, sexual behavior, attitudes/perceptions, and knowledge base regarding HIV/AIDS. The purpose and methods of the study were described by the investigators, along with any risk or benefit to the participants, before each subject was asked to give verbal consent. Interviewees were matched with an interviewer and translator of the same gender. Interviews were performed using a survey translated and back-translated before data collection began.

**Results:** Awaiting further analysis. Descriptive statistics: of the 405 subjects interviewed, 194 (47.9%) were men and 211 (52.1%) were women. Median age was 35[18, 81]. Median number of spouses was

1[0,8]. Median number of children was 5[0,22]. Median number of sex partners ever was 3[0,112]. Desired number of annual HIV tests was 3[0,36]. For individuals already tested for HIV, the median distance traveled to the testing center during last test was 4.5km[0,400]. Median cost of transport to and from testing center was 1500 Ugandan shillings(UGX) [0,20], or \$0.75[0,\$10]. Median total cost of testing and transport to and from testing center was 2000UGX[0,23], or \$1[0, \$11.50]. Median total wait for testing service was 3h[0,>24].

**Conclusion:** Awaiting further analysis.

### References:

- 1) WHO. The right to know: new approaches to HIV testing and counseling. Geneva: WHO; 2003.
- 2) The voluntary HIV 1 Counseling and Testing Efficacy Study group Coates TJ et al. 2000. Efficacy of voluntary HIV1 counselling and testing in individuals and couples in Kenya, Tanzania, and Trinidad: a randomized trial. *The Lancet* Vol. 356: 103-112.
- 3) Were W, Mermin J, Bunnell R, Ekwaru JP, Kaharuza F. 2003. Home-based model for HIV voluntary counseling and testing. *The Lancet* 361: 1569.
- 4) Sweat M, Gregoirch S, Sangiwa G. 2000. Cost-effectiveness of voluntary HIV-1 counselling and testing in reducing sexual transmission of HIV-1 in Kenya and Tanzania. *The Lancet* 356:113- 121.
- 5) World Health Organization: the Health Sector Response to HIV/AIDS: coverage of selected services in 2001. Preliminary Assessment Genev: World health Organization, 2002.
- 6) Baryarama F, Bunnell RE, Montana L, Hladik W, Opio A, Musinguzi J, Kirungi W, Brigit-Waswa L, Mermin JH. 2008. HIV Prevalence in Voluntary counseling and testing centers compared with national HIV sero-survey data in Uganda. *Journal of Acquired Immunodeficiency Syndromes*. 49(2): 183-189.
- 7) Bateganya MH, Abdulwadud OA, Kiene SM. 2007. Home-based HIV voluntary counseling and testing in developing countries (Review). *Cochrane Database of Systematic Reviews*. Issue 4.
- 8) Menzies, N, Abang B, Wanyenze R, Nuwaha F, Mugisha B, Coutinho A, Bunnell R, Mermin J, Blanford JM. 2009. The costs and effectiveness of four HIV counseling and testing strategies in Uganda. *AIDS* 23: 1-7.
- 9) Coovadia HM. 2000. Access to voluntary counseling and testing for HIV in developing countries. *Annals of New York Academy of Sciences*. 918: 57-63.
- 10) Van de Perre, P. 2000. HIV voluntary counseling and testing in community health services. *The Lancet*, 356 86-87.
- 11) Mermin J, Musinguzi J, Opion A, Kirungi, W, Ekwaru JP, Hladik W, Kaharuza F, Downing R, and Bunnell R. 2008. Risk Factors for recent HIV infection in Uganda. *JAMA* 300(5): 540-549.
- 12) Uganda bureau of Statistics and ORC/Macro International Inc. 2006. 2005 Uganda Demographic and Health Survey.
- 13) Allen S, Meinzen-Derr J, kautzman M, Zulu I, trask S, Fideli U. 2003. Sexual behavior of HIV discordant couples after HIV counseling and testing. *17: 733-740*.
- 14) Wolff B, Nyani B, Katongole G, Ssesanga D, Ruberantwari A, Whitworth J. 2005. Evaluation of a home-based voluntary counseling and testing intervention in rural Uganda. *Health Policy and Planning*; 20(2) 109-116.
- 15) Matovu JKB, Kigozi G, Nalugoda F, Wabwire-Mangen F, Gray RH. 2002. The Rakai Project counseling programme experience. *Tropical Medicine and International Health*. 7(12): 1064- 1067.
- 16) Hladik W, Musinguzi J, Kirungi W, Opio A, Stover J, Kaharuza F, Bunnell R, Kafuko J, and Mermin J. 2008. The estimated burden of HIV/AIDS in Uganda, 2005-2010. *AIDS* 2008, 22:503-510.
- 17) Shafer LA, Biraro S, Nakiyingi-Miiri J, Kamali A, Ssematimba D, Ouma J, Ojwiya M, Hughes P, Van der Paal L, Whitworth J, Opio A, Grosskurth H. 2008. HIV prevalence and incidence are no longer falling in southwest Uganda: evidence from a rural population cohort 1989-2005.