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Basic Science & Clinical Research

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The Effects of Elevated Glucose Levels on Dermal Fibroblast Migration and Matrix Metalloproteinase Expression

Introduction:

Advanced chronic venous disease manifested by edema, skin diseases such as lipodermatosclerosis (LDS) and leg ulceration affects over 2.5 million patients per year in the United States. The healing processes of venous ulcers can take as much as 6 to 12 months. Venous disease is categorized from the most benign form of the disease, varicose veins (C1), to the most severe form of the disease, chronic venous ulceration (C6). It is due to venous insufficiency leading to increased pressure in the venous system.

Objective:

To determine the effects of varying concentrations of glucose fibroblast migration as well as the effects of varying concentrations of glucose fibroblast MMP-2 and MMP-9 expression and secretion.

Background:

There is no single theory that can explain why chronic wounds fail to heal; however in chronic inflammation, fibroblast is a major contributory factor in its persistency. It leads to localized cellular aging, with compromised vasculature and dysregulation of extracellular matrix composition and turnover. The extracellular matrix is an important structural and functional scaffolding made up of proteins that are necessary for cell function, wound repair, epithelialization, blood vessel support, cell differentiation and signaling, and cellular migration. The complex process of vascular remodeling involve enhances collagen decomposition and ECM reorganization. Vascular remodeling, one of the many outcomes of inflammation, is mediated by the enzymatic activity of matrix metalloproteinase (MMPs). Fibroblast express numerous extracellular matrix related enzymes and proteases including MMPs. In an early report evaluating wound fluid collected from patients with venous ulcers, it was determined that compared to acute wound fluid, chronic wound fluid contained up to tenfold increased levels of MMP-2 and MMP-9 (gelatinases) suggesting high tissue turnover. Vascular MMP activity is enhanced in diabetes through induction of promoter activity, mRNA protein expression and gelatinase activity. Activity of MMPs in vascular cells can therefore be modulated by high glucose. Understanding the healing mechanism of venous ulceration as it relates to the MMPS can result in several preventative measures as well as treatment alternatives.

Methods:

Early passage (P1-P3) of neonatal fibroblasts was cultured to confluency. Zymography, and Western Blotting were performed to determine the expression and secretion of MMP-2 and MMP-9 treated at varying concentrations of glucose (0 mM, 2.5mM, 5.5mM, 10 mM, 15 mM,

20mM, 25mM, and 50mM) in additon to FBS control. Cells and media were harvested and MMP-2 and MMP-9 secretions were determined by intensity using Kodak imaging technique.

Scratch assays were also performed to determine the migration pattern of fibroblasts in the aforementioned glucose concentrations. Before and after photos were taken at 0, 8, 24, and 48 hours and measurements were performed before and after to determine the extent of migration of the neonatal fibroblasts.

Results:

When the amount of enzymatic activity of MMP-2 was measured, MMP-2 activity in the media was variable with no clear pattern. Compared to physiological glucose concentration (5.5mM), MMP-2 activity in the cells is increased by 17.8% and 23.6% for 25mM and 50mM, respectively. When the amount of enzymatic activity of MMP-9 was measured the activity in the media is also variable with no clear pattern. Compared to physiological glucose concentration (5.5mM), MMP-9 activity in the cells is increased by 5.08% and 0.8% for 25mM and 50mM, respectively.

Conclusion:

Data determined by experiments are inconclusive as the number of trials is inadequate to make a clear, definitive explanation. Nevertheless, it can be inferred that there is a difference in migration patterns of neonatal fibroblasts in concentrations less than and greater than physiological glucose concentration (5.5 mM). It can also be inferred that there is a change expression of MMP-2 and MMP-9 in the cells, however whether that change is increasing or decreasing is yet to be determined. Media concentrations were insignificant. This may be due to time allotted for the fibroblast to grow in respective media and time of cell harvest which may have been insufficient for cells to synthesize, package, transport, and release adequate and measurable enzyme into media.

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Basic Science & Clinical Research

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Alternative Distal Lower-Extremity Amputations in Patients with Foot Ulcers Secondary to Diabetes Mellitus

Introduction: Foot ulcers represent a common and debilitating problem for diabetic patients. The lifetime risk for a diabetic patient developing a foot ulcer has been estimated at 15% (1). Infected foot ulcers are the most common reason for hospital admission of diabetic patients, accounting for 25% of admissions (2). The toes represent the most common location for an ulcer, followed by the plantar surfaces of the metatarsal heads, midfoot, and heel (3). Conservative treatment for ulcerations include wound irrigation and debridement, off-loading and pressure reduction attempted through bracing and casting, and dressing changes and wound care. Failure of conservative treatment often leads to osteomyelitis, the primary indication for amputation. Approximately 15% of foot ulcers progress to require amputation (2, 4, 5). Orthopaedic foot and ankle surgeons often perform below-knee amputations (BKA) to treat patients with recalcitrant foot ulcers of the midfoot, hindfoot, or ankle. Unfortunately, the procedure leaves patients with a decreased ambulatory status due to the increased energy and oxygen demands on the patient after amputation (6, 7). Patients undergoing BKA experience significant mortality post-operatively. One-year mortality rates reported in the literature for BKA patients range from 20.8% (8) to 35.5% (9) and five-year mortality has been reported as 63.3% (10). Diabetic patients with non-healing foot ulcers may have surgical alternatives to BKA that allow amputation at a more distal level on the lower-extremity while successfully eradicating infection and leaving a stable soft tissue envelope with a primary closure. Orthopaedic foot and ankle surgeons perform total calcanectomy, partial calcanectomy, transmetatarsal, and Chopart's amputations on patients whose ulcers would traditionally make them possible candidates for BKA. These procedures seek to salvage as much of the native foot and ankle as possible while allowing complete excision of necrotic tissue and primary wound healing. This offers patients the chance for unassisted ambulation on an end bearing limb.

Objective: The purpose of this retrospective study was to examine mortality and ipsilateral re-amputation rates among patients with recalcitrant foot ulcers treated with alternative distal amputations.

Methods: Data were collected to monitor the outcomes of lower extremities subjected to total calcanectomy, partial calcanectomy, Transmetatarsal, Choparts, and below-knee amputations for lower-extremity ulceration secondary to diabetes mellitus. The information collected was used to view the outcomes of each surgical procedure with respect to mortality and ipsilateral re-operation rate. This information was compared to historic control data and our data on BKA. Institutional Review Board approval was obtained for this retrospective study.

The hospital billing database was accessed and a search was conducted using Current Procedural Terminology (CPT) codes to identify lower-extremities undergoing one of the above referenced amputations between January 1, 1995 and July 1, 2009. Charts were obtained and reviewed. Demographic data and pertinent medical history were abstracted and the American Society of Anesthesiologists (ASA) Physical Status score was recorded from the anesthesia record for each operation. The ASA Physical Status score is a widely used, well-accepted, and validated scoring system that measures a patient's overall health status prior to undergoing an operation independent of surgical or anesthesia risk (11, 12). Patients are assigned a score between 1 and 6, with 1 being the healthiest (13).

Mortality was the primary endpoint. The Social Security Death Index was searched to determine whether patients were deceased and the date of death was recorded. Mortality rates based on survival analysis methods were calculated for each cohort at one, three, and five years. Kaplan-Meier survival curves were generated for each cohort to illustrate survivorship from time of amputation to death, irrespective of whether any subsequent amputation was required. Follow-up time for each lower- extremity was defined as the time from the date of surgery until the date of death or, if the patient was living at the end of the study, the time from the date of surgery until study completion on July 1, 2009. The secondary endpoint was failure of the index amputation. Failure was defined as subsequent proximal amputation to the ipsilateral lower- extremity. Operative and clinic notes were analyzed to determine whether each lower-extremity had been subjected to a more proximal amputation subsequent to the index amputation. Kaplan-Meier survival curves were generated to express the period of time a lower- extremity was free from a more proximal amputation. To account for patients who died prior to requiring re-amputation, we defined the endpoint for this analysis as the earlier of either subsequent proximal re- amputation or death.

Results: Seventy-eight patients and a total of eighty-one lower extremities were enrolled. All patients had diabetes mellitus documented in their charts.

BKA: Eighteen index below-knee amputations were enrolled. Mean age at surgery was 58.6 +/- 12.3 years and mean ASA score was 3.06 +/- .64. Eight (44%) patients in the BKA cohort died during the study period. Mortality rates at 1, 3, and 5 years for patients in the BKA cohort were 23%, 29%, and 45% respectively (TABLE 1). A Kaplan-Meier survival curve illustrates BKA survivorship (FIGURE 1).

Chopart: Ten index Chopart amputations were enrolled. Mean age at surgery was 56.7 +/- 12.6 years and mean ASA score was 2.78 +/- .44. Four (40%) patients in the Chopart cohort died during the study period. Mortality rates at 1, 3, and 5 years for patients in the Chopart cohort were 20%, 30%, and 40% respectively. A Kaplan-Meier survival curve illustrates Chopart survivorship.

Partial Calcanectomy: Seventeen index partial calcanectomies were enrolled. Mean age at surgery was 53.4 +/- 13.6 years and mean ASA score was 2.82 +/- .53. Ten (59%) patients in the partial calcanectomy cohort died during the study period. Mortality rates at 1, 3, and 5 years for patients in the partial calcanectomy cohort were 12%, 38%, and 69% respectively. A Kaplan-Meier survival curve illustrates partial calcanectomy survivorship.

Total Calcanectomy: Fifteen index total calcanectomy amputations were enrolled. Mean age at surgery was 64.7 +/- 12.9 years and mean ASA score was 3.27 +/- .59. Eleven (73%) patients in the total calcanectomy cohort died during the study period. Mortality rates at 1, 3, and 5 years for patients in the total calcanectomy cohort were 40%, 47%, and 66% respectively. A Kaplan-Meier survival curve illustrates total calcanectomy survivorship.

Transmetatarsal: Twenty index transmetatarsal amputations were enrolled. Mean age at surgery was 53.6 +/- 13.1 years and mean ASA score was 3.00 +/- .46. Six (30%) patients in the transmetatarsal cohort died during the study period. Mortality rates at 1, 3, and 5 years for patients in the transmetatarsal cohort were 0%, 6%, and 32% respectively. A Kaplan-Meier survival curve illustrates transmetatarsal survivorship.

Discussion: According to the Centers for Disease Control and Prevention (CDC), in 2007 there were 23.6 million Americans with Diabetes (7.8% US population) (14). Diabetes is the 7th leading cause of death. The diabetic patient profile reveals 68% have coronary artery disease (CAD), 75% hypertension (HTN), and 16% stroke. Diabetes is the leading cause of kidney failure and new cases of blindness. Over 60% of non-traumatic lower limb amputations occur in people with diabetes. The economic burden of this disease is staggering with \$58 billion in indirect costs and \$116 billion in direct medical costs for the US in 2007. Direct medical costs are 2.3 times higher in diabetic patients than patients without diabetes after adjusting for age and sex. Recognizing that the sedentary life style that often occurs after a BKA may worsen this profile, alternatives to a BKA are needed. Partial distal foot amputations including partial and total calcanectomies, Chopart's, and transmetatarsal amputations may provide more functional level amputations and with this logic, potentially lead to lower mortality rates. Little is known about the longevity of these distal

amputations and if the presumed improvement in metabolic status decreases mortality rates.

The one-year BKA mortality rate of 23% determined in our study is comparable to the range of one-year mortality rates found in the literature (20.8% to 35.5%) (8, 9). The revision rate for this amputation is low, with only one failure (6%) during the study period. While this amputation is stable, it has a high mortality rate.

The 20% one-year mortality rate we report for Chopart amputation compares favorably to BKA mortality. However, over half (55%) of all patients subjected to a Chopart amputation required revision to a BKA, with the average time to revision was 2.4 years. A literature search using Ovid Medline provided no information on the mortality or reamputation rates for Chopart amputation. Chopart amputation provides patients with an end-bearing limb with no increased risk of mortality compared to treatment with BKA. However, the high revision rate with Chopart's amputations requires that patients and surgeons accept a more unpredictable post-operative course than with BKA. No patients in the transmetatarsal cohort died within the first year and the five-year mortality rate was 32%, both lower than BKA mortality rates. Transmetatarsal amputations appear quite stable, with only 10% proximal revision rate at a mean of 2.3 years following the index amputation. A literature search using Ovid Medline revealed short-term (<30 days) post-operative mortality rates for transmetatarsal amputations but provided no longer term mortality data. The 12% one-year mortality rate for partial calcanectomies was lower than 23% one-year BKA mortality, while total calcanectomy had a higher one-year mortality rate (40%). The five-year mortality rates for partial and total calcanectomy were high, 69% and 66% respectively. These rates are higher than the 45% five-year mortality rate for the BKA cohort. Calcanectomies failed at high rates and failed rapidly. 41% of partial calcanectomies failed and the mean survival time of the index amputation was 0.7 years. 27% of total calcanectomies failed and the mean survival time of the index amputation was 0.3 years.

Chopart amputations and transmetatarsal amputations appear to offer excellent alternatives to patients who would otherwise have been candidates for BKA. These amputations provide the opportunity for an end-bearing limb, which allows patients to expend less energy ambulating and may allow patients to ambulate at a higher-functional level. The mortality rates associated with these amputations compare well with those for BKA. The risk of these procedures is that they may require subsequent revision, which poses the risk of additional mortality and morbidity associated with another surgical procedure and the emotional toll of undergoing and recovering from another surgical procedure.

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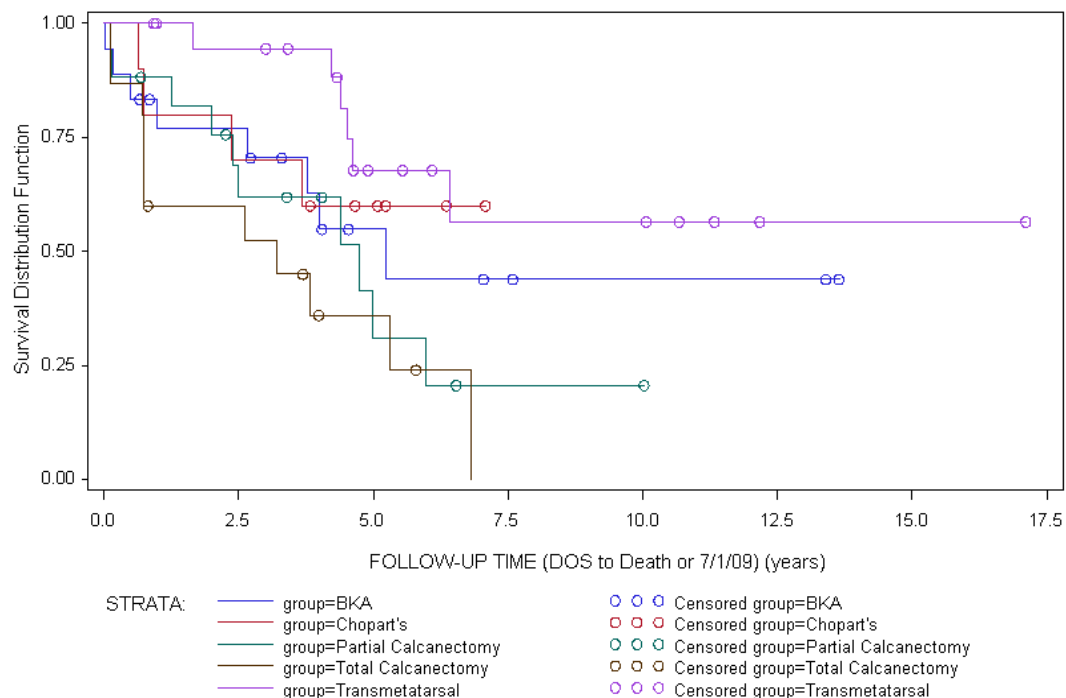
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Figures and Tables:

Table 1: Lower-Extremities Enrolled, Mortality Rates, and ASA Score by Cohort

	BKA	Chopart	Partial Calcanectomy	Total Calcanectomy	Transmetatarsal
Lower-Extremities	18	10	17	15	20
Mean Age	58.6	56.7	53.4	64.7	53.6
Deaths	8	4	10	11	6
1-year Mortality Rate	0.23	0.20	0.12	0.40	0.00
3-year Mortality Rate	0.29	0.30	0.38	0.47	0.06
5-year Mortality Rate	0.45	0.40	0.69	0.66	0.32
Mean ASA Score	3.06	2.78	2.82	3.27	3.00

Figure 1: Survival to Death from Index Amputation





Basic Science & Clinical Research

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Relation of Body Mass Index to Sudden Cardiac Mortality and Defibrillator Efficacy in Patients with Left Ventricular Dysfunction

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Objective: The aims of this study were to evaluate the relation between body mass index (BMI) and all-cause mortality and sudden cardiac death (SCD) and assess the benefit of primary implantable cardioverter defibrillator (ICD) therapy among patients with left ventricular dysfunction.

Background: Obesity has been identified as a risk factor for cardiovascular disease and heart failure (HF). However, data regarding the relation of body-mass index to outcome among patients with established HF are conflicting.

Methods: We examined the risk of all-cause mortality and SCD among 1231 patients with left ventricular dysfunction enrolled the Multicenter Automatic Defibrillator Implantation Trial-II. Interaction-term analysis was utilized to assess the benefit of the ICD in upper- (obese: $\geq 30 \text{ kg/m}^2$ [n=361]) and lower- (non-obese: $< 30 \text{ kg/m}^2$ [n=870]) BMI categories.

Results Mean BMI in the study population was $27.9 \pm 5.1 \text{ kg/m}^2$. In multivariate analysis, reduced BMI was shown to be independently associated with an increase in the risk of all-cause mortality (23% risk increase per 5 unit BMI reduction ($p=0.009$)) and SCD (41% risk increase per 5 unit BMI reduction ($p=0.01$)).

Consistently, patients with BMI $< 30 \text{ kg/m}^2$ exhibited a 46% ($p=0.03$) and 76% ($p=0.04$) increase in the risk of all-cause mortality and SCD, respectively, as compared with patients who had higher BMI values. The benefit of the ICD was pronounced among higher-risk patients with BMI $< 30 \text{ kg/m}^2$ (HR=0.68 [$p=0.017$]), and maintained in the lower-risk subgroup of patients with BMI $\geq 30 \text{ kg/m}^2$ (HR=0.73 [$p=0.32$]; p-value for ICD-by-BMI interaction = 0.86).

Conclusion: Our findings suggest an independent inverse association between BMI and sudden cardiac mortality risk in HF patients that may be used in risk assessment for primary ICD therapy.

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Basic Science & Clinical Research

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Risk factors for Long-Term Mortality Following Device Therapy in Patients with Ischemic Left Ventricular Dysfunction

Objective: The present study was designed to identify independent predictors of long-term mortality among patients who received device therapy in the Multicenter Automatic Defibrillator Trial-II (MADIT-II).

Background: The implanted cardioverter defibrillator (ICD) improves survival in high-risk cardiac patients through termination of life-threatening ventricular tachyarrhythmias (ventricular tachycardia or fibrillation [VT/VF]). However, previous studies have suggested there may be an increase in mortality risk following ICD shock therapy.

Methods: We evaluated the risk of all-cause mortality during an extended 5-year post-trial follow-up of ICD-treated patients in MADIT-II. Multivariate Cox proportional hazards modeling was used to evaluate the independent contribution of appropriate- and inappropriate- ICD therapy to the occurrence of long-term mortality. Ventricular tachyarrhythmias that were terminated by the defibrillator were further categorized by the type of therapy that was delivered by the ICD (shock therapy, antitachycardia pacing, vs. no therapy), the heart rate at which therapy was delivered (fast heart rate VT/VF: >220 bpm, intermediate heart rate VT/VF: 180-120 bpm, and slow heart rate VT/VF: <180 bpm vs. no therapy), arrhythmia frequency during the trial (≥ 2 , 1, vs. no therapy) and the time-period following device implantation in which the arrhythmia occurred (≤ 1 year, >1 year, vs. no therapy).

Results: Patients who experienced fast heart rate VT/VF had significantly higher long-term mortality rates than patients who experienced slower heart rate VT/VF or no ventricular tachyarrhythmias ($P < 0.001$; Figure). Consistently, multivariate analysis demonstrated that independent predictors of long-term mortality among patients who received ICD therapy, included the occurrence of fast heart rate VT/VF (HR = 1.72; $P = 0.001$), the occurrence of ≥ 2 ventricular tachyarrhythmias during follow-up (HR=1.29; $P = 0.04$), and the occurrence of a ventricular arrhythmia within 1 year of device implantation (HR=1.25; $P = 0.018$). By contrast, shock therapy was not shown to be associated with a significant increase in mortality risk after adjustment for VT/VF heart rate (appropriate ICD shocks: HR=0.92 [$P = 0.639$]; inappropriate ICD shocks: HR=1.29 [$P = 0.82$]).

Conclusion: Among patients who receive appropriate ICD therapy, the clinical characteristics of the ventricular tachyarrhythmia, including VT/VF heart rate, frequency, and timing following implantation, can be used to assess the risk of long-term mortality. Defibrillator shock therapy was not associated with an independent increase in long-term mortality risk in MADIT-II patients.



Basic Science & Clinical Research

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The effects of elevated glucose on dermal fibroblast migration and TGF- β /TGFR-I & II expression

Introduction: Chronic venous disease is associated with reduced quality of life, particularly in terms of pain, physical function, and mobility. The high prevalence of varicose veins and chronicity of leg ulcers has a considerable impact on healthcare, accounting for 1-3% of the total healthcare budgets in countries with developed systems [1]. In the United States, the cost of treating patients with chronic venous ulcers per year is estimated to exceed \$3 billion. These ulcers are often painful, resulting in an estimated loss of 2 million workdays due to disability [2-3]. Previous studies indicate a 70% recurrence rate of venous ulcers, with some taking as long as 6-12 months to completely heal [4]. To date there are no effective therapies facilitating the healing of venous ulcers; the development of a clinical assay for early identification of patients at risk for fibrosis associated with advanced chronic venous insufficiency would allow for early intervention, alleviate costs, and improve patient care.

Objective: To study the effects of elevated glucose levels on dermal fibroblast migration and TGF- β /TGFR-I/TGFR- II expression.

Background: Extensively studied in wound healing, transforming growth factor- β 1 (TGF- β 1) is a polypeptide that regulates different cellular functions such as proliferation, migration/differentiation, and extracellular matrix production [5]. These regulatory mechanisms are necessary in normal wound healing, and abnormalities in TGF- β 1 signaling have been reported in chronic venous ulcerations [6-8]. In acute wounds, the expression of both type I and type II TGF- β 1 receptors has been shown to be elevated, mediating normal healing [9]. In venous ulcer fibroblasts, however, a deficient TGF- β 1 receptor complex has been reported and may be the underlying factor in wound chronicity [10]. The over expression of TGF- β 1 is implicated in a number of fibrotic diseases, including pulmonary fibrosis and scleroderma [11- 12]. TGF- β 1 expression is also increased in diabetes, and overproduction of pro-sclerotic TGF- β 1 has been implicated in the pathogenesis of diabetic nephropathy [13]. As diabetic foot ulcers often become chronic, signaling by TGF- β 1 and its receptor complex may be affected by the hyperglycemic state, suggesting a dynamic interplay between metabolism and wound-healing. This study aims to elucidate the specific role of elevated glucose levels on two key aspects of wound healing in dermal fibroblasts: migration and TGF- β /TGFR-I/TGFR-II expression.

Methods:

Fibroblast Migration. To determine the effects of glucose on fibroblast migration, neonatal dermal fibroblasts were exposed to increasing concentrations of glucose [0-50 mM] for 24 hours. A scratch wound assay was then conducted, and migration was measured at 48 hours post-glucose treatment.

TGF- β & TGFR-I/II Expression. To determine the effects of glucose on fibroblast TGF- β & TGFR-I/II expression, neonatal dermal fibroblasts were exposed to varying concentrations of glucose [0-25 mM] for 24 and 48 hours. TGF- β & TGFR-I/II expression was then determined by fluorescence-activated cell sorting (FACS) analysis.

Results:

Fibroblast Migration. After 24 hr of 0 mM glucose treatment, fibroblast cells migrated on average of 10 units. Cells treated with 5.5 mM and 50 mM glucose migrated on average of 17 and 21 units, respectively. As a positive control, cells treated with fetal bovine serum (FBS) were completely confluent (full migration) after 24 hr exposure.

TGF- β & TGFR-I/II Expression. The percent (%) positive cells for TGF- β expression at 24 hr-post treatment with 0 mM, 5.5 mM, and 25 mM glucose were 86, 86.9, and 79.8%, respectively. All data values will now be listed with respect to these three glucose concentrations. Mean fluorescent intensity (MFI) values for TGF- β expression at 24 hr were 1069, 1350, and 1340 units. At 48 hr, % positive cells for TGF- β expression were 60.8, 83.2, and 54.8%; MFI values were 552, 911, and 441 units. Percent positive cells for TGF-RI expression at 24 hr were 95, 27.5, and 95%; at 48 hr, 90.6, 51.6, and 85.2%. MFI values for TGF-RI expression at 24 hr were 1833, 730, and 3009 units; at 48 hr, 1218, 295, and 1001 units. Percent positive cells for TGF-RII expression at 24 hr were 3.9, 1.9, and 2.3%; at 48 hr, 1.2, 0.3, 2.1%. MFI values for TGF-RII expression at 24 hr were 434, 243, and 239 units; at 48 hr, 261, 178, and 184 units.

Conclusion:

Differences in glucose concentration have a moderate effect on neonatal dermal fibroblast migration in a wound setting. The data suggest a trend towards increased migration with higher concentrations of glucose, suggesting a potential basis for fibrosis development under hyperglycemic conditions. FACS analysis showed differential expression of TGF- β & TGFR-I/II after 24 and 48 hr treatment with varying concentrations of glucose. The three concentrations tested (0, 5.5, and 25 mM) showed that TGF- β & TGFR-I/II expression at physiological levels (5.5 mM) was markedly distinct. For TGF- β , the expression at 5.5 mM glucose was higher than that at 0 mM or 25 mM; for TGF-RI/II, the expression at 5.5 mM glucose was lower than that at 0 mM and 25 mM. Interestingly, cells that were treated with sub-physiological and hyper-physiological glucose concentrations showed similar deviations in expression level from cells that had been treated with a physiological concentration. This observation suggests a potential homeostatic response in TGF- β & TGFR-I/II expression to fluctuating levels of glucose exposure in the body. The TGF- β signaling cascade is complex and the mechanisms behind its interplay with crucial metabolic factors such as glucose are intriguing areas for further research.

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Basic Science & Clinical Research

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Inter-relationships of Carpal Tunnel Syndrome with Body Mass Indices in the Massive Weight Loss Population

Introduction: Obesity is associated with an increased prevalence of carpal tunnel syndrome (CTS). A growing number of patients are presenting for bariatric surgery to treat the comorbidities of morbid obesity. We investigated the inter-relationships between body mass, comorbidities, and prevalence of CTS in the massive weight loss population

Objective: The objective of this study was to investigate the inter-relationships between weight loss, comorbidities, and prevalence of carpal tunnel syndrome in patients who have undergone massive weight loss.

Background: Obesity has been previously identified as a risk factor for carpal tunnel syndrome (CTS). The incidence in obese patients is reported to range from 20-50%, compared to 2-10% in the non-obese population.¹⁻⁹ The suggested mechanisms through which obesity contributes to carpal tunnel syndrome include the accumulation of adipose tissue or increased hydrostatic pressure within the carpal tunnel, increased force on the wrist during activities of daily living, or as a result of comorbidities associated with metabolic syndrome.^{3,10-14}

Bariatric surgery is associated with an improvement in comorbidities associated with morbid obesity including, hypertension, diabetes mellitus, sleep apnea, gastroesophageal reflux disease, dyslipidemia, and degenerative joint disease. The role of weight loss on CTS resolution is somewhat less clear, as there have been conflicting reports in the literature.^{15, 16}

Compression neuropathies are becoming of greater concern in body contouring cases where patients are positioned prone, supine, and/or upright at 90 degrees for prolonged periods of time.¹⁷ As the rise in body contouring surgery parallels the rise in bariatric surgery, concern that long operative procedures may exacerbate pre-existing or undiagnosed CTS necessitates our study.

Methods: 92 consecutive MWL (>50 lbs) patients were assessed for BMI, medical comorbidities, nutrition, history of CTS or release (CTR), treatment modalities, current symptoms, and recurrence. Logistic regression analyses determined the influence of independent variables on presence of CTS.

Results: Prior to weight loss, CTS was present in 45 patients (49%, mean Max BMI=55.4, mean age=48.6), and 17 had CTR (38%). Among the 28 who did not have surgery, 24 (86%) had conservative management. After MWL, patients who had prior CTR had no recurrence requiring secondary release. Of the 24 patients managed conservatively, 17(71%) had resolution of symptoms after MWL ($p=0.04$) (mean Current BMI=30.1, mean Delta BMI=21.7). 7 patients (12.5%) reported residual CTS (mean Current BMI=37.1, Delta BMI=19.3). Current BMI was lower ($p=0.03$) for the group with symptom resolution. Weight loss method (diet and exercise versus bariatric surgery) was not significantly associated with resolution of CTS.

Conclusions: Almost half of the MWL patients reported symptoms of CTS while obese. A majority of patients have resolution of CTS or symptoms with weight loss, and may avoid the need for CTR in the future. Patients presenting for body contouring should be examined for pre-existing CTS prior to further surgical intervention.

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Basic Science & Clinical Research

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Demographic Characteristics of Patients Having Catheter Ablation for Atrial Fibrillation

Introduction:

Atrial fibrillation is a common arrhythmia affecting 2.2 million people in the U.S. There are many concerning complications with atrial fibrillation including the potential for clot formation, stroke, and congestive heart failure. Currently, the two major ways of treating atrial fibrillation are either to give anti-arrhythmic drugs, or to use pulmonary catheter ablation. A topic of interest has been if there are factors, such as structural heart dimensions, that may be able to predict future recurrences of atrial fibrillation after catheter ablation.

Objective:

To determine if structural heart dimensions measured by CT predicts recurrence of atrial fibrillation after catheter ablation.

Background:

Previous studies using echocardiogram to get left atrial diameters have had inconclusive results in their ability to predict recurrent atrial fibrillation. Whereas echocardiogram can give two-dimensional measurements, a CT can provide accurate three-dimensional measurements, as well as provide imaging of pulmonary veins and their variants. Four studies in 2009 have all been able to establish that left atrial volume is a predictor for recurrence of atrial fibrillation. We aim here to look at not just left atrial volume, but other parameters that may predict recurrences.

Methods:

The patient population was selected from the database at New York Presbyterian/Weill Cornell Medical Center. Patients were chosen who had an ablation done from December 2004 to December 2008. All patients must have gotten a pre-ablation CT.

Data collection is still ongoing. Data is being collected on patients' type of atrial fibrillation (paroxysmal, persistent, long standing persistent), history of heart disease or risk factors for heart disease, left ventricular ejection fraction, ablation parameters, whether or not the ablation achieved electrical isolation, and whether or not there were any complications during or following the ablation procedure. CT measurements to be obtained include left atrial volume, pulmonary vein diameters, the presence of any pulmonary vein variants (common or accessory pulmonary veins), left ventricular volume and left ventricular mass.

Results:

A total of 153 patients were compiled who met the criteria for the study. Of 102 patients whose data has been collected already, 82 patients have had paroxysmal atrial fibrillation, 17 have had persistent atrial fibrillation, and 3 have had long standing persistent atrial fibrillation. 19 have had a prior ablation for a previous arrhythmia before. 37 had a baseline rhythm of atrial fibrillation at the time of the ablation, and 63 had a baseline rhythm in sinus. All patients achieved electrical isolation of

pulmonary veins except for those who had to terminate the procedure due to complications (3 of them). Since the database is not yet complete and the CT measurements are still pending, statistical analyses have not yet been done.

Conclusion:

As the results of the study are still pending, no conclusion has been reached yet.

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Basic Science & Clinical Research

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IGF-1 and Cognitive Function

Introduction

Existing research suggests that hormonal and inflammatory biomarkers affect cognitive function. In particular, growth hormone insulin-like growth hormone I (IGF-1) and related to memory performance. Circulating IGF-1 can cross the blood-brain barrier and bind to areas of the brain affecting mood and memory (Arwert 2005). Higher serum IGF-1 has been correlated with better performance on memory challenges, such as the Mini Mental State Examination (MMSE), Brown-Petersen Auditory Consonant

Trigram (CCC), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), and Rey Auditory-Verbal Learning Test (RAVLT). In particular, increased serum IGF-1 may be associated with better verbal memory performance among older individuals.

Objective

Our primary objective was to investigate the association between serum IGF-1 and verbal memory in healthy older men and women. In addition, we aimed to determine any potential gender differences within this IGF-1/verbal memory association.

Background

Previous research has found a positive association between higher circulating IGF-1 levels and better performance on verbal memory examinations. This trend has been notable among elderly individuals, ages 50 and older, though more so among men than women. In a study of 460 male participants, a “significant trend of better performance with increasing free IGF-1” was found (Okereke 2006). This association may not be significant among elderly women. Okereke did a similar study among 590 women, all between the ages of 60 and 68. No significant association was found between circulating IGF-1 and verbal memory performance (2007).

Methods

This study included 68 women and 43 men, age range 50 – 87 years. Participants were given memory tasks to complete, specifically RBANS, RAVLT, and CCC. Within the course of this experimental trial, participants had their blood drawn. Individual serum IGF-1 levels were measured and correlated with performance on the cognitive tests. SPSS software used to analyze the data and determine possible correlations between performance on memory tasks and measured levels of IGF-1 among healthy male and female participants.

Results

Focusing specifically on results from the RAVLT, a significant, positive correlation was found between verbal immediate recall and IGF-1 ($r = 0.36$, $p = 0.03$). This association was found only among the male participants. We found no apparent trend between cognitive recall and plasma IGF-1 levels among our women volunteers.

Conclusion

We observed a correlation between plasma IGF-1 and verbal memory in healthy older men, however not in older women. These results were consistent with prior research by Okereke involving cognition and IGF-1 among older individuals. IGF-1 gender differences may also correspond to all-cause mortality. Friedrich found increased all-cause mortality in elderly men with lower IGF-1 (2009). This correlation was not seen among older women. Our research thus suggests multiple possible gender differences with regards to IGF-1.

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Basic Science & Clinical Research

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The Effect of Neuroimaging on Treatment Plans for Patients with Primary Brain Tumors

Introduction: Patients diagnosed with primary brain tumors are often monitored clinically with the use of MRI and CT neuroimaging. However, there does not exist any guidelines or recommendations for how frequently these patients should be imaged to identify any changes in the state of the disease that will alter the physician's treatment plan.

Objective: The goals of this study are to determine how often patients with primary brain tumors are screened with neuroimaging and how often the treatment plan changes as a result of the scans.

Methods: This study is a retrospective analysis of patients who were diagnosed with a primary brain tumor between July 2001 and January 2009 and were subsequently treated at University of Rochester Wilmot Cancer Center. Patients needed to have undergone at least two scans as a part of their treatment in order to be included in the analysis. To determine the frequency of scans, we only considered the scans that were ordered for monitoring disease progression, i.e. images performed as a part of radiological or neurosurgical procedures were not included in the data. For instances where multiple scans were performed on one day, we denoted this as one event in the data set. To determine the frequency of changes in therapy, the first image obtained for the patient was considered to be the baseline. Consequent changes in treatment were defined as any alteration in the medication, dosing, radiation, or decision to operate. These changes needed to be a direct result of the findings on the scans and were determined from the medical notes of the treatment team. The frequency of treatment plan alterations was then compared to the frequency of scans.

Results: N=78 patients with 19 different types of primary brain tumors were analyzed. The average patient received 10.21 non-procedural scans over the course of 32.5 months. Aside from the baseline scans, 668 scans were analyzed for change in treatment. Of these, 50.40% resulted in a change in therapy. Moreover, the analysis showed that the average length between scans is 4.61 months while the average length between changes in therapy is 7.78 months. The data was also separated and analyzed for individual diagnoses. For the diagnoses with $n > 1$, the treatment of glioblastoma multiforme ($n=26$) showed the best efficiency with 67.01% of scans resulting in treatment changes. The treatment of low-grade oligodendrogliomas ($n=4$) proved the least efficient with only 38.46% of scans resulting in treatment changes.

Conclusion: Based on these preliminary results, one in two scans ordered to monitor the status of disease in primary brain tumor patients resulted in an alteration in the patient's treatment plan. This yield is satisfactory and suggests that we are imaging patients at adequate intervals. The data will need to be further analyzed to attempt to distinguish between the scans that are more or less likely to alter therapy. More studies should be conducted on this topic to evaluate risk-benefit ratios and cost analysis of imaging primary brain tumor patients so that guidelines for monitoring a patient's disease status may begin to be developed.



Basic Science & Clinical Research

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Burden of Care Associated with Tourette Syndrome

Introduction: Tourette syndrome (TS) is a neuropsychiatric disorder that consists of motor and vocal tics beginning in childhood. The specific criteria for diagnosis with TS include the presence of at least two motor and one vocal tic present for at least one year before the age of 18. The different tics do not have to be occurring during the same time period. TS is associated with ADHD, learning disorders, anxiety, obsessions and compulsions, emotional lability, irritability, explosive and aggressive behavior and self-injurious behavior. Tics often are present in early childhood, peak in late childhood or the early teen years and for most lessen in severity during the late teen years and into adulthood. Tics usually have a waxing and waning course. Many people with TS do not find their symptoms to be severe enough to require treatment. For others, their symptoms interfere enough with their daily life to require outpatient pharmacological or psychosocial treatment for the management of their tics or for their comorbidities. People rarely require hospitalization for their symptoms.

Objective: The purpose of this chart review is to assess the burden of care associated with TS in different age groups. The primary objective is to study the burden of care associated with tics in TS. Secondly, the burden of care associated with the comorbidities of TS was assessed. By examining the burden of care, we hope to gain another way of looking at the natural history of the disease.

Background: Previous studies have been conducted on the natural history of TS by interviewing patients retrospectively to determine when their tics were the worst. One study by Lechman suggests that the onset of ticks occurs at 5.6 ± 2.3 years of age and reaches a peak severity between ages 10.0 ± 2.4 years (2003). After this peak in severity, tics seem to decline in a linear fashion through adolescence with a marked reduction or the absence of tics by adulthood. The goal of our study would be to analyze the natural history of TS from a different perspective by instead looking at the burden of care associated with the syndrome in different age groups.

Methods: This study reviewed the charts of 668 patients with TS that received care at the Neurology Clinic at Strong Memorial Hospital. The number and type of clinic calls and office visits made by the subject in a one year period were recorded. Once a chart entered the study, it was reviewed for a period of one year beginning on the patient's most recent birthday. Subjects were placed into one of four age categories: 5-8, 8-12, 12-15 and 15-18. The number and type of clinic calls and office visits were then recorded. Clinic calls were subdivided into patients calling for changes in the frequency or severity of their tics, for medication refills, for medication side effects, and in relation to comorbidities including ADHD, OCD, anxiety and behavioral problems. Clinic visits were subdivided into those that were actionable (a change in treatment was recommended) and those that were non-actionable. Actionable visits were further subdivided by reason for the change including: increased severity of tics, ADHD, OCD, anxiety, and behavior.

Results: Patients in the 8-11 age group made the most office visits (39.9%) this was followed by the 12-

14 and 15-18 age groups (27.8% and 27.8% respectively) and finally the 5-7 age group (4.4%). The 8-11 age group also had the highest percentage of actionable visits versus total visits (61.9%). Next came the 12-14 age group (51.1%), then the 5-7 age group (50.0%) and finally the 15-18 age group (43.18%). Patients in the 12-14 age group had the highest proportion of visits actionable for an increase in tic frequency or severity (19.3%), followed by the 5-7 age group (14.3%), the 8-11 age group (12.7%) and the 15-18 age group (9.1%).

Conclusion: In our study, the burden of care associated with tic severity peaked in the 12-14 age group as measured by the proportion of visits actionable for an increase in tic frequency or severity out of total office visits for the age group. Assuming that the worst period of tics would be associated with the greatest burden of care associated with tics, this finding goes against previous studies that have demonstrated the peak in tic severity to occur at 10 years of age. However, patients in the 8-11 age group did have the most office visits and the highest proportion of actionable office visits of the age groups. These findings agree with the idea that the features TS are worst at around 10 years of age.

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Basic Science & Clinical Research

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Neuroprotective Effect of Continuous P188 Infusion

Introduction:

Intracranial hemorrhage (ICH) is a type of stroke that is manifested by direct bleeding into the brain parenchyma. It causes 10 to 15% of all strokes, and has a 30-day mortality rate of 35 to 52% (2). Current medical and surgical treatments both aim to reduce the increased intracranial pressure (ICP) caused by ICH (2, 8). Unfortunately, these treatments show limited success at best (8). Moreover, no cellular approach to neuroprotection is currently available clinically. Therefore, it is the aim of this project to further investigate the neuroprotective effect of a surfactant poloxamer known as Poloxamer 188 (P188) after induced ICH injury.

Background:

P188 is a synthetic tri-block polymer that has been demonstrated to be excreted unmetabolized in humans (6). It is also approved by the US Food and Drug Administration for oral and intravenous administrations (6). *In vivo*, P188 was shown to reduce platelet aggregation, inflammation, and to protect striatal cells against excitotoxicity (1, 4, 5). *In vitro*, P188 can reseal membranes after electroporation, and block lipid peroxidation (9). These findings suggest that P188 may play a significant role in the later phase of cell necrosis when plasma membranes are destroyed. Consistent with this mechanism, P188 has been demonstrated to protect hippocampal neurons from oxidative and excitotoxic chemicals by direct insertion into cell membrane bilayer (9, 10). Furthermore, P188 has been found to decrease polymorphonuclear cells' (PMN) oxidative bursts and alter their marker expression. Since PMN are known to mediate response to trauma by promoting inflammation and edema formation via oxidative bursts, P188's effect on PMN cells again highlights its role in neuroprotection (7). Given the innocuous nature of P188 and its anti-thrombotic, anti-inflammatory and neuroprotective properties, P188 presents an excellent alternative for ICH therapy.

Previous studies at the Frim lab have demonstrated that P188 administration can reduce neuronal injury caused by prolonged blood exposure in the brain in an acute ICH model (3). Specifically, after ICH induction, animals receiving a single dose of P188 had smaller lesion volume than the control group two days post-induction, and animals that received daily injection of P188 had significantly smaller lesion volume than corresponding controls. This suggests that continuous infusion of P188 may confer even greater neuroprotection. To test this possibility, mini-osmotic pumps were used for continuous delivery of P188 in this project.

Objective:

1. Design a rat surgical procedure that would allow for rapid collection and injection of autologous blood into striatal parenchyma, and implantation of MR compatible mini-osmotic pumps.
2. Using the procedure to examine the neuroprotective effect, as defined by less neuronal loss, of continuous P188 infusion via implanted osmotic pumps.

Methods:

Objective 1

- *Blood draw:* 28 Gauge (G) insulin syringe, 24G, 25G, and 27G IV catheters were used for blood draw from the great saphenous vein at the medial thigh, over the medial malleolus, and the small saphenous vein over the lateral malleolus.
- *Blood injection:* 22G 7" Quincke spinal needle (BD) were used to inject approximately 25 μ L of autologous blood into 4 hemispheres of 2 rats. Different injection depths were used for rat 1. Rat 2 were injected at the same depth, but the stylet of the spinal needle was greased for right hemispheric injection, while both stylet and bore hole were greased for left hemispheric injection. Brain tissues were collected and analyzed for lesion size.
- *MRI compatible pump:* Polyetheretherketone (PEEK) tubing was used to replace inner delivery tube of mini-osmotic pump (Alzet). Polyethylene (PE) is then connected to the PEEK tubing. A cap made of fast polymerizing bone cement was used to encase the PEEK/PE connection to prevent leakage.

Objective 2

- 10 Sprague-Dawley rats were injected with 25 μ L autologous blood. 5 rats were implanted with P188 filled osmotic pumps (experimental group) and 5 rats were implanted with artificial CSF filled osmotic pumps (control group). Animals were sacrificed 10 days post surgery. Brain tissues were collected and are waiting to be analyzed histologically for lesion size and neuronal loss.

Results:

Objective 1: Injection with the initial penetration depth of 5.5 mm followed by withdrawing to 3.3 mm created a lesion of 1.7 mm³. Injection at 4.5 mm created a lesion of 1.67 mm³. Greased stylet injection at the former injection depth produced a lesion of 2.1 mm³ and greased stylet and bore hole with same injection depth produced a lesion of 5.0 mm³.

Objective 2: Tissue analysis is still pending.

Conclusion:

Objective 1: Blood collection using a 28G insulin syringe at the small saphenous vein over the lateral malleolus aspect of the hind leg yielded the greatest amount of blood, while injection with a greased stylet and bore hole yielded the largest lesion size.

Objective 2: Awaiting tissue analysis.

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Basic Science & Clinical Research

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VDT and Eye Irritation

Objective:

Working in front of a computer screen or watching TV for hours causes a lot of people to complain of dry eyes. While treatment for this problem has received a lot of attention, there has never been a careful study of how these tear films are made and how they change over time. This project aims (1) to define tear film production and dynamics in patients with extended use of VDT (visual data terminal), (2) to observe the effect of extended VDT on patients already diagnosed with Dry Eye Disease, and (3) to see if putting the VDT 15° below the horizon improves tear film volume and consistency.

Background:

Tear production in the eyes is important for protection, comfort, and simply being able to see. When a person with healthy eyes blinks, the eyelid smoothes the tears into an even film. If this film is not intact, it brings the patient discomfort, and new research suggests compromised visual acuity.^{1,2}

The breakdown of the tear film is known as Dry Eye Disease, and it affects millions of people in the United States.³ While it has no set criteria, patients with dry eyes complain of irritation, burning, and redness.⁴

Until recently, it was difficult to provide quantitative evaluations of the tears—the fluid volume and dynamics, but the development of optical coherent tomography (OCT) makes this possible in an easy and non-invasive way. Looking at the tear film with OCT allows precise measurements of its thickness and boundaries in real-time.⁵

Methods:

1. Subjects had a baseline OCT reading at T = 0.
2. Subjects watched a film on a computer monitor.
3. Further OCT readings were taken after 10 minutes, 20 minutes, and 30 minutes.
4. Subjects returned after a two-day washout period and watched the film 15° below the horizon with readings again at T = 0, 10, 20, and 30.

Results:

Subjects showed a marked increase in tear films after ten minutes of watching the monitor. This declined to baseline by 30 minutes. There was some additional tear volume in patients with 15° downward gaze.

Conclusion:

This data shows (1) that the monitor was an eye irritant because it induced a tear response and that (2) a downward gaze reduces evaporative loss.

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Basic Science & Clinical Research

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Assessing the Role of Soft Contact Lenses in Preoperative Conditions Following Keratoprosthesis Implantation

Introduction: The keratoprosthesis (KPro), an artificial cornea, has proven effective at establishing a clear pathway for light through an opaque cornea. To qualify for the surgery, patients who underwent KPro surgery had poor prognoses for simple penetrating keratoplasty. These included patients with multiple graft rejection (54%), chemical injury (15%), bullous keratopathy (14%), and herpes simplex virus keratitis (7%). The quality of life of the patients was greatly increased with the restoration of vision, in some cases as in some cases, from light perception only to 20/400 vision.

Some of the difficulties arising from the KPro surgery have been desiccation by evaporative forces, epithelial defects, stromal thinning, and dellen formation. Other problems caused by the physical presence of the device itself, are instability of the KPro, and aqueous humor leakage. To help protect the cornea from some of these complications, a soft contact lens (SCL) is routinely placed as the last step of surgery. The lens protects the corneal surface by diffusing the evaporative forces and maintaining a fluid meniscus at the edge of the front plate of the KPro. It also works to correct postoperative refractive error and can be used for cosmetic effect to match its paired eye.

Objective: To evaluate associations between patient pre-operative diagnosis with SCL retention, complications, and outcomes.

Background: The use of a soft contact lens (SCL) following the implantation of a Boston Keratoprosthesis (KPro) has become an accepted method at the Massachusetts's Eye and Ear Infirmary (MEEI) and the University of Rochester Eye Institute (UREI) to decrease post-surgical complications that arise on the corneal surface. Long-term SCL use keeps the cornea hydrated and protected from the abrasive forces of the eyelids but comes with its own set of complications including increased risk of infection and SCL deposits.

It has been recognized that pre-operative categories of patients, most broadly divided into autoimmune disorders, chemical injury, and other (this includes infection, aniridia, and noninflammatory disorders such as keratopathies, keratoconus, dystrophies, and trauma) can be prognostic of post-surgical visual acuity outcomes. The autoimmune disorders make up the worst prognostic category while "other" fares the best. Chemical injury shows restoration of visual acuity in the middle ground. There is however, a scarcity of data evaluating the pre-operative groups for prognostic value in the management of post-operative SCL use and complications.

Methods: A retrospective chart review was conducted of 92 patients' (103 eyes) charts who underwent a Boston KPro Type I at the MEEI or the UREI by one of two surgeons (J.V.A, or C.H.D). The medical records were reviewed and analyzed for pre-operative diagnosis, past ocular surgical history, SCL retention, and subsequent complications and outcomes.

Results: Prediagnostic categories included 16 patients with autoimmune disease (Stevens Johnson Syndrome, ocular cicatricial pemphigoid, rheumatoid arthritis, and uveitis), 9 with chemical injury, and 67

“other” (aniridia, infection, trauma, dystrophies, and keratopathies). Among these groups, the time to first soft contact lens (SCL) loss was shortest for chemical injury and longest for autoimmune patients with “other” in between. A small subset (n=17) of the population experienced more than 2 SCL losses per year. This comprised 6% of the autoimmune group, 22% of the chemical injury group, and 21% of the “other” group. The autoimmune category experienced the highest yearly complication rate and the “other” category the lowest. Patients over the age of 70 years were significantly less likely to experience a complication compared to those younger than 70. Among all three categories, complication rates were higher when patients were not wearing their contact lenses. The most common complication experienced was corneal melt resulting in aqueous humor leak.

Conclusion: While the preoperative category of autoimmune disorders has been shown to have the worst visual acuity prognosis following keratoprosthesis (Kpro) implantation, it shows the most promise for retention of soft contact lenses which is a key factor in decreasing the number of post-surgical complications. It is likely that the hyper-autoimmune response of this group is responsible for the increased complication rate, most notably melt. The ocular surface damage done in a chemical injury is likely the cause of this group’s second number of complication. The shearing forces of the eyelids against the irregular ocular surface is not only more likely to create small epithelial defects that could lead to more serious complications, but likely is responsible for the short time until first SCL loss. The “other” category consists of mainly of noninflammatory disorders that do not have the same risk for complication that autoimmune states or inflammatory processes. This group thus has the best outcomes for low occurrence of complication.

One limitation of this study is the nature of retrospective record review. Any contact lens losses that were not reported (the lens was replaced at home) at the time of an appointment may skew the data towards fewer lens losses, and increased time between losses. Although this study demonstrates that there are significant differences between preoperative categories of patients, more rigorous prospective studies are needed before true prognosis for these groups can occur.

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Basic Science & Clinical Research

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Trigger-Specific Risk Factors for Cardiac Events in Patients with the Congenital Long-QT Syndrome Type 2

Introduction

The long-QT Syndrome (LQTS) is a rare heterogeneous, autosomal dominant genetic disease in which most affected individuals have delayed ventricular repolarization manifested on an electrocardiogram (ECG) as QT prolongation.¹ This disease is caused by mutations in myocyte cell membrane ion channel genes and occurs with an overt prevalence estimated at about 1:3,000-1:5,000 in the general population. Clinical manifestations of these channelopathies include syncope, polymorphous ventricular tachycardia (torsades de pointes), and sudden arrhythmic death.²

Prolongation of the heart rate-corrected QT interval (QTc) and stress-induced syncope are the two clinical features of greatest diagnostic importance. The QT interval of the ECG describes the duration of the ventricular depolarized state, often referred to as the plateau phase of the ventricular action potential. A normal QT interval typically spans 450 milliseconds and its duration is dictated by inactivated voltage-gated Na⁺ channels and active cardiac K⁺ channels.³ A prolonged QT interval may be attributed to decreased repolarization by the K⁺ channels or an inappropriate depolarizing leak of sodium into the myocyte. In most forms of LQTS, QT prolongation is the result of decreased K⁺ channel repolarization due to mutations in the α -subunit of the I_{KS} or I_{KR} K⁺ channels.² In LQTS patients, it has been determined that a baseline QTc interval ≥ 500 ms directly correlates to an increased risk of the aforementioned cardiac events.⁴

Currently, ten LQT genes, LQT1-10, have been identified, each of which is associated with an ion channel; exceptions are LQT4 and LQT9, which code for ion channel-anchoring proteins.¹ The overwhelming majority (95%) of genotyped LQTS patients have mutations located in the first three LQT genes (LQT1, LQT2, LQT3).⁵ LQT1 results from a mutation of the KCNQ1 gene on chromosome 11p15.5 which codes for the slowly activating delayed rectifier K⁺ channel, I_{KS}. A mutation of the human ether-a-gogo-related gene (HERG) on chromosome 7q35-36, which encodes the I_{KR}, or rapidly activating delayed rectifier K⁺ channel, results in LQT2. LQT3 is associated with the SCN5A gene on chromosome 3p21-24, which encodes the α -subunit of the Na⁺ voltage-gated channel.⁶ The more common autosomal dominant form of LQTS, Romano-Ward syndrome (RWS), results from a single mutation in any of the LQTS genes. A more severe form of LQTS called Jervell and Lange-Nielsen syndrome (JLNS) is associated with two mutations in either the LQT1 or LQT5 genes. Compared to RWS, JLNS is rare, comprising less than 1% of LQTS affected patients; however, in addition to the cardiac abnormalities seen in RWS, JLNS contains the added phenotype of sensorineural deafness.⁵

Objective

The goal of this study is to evaluate the role of clinical and genetic factors when assessing risk in patients with the LQT2 genotype.

Background

The risk for cardiac events in each of the most common LQTS genotypes, LQT1-3, has been shown to be

strongly associated with specific triggers. In patients with LQT2, mutations in the HERG gene have been predominantly linked with arousal and exercise-induced triggers.⁷ Furthermore, Moss et al demonstrated that patients with mutations in the pore region of the HERG channel have increased risk for arrhythmic events.⁸ It has also been shown that females are at higher risk for cardiac events than men in LQT2.^{9, 10} Previous studies suggested that these risk factors were characteristic of the LQT2 genotype; however, we wanted to investigate whether or not these risk factors actually differed by trigger type within this population. We hypothesized that clinical and genetic risk factors for cardiac events in LQT2 are in fact trigger-specific.

Methods

Multivariate Cox proportional hazards regression modeling was employed to evaluate trigger-specific risk factors for cardiac events among 422 genetically-confirmed LQT2 patients from the US portion of the International LQTS Registry.¹¹

Results

One hundred and forty two study patients experienced a cardiac event, of whom 51 (36%) were associated with arousal triggers, 23 (16%) were associated with exercise triggers, and 68 (48%) were associated with non-arousal/non-exercise triggers. In the arousal group, 34% of patients had transmembrane (TM) mutations and 24% had mutations in the Per-Arnt-Sim (PAS) region, whereas in the exercise group 70% had TM mutations and none had PAS mutations. Multivariate analysis demonstrated that female sex (Hazard Ratio=2.49, P=0.002), QTc duration (Hazard Ratio=1.64, P=0.034), and mutations in the TM (Hazard Ratio=1.7, P=0.045) and PAS regions (Hazard Ratio=1.61, P=0.097) were associated with increased risk for arousal-triggered events, whereas TM mutations (Hazard Ratio=3.7, P=0.003) dominated the risk for exercise-triggered events.

Conclusion

Our findings indicate that specific clinical and genetic risk factors contribute to arousal-triggered cardiac events in patients with the LQT2 genotype. The elevated risk with TM mutations in both trigger groups supports the previous work by Moss et al regarding increased risk in the pore region since this is contained within the TM portion of the channel.⁸ The emergence of mutations in the PAS region as a potentially important risk factor in only the arousal group may lead to a better understanding of the mechanism behind trigger-induced events. Previous studies of the HERG PAS region have shown that mutations in this area accelerate channel deactivation thus decreasing the effectiveness of I_{Kr} in repolarization and prolonging the duration of the action potential.^{12, 13} Recognizing the trigger-specific nature of these clinical and genetic variables will lead to better risk assessment in those with the LQT2 genotype.

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Basic Science & Clinical Research

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Efficacy of Cochlear Implantation in Patients Outside of Current Candidacy Recommendations

Introduction and Background: According to current recommendations set forth by the FDA, children of age 12-24 months with profound sensorineural hearing loss who receive little to no benefit from traditional amplification are appropriate candidates for cochlear implantation. It has been well demonstrated that early access to sound is optimal for English speech and language development. New standards are now considering a broader range of patients to be candidates, such as those under 12 months of age, those receiving marginal benefits from hearing aids performing poorly on speech perception tasks, and those with inner ear malformations. Studies demonstrate that many of such patients formerly considered a contraindication have received implants and performed well, as indicated by performance on speech perception and language tasks.

Objective: The objective of this study is to demonstrate that individuals are benefiting from cochlear implants, as evidenced by improvement in speech perception scores, even when they do not meet the candidacy criteria set forth by the FDA.

Methods: The study design was a retrospective chart review performed at the Eye Institute of the New York Eye and Ear infirmary. The database of current and former patients served as the sampled population. Individuals were classified as “borderline” for current cochlear implant candidacy and included in the study when possessing certain characteristics (ie, under 12 months of age, unilateral deafness, severe or moderately severe hearing loss, etc.). Individuals were then assigned to one of three groups, according to recorded pure tone averages obtained prior to implantation, and matched with controls with similar characteristics.

Results: Proposed analysis consists of using a between-subjects ANOVA to determine whether or not a significant difference in performance exists between the cochlear implant group and their hearing aid matched peers one year after implant use. Although analysis is currently ongoing, raw data indicates improvement in speech perception tasks and substantial benefit in those implanted outside of the current guidelines when compared to hearing-aid counterparts.

Conclusion: There is potentially significant benefit for those individuals using cochlear implants, as evidenced by improved speech and language scores, even when they do not meet candidacy criteria set forth by the FDA. Along with improved technology and surgical techniques, broadening access to cochlear implantation offers patients promising prospects.

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Basic Science & Clinical Research

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Effect of Hardware Orientation on Structural Integrity in the Repair of Fractured Clavicles

Introduction:

Management of clavicle fractures include operative or non-operative treatment plans. Non-operative treatment involves reduction of the fracture followed by shoulder immobilization. Operative treatment typically involves the open reduction and plating of the fracture followed by a briefer period of shoulder immobilization. Two plating orientations are used to repair midclavicular fractures; anterior-inferior placement and superior placement. The majority of fractures are treated non-operatively, however operative treatment is recommended for those who have sustained a mid-clavicle and/or open fracture. Previous studies have shown that non-operative treatment in these patients results in both an increased likelihood of nonunion and malformation of the clavicle partially due to the lack of protecting muscles and tendons surrounding the fracture.

The majority of patients who undergo surgical repair will require no further treatment. A subset of patients however, will require the hardware to be removed upon healing due to various implant irritations. Unfortunately, the holes drilled into the clavicle to secure the plate implantation refill themselves with soft tissue as opposed to the original bone matrix. Presumably these holes present a structural weakness with a lower force threshold for re-fracture.

Objective:

In the setting of operative repair, the aim of this study is to determine if one plating orientation results in less weakening of the clavicle upon removal of hardware and therefore results in a lower risk of repeat fracture. The ultimate goal is to develop clavicle plate placement guidelines for patients at high risk for needing a recommended plate placement for a patient who is likely to need eventual hardware removal.

Background:

It has been reported that the clavicle is the site of 2.6-5% of fractures. The majority of these fractures are classified as group I fractures and occur in the middle third of the bone. Several methods have been described for the management of these patients including operative and non-operative methods. Not surprisingly, the recommended treatment varies greatly depending on the location of the fracture, how the insult occurred, whether displacement of the bone has occurred and whether the surrounding tissue and vasculature has been damaged.

Previous studies have used at patient outcomes, cadaver models, and stress testing to determine the optimal management protocol. To date, no studies have directly compared the structural integrity of clavicles repaired with the anterior-inferiorly placed plates versus superiorly placed plates.

Methods:

In the first phase of the project, 30 clavicles were harvested from fresh frozen cadaver shoulders. Each clavicle was scanned (micro CT) to determine their cortical thickness (mm) and other structural properties. One anterior plate and one superior plate were used as templates to drill screws into 15 clavicles respectively (30 total). Finally, these screws were removed to complete the experimental repaired clavicle model. With the surgical removal of clavicle hardware in live patients, these holes do not refill with bone matrix but rather fill with soft tissue hypothesized to weaken the clavicle.

Upon completion of the first phase of the project, the clavicles will undergo 4 point bend testing to determine the force required to create a mid-shaft fracture. The independent variable to be tested is the orientation of plate placement while the depended variable will be the force required to fracture the clavicle. The minimum force (measured in N) required to fracture the clavicles will be measured with the biomechanical bending setup and recorded with an excel spreadsheet. The data will then undergo statistical analysis to determine any significant differences between anterior-inferior vs. superiorly placed screw holes and to compare those values with forces required to fracture an intact clavicle as seen in the literature.

Results:

The project has not been completed yet. This is due to a decision to to increase the power of the experiment by doubling the number of clavicles undergoing testing from 15 to 30. The lab is waiting for the additional cadaver shoulders to arrive to complete dissections and begin 4-point bend testing. The decision was made to delay testing of available clavicles until all samples were available to eliminate unknown confounding factors and test in one batch.

Conclusion:

The results and conclusions of the experiment are to be determined.

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Basic Science & Clinical Research

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Epidemiology and Eligibility of Assisted Living Residents to Use Telemedicine to Decrease Emergency Department Use

Objective:

- 1.) To characterize the population of patients in the Strong Health Geriatrics Group Assisted Living Residence (ALR) program.
- 2.) To evaluate the feasibility of substituting telemedicine for emergency department (ED) and primary care physician (PCP) visits for acute illnesses within this population.

Background:

Challenges of Acute Illness in Elderly Populations

Acute illness among the elderly, particularly among those living in assisted living residences (ALR), currently presents a considerable burden on those patients and the health care system. During episodes of acute illness among these patients, there are a number of obstacles to obtaining care. Within ALR populations, the typical response of ALR staff, family members, or patients is to either contact the patient's primary care provider or to request an ambulance by calling 911.

The dependence on emergency medical systems to handle acute illness in elderly patients often results in sub-optimal care. ED physicians have to work with incomplete patient histories potentially leading to discontinuity of care and complications that would have otherwise been preventable.^{i, ii, iii} These difficulties are reflected by the increased complication rates among elderly patients treated in an ED relative to those treated elsewhere. These difficulties include duplication of services, administration of contraindicated medications, conflicting care recommendations and distress for the patient.^{i, ii, iii}

Telemedicine as a Solution

Over the past ten years, telemedicine has had an expanding role in care delivery across a variety of patient populations. Numerous studies among younger patients have found that telemedicine has led to improved outcomes across a wide range of metrics including patient satisfaction, access, quality of care, cost and optimal utilization of health care systems.^{iv, v, vi, vii, viii, ix, x}

Preliminary studies in older patients, primarily living in nursing homes, have also provided encouragement. Application of telemedicine under these circumstances has demonstrated feasibility, acceptability to patients and providers and enhancement of resident management.^{xi, xii} Further, the use of telemedicine has been shown to provide elderly patients access to a clinical evaluation when trained practitioners were not on the nursing home premises.^{xiii, xiv, xv}

Initial interest for expanding the use of telemedicine to the Strong Health Geriatrics group was spurred by the success of a similar program already implemented in the pediatric population in Rochester. Within

this population, children with access to telemedicine had office visit rates 3.3% lower than those without access to telemedicine. ED visit rates were found to be 23.7% less among those children with access to telemedicine. Insurance payments for diagnoses made via telemedicine or in an office were on average one-seventh the cost of those made in the ED, corresponding to an estimated healthcare cost savings of \$1,423 per 100 children. It is hoped that this study will help lay the foundation to expand Rochester's existing telemedicine program to the local Strong Health ALR population.

Methods:

This study is a retrospective chart review of the medical records from the Strong Health Geriatrics Group ALR program. General patient demographics will be obtained, as well health care use for acute illnesses during a 6 month period. Data regarding each telephone contact, ED or emergent PCP visit will be abstracted and evaluated by the three investigators including emergency and geriatric specialists to determine if the visit could have been substituted by using the proposed telemedicine system.

Results: Pending Conclusion: Pending References:

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Basic Science & Clinical Research

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Variable Expression of the Sca-1 Gene in Acute Lymphoblastic Leukemia Cells

Introduction: Acute lymphoblastic leukemia is the most common cancer among children. Though 75% of children with this cancer are successfully cured, 25% experience relapse. Studies of gene expression within acute lymphoblastic leukemia cells have revealed potential genetic factors that may contribute to survival of the cancer cells in these patients (Mori et al, 2003). Among the genes that demonstrates altered expression in acute lymphoblastic leukemia cells surviving after transplantation is “stem cell antigen-1” (Sca-1), also known as Ly6a (Holmes & Stanford, 2007). Sca-1 belongs to the UPAR (urokinase plasminogen activator receptor) family of proteins which play a role in cell adhesion and migration (Stanford et al, 1997; Bradfute et al, 2005). Changes in Sca-1 expression may effect how cells adhere to and interact with each other, as well as where the cells remain.

Objective: In order to understand what role the upregulation of Sca-1 plays in tumor cell survival after transplantation, we attempted to amplify and observe its effects by inducing constitutive expression of the gene. We investigated the construction of a vector carrying the Sca-1 gene and its insertion into acute lymphoblastic leukemia cells.

Methods: Sca-1 cDNA was obtained from a plasmid available through ATCC (MGC-6188) and was cloned into the retroviral vector plasmid pMXs (Cell Biolabs). Calf intestine phosphatase was used during the ligation process to reduce the amount of self-ligations. The Sca-1 gene was under the influence of the high level constitutive retroviral LTR promoter. The Sca-1 vector containing plasmid was grown in *E. coli*, and plasmid DNA purified using Promega plasmid mini-prep kits. Purified plasmid was transiently transfected into retroviral packaging cell lines using lipofectamine and after 48-72 hours retroviral vector containing supernatant was collected. Acute lymphoblastic leukemia cells (NSTY, a C57BL/6 murine pre-B acute lymphoblastic leukemia line driven by human bcr-abl oncogenes) were grown in medium containing vector particles in vitro for 48 hours. Cells were purified using anti-Sca-1 monoclonal antibodies and flow cytometric cell sorting.

Results: Though the Sca-1 gene was readily isolated using a variety of different restriction enzymes, integration of the gene into the cloning vector proved difficult. The restriction enzymes we had originally intended to use proved to be in poor orientation relative to each other leading to a failure of ligation. We next attempted to use Eco-R1 restriction sites exclusively, which yielded a high level of autoligation. Treatment with CIAP to reduce the level of autoregulation yielded very poor levels of ligation. One ligation reaction did yield a viable product, which was used to transfect NSTY cells. However, flow cytometric sorting yielded no cells with Sca-1 expression.

Conclusion: The inability of the pMXs cells to successfully ligate after treatment with CIAP suggest that the protocol should be reconsidered. It is possible that treatment with CIAP may not be a viable option for preventing autoligation in this instance. Other methods of gene cloning should be considered, such as PCR. The failure of the transfected cells to express Sca-1 was most likely the result of transfection with plasmids

that did not contain the Sca-1 insert. These plasmids were most likely autoligating pMXs cells that were introduced into the E. coli as a result of contamination. It is still hypothesized that increased Sca-1 expression in acute lymphoblastic leukemia cells will infer multiple advantages and changes in cell behavior.

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Basic Science & Clinical Research

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URSM

Optimal Instrument Length for da Vinci Robotic Transumbilical LESS Surgery

Introduction:

This is a cross-sectional study that presents computed tomography (CT) measurements from the umbilicus to 11 intra-abdominal sites of interest in order to help design robotic and traditional instrumentation that is better suited for abdominal single port surgery instead of traditional multi-port approaches.

Objective:

To recommend an instrument length that would accommodate 95% of patients in our study and afford the ability to reach surgically important intra-abdominal landmarks, as current instruments are too short for certain surgeries or certain patients – those patients that are too tall and those whose weight is too large.

Background:

The advent of the robotic age in surgery has brought with it a call for the minimalist approach to minimally invasive surgery. Where there were once six ports affording the da Vinci Surgical System access to the abdominal cavity for a standard prostatectomy, there could now be one – whose scar would vanish into the umbilical cicatrix upon recovery. This single port is placed in the umbilicus, an embryologically natural orifice, and is slightly larger than the standard port size, allowing for the extraction of larger samples and the avoidance of sample degradation through shredding.^{i, ii}

As current instrumentation is designed for the standard multiport approach, the variety of candidate surgeries for a single port approach is mechanically limited by the current instrument's ability to reach the desired field. In order to provide information essential to creating the next generation of robotic and laparoscopic instrumentation, we have quantified the distance between the umbilicus and the following: xyphoid process, superior most aspect of the spleen, neck of the gallbladder, bifurcation of the descending aorta, adrenal glands, left and right superior poles of the kidneys, inferior more aspect of the inguinal canal, suprapubic margin, and the apex of the prostate (or female neck bladder).

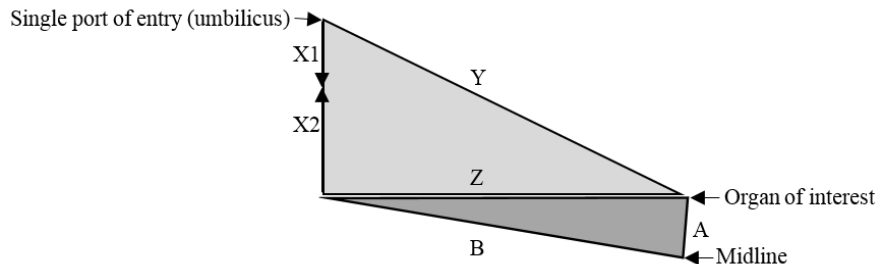
Methods:

In order to find the necessary instrument length to reach an intra-abdominal point of interest, we can imagine two triangles that share a common side and are perpendicular to each other – the first of which can describe how deep in the abdominal cavity the organ of interest is and the second of which can describe how far laterally the organ is displaced from midline. As in Figure 1, by knowing the height of insufflation (X1) and the vertical distance to the parietal peritoneum to the horizontal plan of the organ of interest (X2) we need only the length Z in order to calculate the actual distance that the instrument must travel (Y) in order to reach the organ.

To find the length of side Z, we utilize a second right triangle with one side (A) that projects into or out of the plane of the page at the organ of interest (significant of the organ's lateral displacement from midline), a second side (Z) that is its hypotenuse, and a third side that completes the triangle (B). By

Pythagorean's theorem, we can calculate the necessary patient-specific instrument length (Y) to reach the organ of interest by using measurements of sides A, B, and X2 taken from the patient's CT scan. Namely: $Z = (A^2 + B^2)^{2/Z}$ and $Y = ((X1 + X2)^2 + Z^2)^{2/Z}$. For our value of the insufflation height (X1) we utilize the mean and maximum values reported by Pick et al ⁱⁱⁱ (6cm and 8cm, respectively) in attaining a pneumoperitoneum of 15mm Hg in 11 robotic prostatectomy patients.

Figure 1: Right triangles describing the depth and lateral displacement of an organ of interest.



Results:

We randomly selected 34 patients that had abdominal CT scans, were seen at Strong Medical Hospital as outpatients between April 1st and June 30th of 2009, and are at least 18 years old. The descriptive statistics are as follows:

Table 1: Descriptive statistics for all 34 patients by gender.

Variable	Females			Males		
	N	Mean	SD	N	Mean	SD
Age (years)	17	51.529	18.702	17	60.941	14.923
Height (m)	17	1.604	0.078	17	1.775	0.071
Weight (kg)	17	83.716	39.736	17	96.373	17.277
BMI (kg/m ²)	17	32.278	13.386	17	30.563	5.200

In recognizing the gravity of lacerations to vasculature at the level of the bifurcation of the descending aorta in creating a pneumoperitoneum – particularly in thin patients – we added this landmark to our study. The mean depth of the bifurcation of the descending aorta in our female patients is 12.3 cm, with a range of 7.21 cm to 19.28 cm, and a standard deviation of 3.43 cm. In our male patients, the mean is 13 cm, with a range of 8.79 cm to 17.07 cm, and a standard deviation of 2.53 cm. When combined, these data are highly positively correlated with BMI. The Pearson correlation coefficient is 0.70 (p-value < 0.0001) and every unit increase of BMI yields a 0.21 cm increase on the distance from the umbilicus to the bifurcation of the descending aorta.

The mean and standard deviation of the necessary instrument lengths to reach the apex of the prostate from the umbilicus are 27.75 cm and 2.50 cm, respectively. The length that would be sufficient for 95% of our patients is 31.87 cm. The mean and standard deviation of the instrument lengths required to reach the female bladder neck are 25.00 cm and 3.47 cm, respectively. The length with 95% coverage is 30.71 cm.

Following those analyses, the patients were then placed into one of two groups, through a hierarchical cluster analysis based on similarities in height, weight, and BMI (see Table 2).

Table 2: Descriptive statistics of similar clusters.

Variable	Group 1			Group 2		
	N	Mean	SD	N	Mean	SD
Age (years)	16	63.813	14.091	18	49.500	17.487
Height (m)	16	1.713	0.096	18	1.669	0.126
Weight (kg)	16	83.892	15.750	18	95.513	39.508
BMI (kg/m ²)	16	28.660	5.545	18	33.875	12.445

Table 3: Instrument lengths for 95% coverage of our patients.

Organ of Interest	Length of 95% coverage (cm)	
	Group 1	Group 2
Xyphoid process_6	31.62	31.52
Suprapubic margin_6	24.87	25.14
L. adrenal gland_6	30.29	31.72
R. adrenal gland_6	30.32	33.87
L. superior pole of the kidney_6	29.66	30.63
R. superior pole of the kidney_6	29.53	32.53
Superior most aspect of the spleen_6	37.74	35.93
Neck of the bladder_6	27.49	27.02
Inferior most aspect of the inguinal canal_6	25.01	25.53
Xyphoid process_8	32.28	32.08
Suprapubic margin_8	26.25	26.60
L. adrenal gland_8	31.82	33.36
R. adrenal gland_8	31.87	35.40
L. superior pole of the kidney_8	31.22	32.30
R. superior pole of the kidney_8	31.12	34.09
Superior most aspect of the spleen_8	38.97	37.13
Neck of the bladder_8	28.70	28.31
Inferior most aspect of the inguinal canal_8	26.39	36.97

Table 3 outlines the calculated instrument length necessary to reach the particular organ of interest from the umbilicus, using either a 6 cm or 8 cm insufflation height, which would be sufficient for 95% of our patients. A working instrument length would be adequate to reach any of the 11 intra-abdominal points of interest in our study of 95% of our patients. If we take the maximum working lengthⁱⁱⁱ of instrumentation attached to the da Vinci Surgical System to be 35 cm, we would need an additional 14 cm in order to drastically broaden the number of viable surgeries and potential patients for da Vinci robotic transumbilical LESS surgery.

Conclusion:

Minimally invasive robotically assisted single port surgery has outstanding potential to improve both cosmetic and clinical outcomes. Currently, instruments designed for standard multi-port approached are of insufficient length to make the da Vinci Robotic Transumbilical LESS Surgery a viable option for the majority of patients. In our study population, we found that increasing the instrument's working length to 39 cm. would be sufficient for 95% of our patients of the spleen, neck of the gallbladder, adrenal glands, left and right superior poles of the kidneys, inferior more aspect of the inguinal canal, suprapubic margin, and the apex of the prostate or female neck bladder. Further, we found that before creating a pneumoperitoneum, every unit increase of BMI yields a 0.21 cm increase in the distance from the umbilicus to the bifurcation of the descending aorta – information essential to avoiding accidental laceration of the abdominal vasculature.

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Basic Science & Clinical Research

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RBPJk-dependent Notch signaling regulates articular cartilage maintenance

Introduction: Articular cartilage is the smooth, surface cartilage in joints that surrounds the bone. This cartilage is being significantly looked at in its involvement in development of osteoarthritis (OA) and other joint diseases. Notch signaling and the downstream pathway involved with Notch has been shown to play a role in the development of articular cartilage. Part of Notch's role in articular cartilage development might be to maintain a stem cell-like phenotype in the very surface of the articular cartilage and suppress bone formation and bone derived Mmp13 expression. Notch signaling might as well regulate synovial tissue maintenance/expansion.

Objective: Observe and document the downstream effects of RBPJk-dependent Notch signaling in articular cartilage development

Background: Notch signaling plays a role in many cell differentiation processes including the stem cells of various organs. The pathway involves the ligands Delta-like 1, 3, or 4 or Jagged1 or 2 binding to Notch cell surface receptors (Notch1-4). This induces the cleavage of an intracellular domain of the Notch receptor via the gamma-secretase complex. The Notch intracellular domain (NICD) then translocates to the nucleus where it interacts with RBPJk, a transcriptional repressor. At this point, NICD converts RBPJk into a transcriptional activator and induces the expression of downstream target genes⁶. The phenotype produced by eliminating the RBPJk signaling cascade and its involvement in articular cartilage development is what we were interested in.

Methods: The experimental design consisted of taking *Prx1Cre; RBPJk^{f/+}* male mice and crossing the males with *RBPJk^{ff}* females. We then used the *RBPJk^{f/+}* and *RBPJk^{ff}* offspring as our controls and used the *Prx1Cre; RBPJk^{ff}* animals as our mutant. The mutant would then not have the expression of RBPJk and loss of RBPJk's downstream effects. The animals were sacrificed at 2, 4, 6, and 8 month time periods and analysis of microCT, histology, histomorphometry, polarized light microscopy, in situ hybridization, TUNEL staining, and immunohistochemistry were performed on paraffin sections of the knee.

Results:

Micro-CT: *Prx1Cre; RBPJk^{ff}* mutant mice display an early increase in bone formation followed by an age related loss of bone. In the mutant mice, mineralization of the meniscus occurs, osteophytes appear in the joint, there is a flattening of subchondral bone, and a deterioration of cortical bone is seen.

Histological Analysis: *Prx1Cre; RBPJk^{ff}* mutant mice display synovial thickening, osteophyte formation, subchondral bone accumulation, as well as fibrosis and loss of articular cartilage. *Prx1Cre; RBPJk^{ff}* mutant mice demonstrate a loss of superficial zone chondrocytes and non-mineralized cartilage.

Polarized Light Microscopy: *Prx1Cre; RBPJk^{ff}* mutant mice exhibit loss of collagen fibers and impaired collagen orientation in the articular cartilage and subchondral bone.

In Situ Hybridization: *Prx1Cre; RBPJk^{ff}* mutant mice exhibit age related loss of *Prg4* expression and

the superficial zone of articular chondrocytes. They exhibit age related loss of *Cilp* expression and exhibit *Col10a1* expression in chondrocytes near the articular surface. *Prx1Cre; RBPJk^{ff}* mutant mice also exhibit enhanced *Mmp13* expression in the subchondral bone.

TUNEL Staining: No difference between mutants or controls

Histomorphometry: *Prx1Cre; RBPJk^{ff}* mutant mice at 8 months had a smaller average thickness of articular cartilage, had a smaller total cartilage area, and had more bone in the secondary center of ossification when compared to the control mice.

Immunohistochemistry: Still pending.

Conclusion:

A model for how Notch signaling might work in the regulation of articular cartilage would include: 1) Notch signaling maintains superficial/intermediate zone chondrocyte phenotype because a loss of this zone in the histology in the mutant is evident. 2) Notch signaling suppresses bone formation and bone derived MMP13 expression because a large increase in subchondral bone and MMP13 expression in the mutant is displayed. 3) Notch signaling regulates synovial tissue maintenance/expansion because synovitis is seen in all of the mutants.

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Basic Science & Clinical Research

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Review of the Behavioral and Psychological Consequences and Interventions of Childhood Obesity

Objective: To review studies of psychological and/or behavioral interventions for overweight or obese pre-adolescents.

Background: Obesity is a major health concern for children and pre-adolescents of various ethnic and socioeconomic backgrounds. The Center for Disease Control (2004) and the American Academy of Pediatrics reports that approximately 30% of American 6 to 12 year old children are overweight (at or above the 85th percentile for age and gender-specific BMI standards) and nearly 16% of this age range are considered obese (at or above the 95th percentile for age and gender-specific BMI scores). This epidemic of childhood obesity is associated with several health implications. Specifically, children with excess body weight are at a higher risk for developing a variety of physical health problems including type II diabetes, asthma, hypertension, sleep apnea, orthopedic complications, and increased incidence of cardiovascular risk factors. Equally important, but less addressed are the negative and damaging emotional and social consequences reported by overweight and obese pre-adolescents. These include peer disapproval, bullying, teasing, poor academic performance, poor health-related quality of life, poorer self-image, eating disorders and depression.

Method: We searched electronic databases (Medline, EconLit, PsycINFO and CINAHL) and reviewed studies published from 1995 to August 2009 using the broad criteria of childhood, pre-adolescence and psychological impact/ behavioral impact. Hundreds of initially identified studies were excluded given the objective of including a psychological and/or behavioral measure of the effectiveness of the intervention in addition to weight –loss.

Results: Very limited evidence supports the modest short-term improvements in psychological measures resulting from lifestyle and behavioral interventions for overweight and obese children and pre-adolescents. While many reports focus on interventions implemented in school settings, racial disparities for both sexes make it difficult to conclude that these programs yield lasting improvements in psychosocial domains of obese children. Consequently, both the short and long-term efficacy of psychological and behavioral interventions for pediatric obesity remain unclear given the limited duration of studies, small sample sizes, focus on volunteers who may differ drastically from non-volunteers, the lack of appropriate control groups, and use of non-comparable quantitative and/or qualitative psychological measures that may have validity and reliability issues.

Conclusions: The epidemic of childhood obesity and its associated short and long-term physical and psychological consequences warrants medical and educational professionals to work together to design appropriately controlled studies, implement consistent efficacy criteria, assess the interventions over longer time periods and use comparable reliable measures to evaluate the effectiveness of various treatment programs, whether addressing high or low socioeconomic groups of targeted children.

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Basic Science & Clinical Research

Robert L. Caldwell Vascular Research Internship

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Preceptor:

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The Role of Endothelial Progenitor Cells in the Vascular Health in Diabetics

Introduction:

The disease process in diabetes mellitus presents researchers with a vascular conundrum; principally diabetics experience pathologic increased and decreased angiogenesis. For example, while diabetic retinopathy, which causes blindness in diabetic patients, enhances angiogenesis, problems in diabetic foot ulcers, the cause of more than 75,000 amputations per year, results in poor angiogenesis.

The role of endothelial progenitor cells (EPC) is not well understood in both processes of angiogenesis and vasculogenesis. EPC's are bone marrow derived cells that display an immaturity marker in conjunction with an endothelial marker. Two common stemness markers are CD34, a sialomucin, and CD133, a cholesterol binding glycoprotein. Two common endothelial markers are KDR (VEGF-2 receptor) and Von Willebrand factor. These markers are plasma membrane proteins and assessed using flow cytometry, a technique which counts cells by size and antibody-attached fluorochromes.

Flow cytometry can help in evaluating the role of EPCs in angiogenesis and vasculogenesis by measuring the difference in response in diabetic and non-diabetic rabbit ears with a neuroischemic lesion. Neuroischemia is a good model for simulating the effects of diabetic foot ulcers.

It is also important to understand the endothelial health of diabetic patients. Endothelial health has been shown to be an independent risk factor for the development of coronary heart disease. While the gold standard to evaluate endothelial health is intracoronary agonist infusion with quantitative angiography, we used the less invasive, flow mediated vasodilatation (FMD) in order to assess its value as a prognostic tool. Flow mediated vasodilatation measures the maximal dilation of the brachial artery due to shear stress compared with nitroprusside (nitric oxide releasing agent).

Objective:

Basic Science:

- 1) Evaluate the phenotype of EPC's
- 2) Evaluate the response of EPC's to neuroischemia in diabetic and non-diabetic rabbits

Clinical:

- 1) Evaluate FMD in diabetics and non-diabetics

Results:**Basic Science:**

- 1) Diabetic rabbits showed no significant increase or decrease in EPC population in response to neuroischemic lesions when compared to non-diabetic rabbits.

Clinical:

- 1) Diabetic patients showed a significant decrease in both shear stress and nitroprusside mediated vasodilatation.

Conclusion:

Basic Science: Ascertaining the phenotypic nature of EPC's is difficult because markers need to be uniquely expressed at the intermediate life cycle stage of the cell. Markers displaying high sensitivity and specificity have not been found. Using multiple immaturity and endothelial lineage markers yields too few triple positives flow cytometry. As a result, the presence of EPCs in the data suggests that there is no difference in the number of EPCs in the healing of neuroischemic lesions in rabbits. However, errors in the procedures are more likely to be the cause of a confirmatory null hypothesis. The optimal flow cytometry settings for searching EPCs due to the unknown phenotype nature of EPCs was a major problem. It is difficult to make generalizations from a scarce population of cells; furthermore not knowing the exact phenotype of the EPC may lead to exclusion of many potential cells. It may also be artificial to define an EPC based on 2 markers, when there could be other more specific markers to be determined. Therefore other methods should be explored in order to understand the potential role EPC's play in neuroischemic lesion healing.

Clinical: Diabetics had a significant decrease in FMD when compared with non-diabetics. Further research should be done in finding subpopulations of diabetics with the poorest response to FMD and study the rates of foot ulcer healing.

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Basic Science & Clinical Research

Anthony Portanova, MS2

Preceptor:

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Renal Radiofrequency Ablation: Our Institutional Experience

Introduction: Radiofrequency ablation (RFA) is a rapidly emerging and minimally-invasive technique used in lieu of surgical resection to treat renal cell carcinoma. Although promising data regarding the short term safety and efficacy of RFA have been reported in the literature, there is little long-term substantiating data.

Objective: The purpose of this study was to retrospectively assess the outcomes of Renal RFA procedures performed at Strong Memorial Hospital since inception in 2005 and to track any subsequent recurrences of carcinoma as determined by follow-up radiological scans.

Background: Renal cell carcinoma (RCC), which accounts for 80-85% of all kidney tumors¹, is a malignant neoplasm of the cortex of the kidney. RCC is a very deadly disease that causes about 13,000 deaths per year in the United States¹. It is all the more dangerous because most RCC lesions do not produce clinical symptoms and therefore grow undetected until discovered in incidental radiologic studies.

RCC is not responsive to chemotherapy or radiation therapy, but it may be treated by surgical resection. The traditional gold standard therapy is radical nephrectomy, but recently there has been an increased reliance on partial nephrectomies to spare any healthy, functional tissue surrounding the lesion. In an even greater effort to spare healthy tissue and avoid surgical complications, two less-invasive techniques are now being utilized: radiofrequency ablation (RFA) and cryoablation². These techniques, which are performed by interventional radiologists or urologists, involve the melting of tumors with radio waves (in RFA) or the freezing and thawing of tumors (in cryoablation)².

RFA and cryoablation are less invasive and less costly than surgical resection. These procedures are usually well-tolerated by patients, and they are not known to cause significant complications. However, despite these promising initial outcomes, there is little data in the literature about their long term effectiveness.

Methods: In this retrospective study of Strong Memorial Hospital's initial experiences with Renal RFA, the hospital's electronic radiological charting system was used to select all patients with enhancing renal lesions who underwent subsequent RFA between August 2005 and June 2009. Safety and efficacy data for these 70 patients were compiled from radiology reports, surgical notes, pathology notes, and clinical visit records.

Results:

Patient Characteristics: Of the 70 people who underwent Renal RFA at Strong between August 2005 and June 2009, 46 were male (66%) and 24 were female (34%). Their mean age was 65 years (std. dev. 10 years).

Lesion Characteristics: Lesions were distributed as follows: 56% in the left kidney vs. 44% in the right kidney, 41% midpole vs. 36% lower pole vs. 23% upper pole, and 89% exophytic vs. 11% parenchymal (this excludes 15/70 lesions which were not labeled as either exophytic or parenchymal). The mean lesion size was 2.4 cm (median 2.5 cm, mode 2.5 cm).

Procedure Parameters: The probe sizes ranged from 2-5 cm (mode 3 cm). The number of surgical passes ranged from 1 to 3 (50% single pass, 43% double pass, and 7% triple pass). The first roll-off time ranged from 65 seconds to 40 minutes. The second roll-off time ranged from 10 seconds to 6 minutes 35 seconds.

Lesion pathology: Of the 70 lesions biopsied and ablated, 40 (57%) were deemed to be RCC (of which 13 were papillary RCC), 9 (13%) were oncocytoma, 18 (26%) were normal/nondiagnostic kidney tissue, 1 (1%) was a cyst, 1 (1%) was degenerative tissue, and 1 (1%) was metanephric adenoma.

Complications: Complications were encountered in 5/70 procedures (7%). One patient coded during extubation. Two patients had a small subcapsular hematoma. One had a mild/moderate perinephric hematoma, and 1 required post-procedure oxygen.

Recurrence: The maximum length of time between the RFA procedure and the most recent radiological follow-up scan ranged from 0 to 44 months, with a mean of 14 months and a median of 11 months. Of the 70 patients, 15 (21%) had at least one subsequent follow-up scan positive for an enhancing renal lesion at the site of RFA. It is not clear, however, if any of these enhancing lesions represent actual carcinoma recurrence or post-operative changes around the original RFA site. In three cases, the suspect lesions did not enhance in subsequent studies. In three cases, the lesions continued to enhance but decreased in size. In two cases, the lesions continued to enhance, but remained stable in size over time. In one case, it was unclear if the enhancement represented recurrence or a radiological artifact. In three other cases, the enhancement was described by the radiologists as mild or unconvincing. This leaves only 3 cases out of 70 (4%) that are most likely indicative of recurrent carcinoma. However, without biopsy, we cannot determine if any of these 15 lesions represent RCC.

Conclusions: From our initial experience, Renal RFA is a safe and effective procedure for patients who are either unwilling or unable to withstand surgical resection. Complication rates and recurrence rates are low, especially considering that many RFA candidates are high surgical risks. However, further studies with longer follow-up periods are warranted to draw any statistical conclusions. Given these encouraging results, we believe that randomized control trials between RFA and nephrectomy are feasible and warranted.

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Basic Science & Clinical Research

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Variability in Health Care Resource Utilization Among Pediatric Concussions Patients Based on Symptoms at Time of Diagnosis

Introduction and Background: A concussion, also known as a mild traumatic brain injury (MTBI), is caused by an impact or acceleration/deceleration force applied to the head that temporarily alters the mental status of the individual. Mental status changes include a brief period of loss of consciousness (LOC), amnesia or just confusion¹. Diagnosing a concussion in children can be problematic but is currently based on their self-report of LOC, amnesia and confusion at the time of injury. There is no accepted treatment or management of mild TBI in children. However, for MTBI sustained during sports, more than 20 different guidelines have been established to aid in the timing of return to contact sports. The return-to-play recommendation is made cautiously since repeated concussions can cause cumulative effects and also make the child more prone to an injury next time⁴. The grading scales used in these guidelines are based on the assumption that a concussion resulting in loss of consciousness is more severe than one that results in amnesia, which in turn is more severe than one that results just in confusion^{1,5}. Since most concussion grading scales are based on the presence or absence of LOC, mental status changes such as dizziness and confusion, and amnesia, a diagnosis of a concussion may involve a combination of any of these factors. Management of the concussion, therefore, depends not on the diagnosis itself, but on the initial symptoms on which the diagnosis is based. Visits with primary care physicians, follow-up with specialists, analgesic use, and return visits to the hospital may all be influenced by the initial symptoms experienced by the child and can potentially influence long term outcomes. Currently it is unclear to what extent these post injury behaviors differ among concussed children with different initial presenting symptoms.

Objective: The main aim of this project was to investigate via a retrospective cohort study whether post-injury treatment and management of pediatric patients with mild TBI are related to the initial mild TBI symptom. The goal was to see whether the use of health care resources after injury reflects the severity of the initial symptoms upon which the diagnosis was based.

Hypothesis: Concussion patients with LOC as the initial symptom will utilize more health care resources in the first three months after injury than concussion patients with amnesia or confusion.

Methods: A pre-existing database of information on mild head injury in pediatric patients was used. These data were collected by Dr. Jeffrey Bazarian for research purposes. The data analysis was limited to patients between the ages of 3 and 18 who were diagnosed with a concussion at the time of the injury (N=386). This group was divided into three subgroups based on whether they presented with LOC (n=188), or amnesia (n=49), or confusion (n=149). Parameters that were measured were limited to the time period beginning at the injury and ending at the 3-month follow-up. These parameters included visits with primary care provider and/or specialists, use of social services, return visits to the ED, hospitalizations, number of school days lost, and analgesic use in the 3-month period. A comparison was then be made between the level and extent of pos-injury management between the three subgroups using Chi Square analysis, Fisher exact test (for n<5), and T-tests.

Results: The LOC and amnesia groups both differed significantly from the confusion group but not from each other. For instance, the mean number of school days lost was significantly higher among those who reported amnesia vs. those with confusion (5.3 days vs. 1.8 days, $p=0.0005$) and between those who reported LOC vs those with confusion (4.6 days vs 1.8 days $p=0.0033$). But there was no significant differences between those who reported LOC and those who reported amnesia (see table).

Variable	LOC (n=188)	Amnesia (n=49)	Confused (n=149)	p value* (sig <0.05)
If DC, FU instructions with PCP				0.0045³
NO (%)	14.46	27.27	28.27	
YES, LBEC, Admitted, missing (%)	85.54	72.73	71.73	
Number of Doctor visits/patient (mean, sd)	1.0532, 1.3903	1.2653, 1.5381	0.604, 1.2883	0.0034² 0.0025³
Visits with a doctor not sure about				0.0365² 0.0432³
YES (%)	9.574	12.24	4.02	
NO(%)	90.426	87.76	95.98	
Number of school days lost/patient (mean, sd)	4.59, 10.69	5.261, 3.446	1.768, 4.003	0.0005² 0.0033³

*Tests between: 1=LOC and Amnesia; 2=Amnesia and Confused; 3=LOC and Confused

Conclusion: The results indicate that the healthcare utilization of LOC patients differs from that of confusion patients, but not from amnesic patients. Since amnesia is considered worse than simply confusion, there might be a ‘threshold’ affect where LOC and amnesia are much closer in symptom presentation and therefore not significantly different in healthcare resource utilization. This was a univariate analysis, and a future study may focus on a detailed multivariate analysis of the variables studied in this project to further study the relationships between the various categories of a concussion.

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Basic Science & Clinical Research

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Preceptor:

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Utility of Optical Coherence Tomography and Fluorescein Angiography in Treating Uveitic Cystoid Macular Edema

Introduction:

Macular edema is the leading cause of blindness in people with Uveitis¹. Correct diagnosis is important so that appropriate treatment can be given. This is done with Optical Coherence Tomography (OCT) and Fluorescein Angiography (FA), two commonly used ophthalmic imaging modalities. OCT quickly and noninvasively reveals macular anatomy while FA provides real time physiologic perspective of the retinal vasculature. It is believed that using this complementary information allows the clinician to obtain a clearer understanding of uveitic CME than using either one alone.

Objective:

To compare baseline OCT and FA patterns in patients with uveitic CME to determine how well, if at all, the modalities correlated with visual acuity. In addition to the single time point analysis, we evaluate longitudinally to determine if a treatment response was appreciable both sets of images. Finally we determine if demographic factors like age, sex, or race are associated with treatment response.

Methods:

Ninety uveitis patients who had received both OCT and FA within six weeks of the other were selected from the National Eye Institute's Uveitis clinic. A database was created which included demographic factors, diagnosis, visual acuity, macular thickness and volume, and course of treatment. OCTs were graded both qualitatively (presence of cysts, subretinal fluid, both, or none) and quantitatively (central thickness, volume). FAs were graded using a well established scale by Yannuzzi et al² which is based on severity of leakage. OCT and FA grades, central thickness, and macular volume were then correlated with visual acuity.

Results:

Result reported herein address the first objective of this project: establishing and comparing OCT and FA data at baseline. Our analysis found that there was a very good correlation between FA grade and central macular thickness on OCT. However there was a poor correlation between FA and central volume on OCT. There was a very good correlation between FA grade and VA and between OCT thickness and VA.

Conclusion:

Our major findings were in alignment with those published in the literature, namely that FA and OCT patterns correlate well with VA. Future work will likely focus on response to treatment and the associated changes seen on OCT and FA.

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Basic Science & Clinical Research

Joshua I. Segal, MS2

Preceptors:

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Correlating Diagnostic Imaging Studies with Autopsy Findings

Introduction: Medical students at the University of Rochester are given an introductory glimpse into the disciplines of Pathology and Radiology in their first year of medical school. Coursework in Human Structure and Function (HSF) integrates the study of physiology, gross anatomy, and histology into problem-based learning (PBL) sessions and laboratory exercises in order to introduce students to a systematic study of the human body. Radiological imaging, introduced in clinical vignettes, is frequently utilized throughout the course in order to emphasize the clinical application of many of the basic science concepts taught in HSF. In addition, the Host Defense course presents first year students with gross and microscopic specimens to help students achieve competence in identifying tissue and distinguishing between various disorders affecting different organ systems. Medical students interested in broadening their clinical sophistication, as it relates to radiology and organ pathology correlates, are able to utilize their first summer experience to dig deeper into these subjects and further explore both specialties.

Objective: An eight-week autopsy shadowing experience was designed to enable a first year medical student to participate in documenting disease progression and organ pathology by capturing digital images of specimens acquired at autopsy. Photographic images of the gross anatomical specimens were subsequently correlated with pre-mortem diagnostic radiological imaging in order to illustrate the ramifications and significance of the radiologic abnormalities. Images obtained during autopsy were concurrently utilized by Pathology house-staff to demonstrate disease processes that likely contributed to the cause of death. The academic focus of this summer project was to create a teaching tool for students interested in Pathology by accumulating a collection of radiologic and gross anatomical correlates.

Background: Medical students interested in Pathology are encouraged to attend weekly Autopsy Conferences currently held on Tuesdays at noon in the Morgue (1-6428). These sessions enable medical students to hear clinical scenarios presented by residents in Pathology and to witness how parallels are drawn between bedside presentation of disease and findings at autopsy. This summer project was borne out of an interest in building on these conferences in order to further explore how to apply pathophysiological principles taught in the classroom to real-life clinical findings. In this project an effort was made to relate the findings of pre-mortem clinical tools – particularly Radiologic imaging – with gross and microscopic findings at autopsy.

Methods: Approximately twenty-five autopsies were observed, and digital images were captured in-situ and after organ removal for more than fifteen different cases. For patients with available radiological imaging, attempts were made at correlating gross anatomical images related with conventional X-rays, CT scans, and MRIs. Patient's charts were reviewed to obtain the clinical picture of events that ultimately led to death.

Results: Illustrative examples of gross findings and related radiological images obtained from ten autopsy cases are presented here. Disease processes demonstrated include: mesothelioma, emphysema,

pulmonary hypertension, systemic atherosclerosis, coronary artery disease, abdominal aortic aneurysm, melanoma with metastases to brain, renal cell carcinoma with metastasis to the right ventricle, and pulmonary embolism. Dramatic correlations between the gross pathology specimens taken during autopsy and clinical radiologic imaging are demonstrated and have been compiled into a powerpoint atlas that may be used as a teaching tool and study guide.

Conclusion: For medical students interested in anatomy and physiology, attendance at weekly autopsy conferences, followed by a summer session spent working alongside residents in Pathology is an excellent way to broaden the student's clinical understanding and to gain an appreciation for the gross and radiological manifestations of disease.

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Basic Science & Clinical Research

James Shaw, MS2

Preceptor:

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LRP2 localizes to the abluminal surface of brain vessels

Background: One of the salient features of brain tissue from patients with Alzheimer's Disease (AD) is the presence of large quantities of plaques composed of amyloid- β ($A\beta$) peptides. At critical concentrations, $A\beta$ forms insoluble plaques in the brain tissue, which initiates a pathogenic cascade of events that ultimately result in neuronal toxicity and neurodegeneration (Hardy et al., 2002). These plaques are especially rich in $A\beta_{40}$ and $A\beta_{42}$, produced by enzymatic cleavage of amyloid precursor protein (APP) (Selkoe, 1998). In particular, recent studies have shown that $A\beta_{42}$ is likely to be the major neurotoxic species involved in AD (Selkoe, 2001; Golde et al., 2005).

The majority of AD cases (~99%) in individuals over 65 years of age (late onset or sporadic) do not have increased production of $A\beta$ (Tanzi and Bertram, 2005). These sporadic forms of AD may be due to faulty clearance of $A\beta$ from the brain (Zlokovic 2008). Certain chaperone molecules, such as apolipoprotein E (apoE) and apolipoprotein J (apoJ), bind $A\beta$ in blood plasma, and can influence the clearance of $A\beta$ from the brain (Bell et al., 2007). In mice, apoJ increases the clearance of $A\beta_{42}$ across the blood brain barrier (BBB). This clearance occurs via receptor-mediated endocytosis involving low-density lipoprotein receptor related protein-2 (LRP2), located on the abluminal surface of blood vessels in brain tissue.

Objective: My objective was four-fold:

- 1) To purify human plasma apoJ.
- 2) To establish where LRP2 is differentially distributed at the luminal and abluminal surfaces of the brain microvessels.
- 3) To determine the kinetic parameters of ^{125}I - $A\beta_{42}$, ^{125}I -apoJ, and ^{125}I - $A\beta_{42}$ -apoJ binding to LRP2, and their endocytotic rates.
- 4) To initiate studies on the trafficking of apoJ and $A\beta_{42}$ -apoJ across the brain endothelial cells.

Methods:

Isolation and Purification of apoJ: ApoJ was isolated by affinity chromatography with an anti-apoJ antibody column followed by purification using high-pressure liquid chromatography (HPLC) (as described Bell et al., 2007).

Distribution of LRP2 on brain microvessels: Mice were anesthetized (100 mg/kg ketamine and 10 mg/kg xylazine), then perfused transcardially with heparinized saline followed by 4% paraformaldehyde. The brain was removed and embedded in Paraplast Plus wax, then sectioned at 6 μm using a microtome. The sections were washed with Xylene, then rehydrated with serial washes in ethanol solutions with increasing ratios of water: ethanol. Antigen retrieval was performed, then blocked in 2% swine serum. Sections were washed with PBS containing 0.05% triton X-100 before addition of anti-Aquaporin 4 antibodies (marker of abluminal surface of the brain microvessels), and anti-LRP2 antibodies (receptor for apoJ). The sections were washed with 0.05% triton in PBS four times before the secondary antibodies were applied, along with Lectin (stain for vessels). The slides were mounted with Dako mounting medium and imaged

using confocal microscopy (Zeiss LSM 510 confocal system), with a 40x water immersion objective and laser power of 5-10%.

ApoJ trafficking in neurovascular unit and ApoJ and A β 42 binding and internalization: These studies are currently still underway.

Results:

Isolation and Purification of apoJ: We obtained ApoJ monomers from Affinity purification, which was verified by Western blot. The HLPC purification steps are still ongoing.

Distribution of LRP2 on brain microvessels: Images obtained from Confocal microscopy demonstrated that LRP2 was localized between the vessel walls (stained with Lectin) and Astrocytic endfeet (stained with AQP-4), indicating that LRP2 is located on the abluminal surface of brain vessels.

Conclusion: Localization of LRP2 primarily on the abluminal surface of brain vessels supports the hypothesis that LRP2 is involved in the transport of A β 42 from brain to blood, as has been indicated in other studies (Bell 2007). Therapeutically, LRP2 could potentially be harnessed to help remove amyloid protein from the brain. Further studies investigating the kinetics of the LRP2-apoJ interaction and the trafficking of endocytosed apoJ-A β 42 complex within vascular endothelial cells will be necessary in order to better understand this particular pathway of A β removal from the brain.

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Basic Science & Clinical Research

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Initial Management of Moderate to Severe Lateral Ankle Sprains *A Prospective Randomized Study Pilot*

Introduction& Background

Lateral ankle sprains are among the most common orthopaedic injuries accounting for 2-6% of presentations to the emergency department in the United States.^{1, 2} Many types of practitioners, including family physicians, emergency room physicians, and orthopaedic surgeons, care for these injuries. There lacks a clear standard of care for the initial treatment of these injuries.^{1, 3, 5-7} Despite there being a wide number of treatment approaches most all incorporate a period of immobilization or stabilization.

Common methods of stabilization include an air cell stirrup brace, high tide fracture boot, and fiberglass casting. It is currently unclear which of these devices is superior in the initial treatment of acute lateral ankle sprains. With a high incidence of these types of ankle injuries establishing a treatment protocol that can shorten recovery time or minimize the amount of work time lost is essential.^{1, 2} A recent study found that a 10-day below knee cast or air cell stirrup ankle brace is superior to a compression stocking in recovery time after a severe ankle sprain.⁶ While this is valuable information, the use of fiberglass casting is not often employed in the treatment of ankle sprains. This maybe due the inherent difficulty that surrounds casting, such as the need for appropriately trained orthotists for cast application, the patient's difficulty with hygiene, and the patient's overall satisfaction.

The high-tide fracture boot provides rigid stabilization similar to that of a below knee cast while allowing for removal of the device for bathing and rehabilitative exercise. Early motion may help facilitate healing and reduce edema.⁵ Furthermore the high-tide fracture boot provides more stabilization than an air cell stirrup ankle brace possibly shortening or eliminating the need for crutches. To date there has not been a comparison between the high-tide fracture boot and air cell stirrup ankle brace in the treatment of acute moderate to severe lateral ankle sprains using an appropriate clinical outcome measurement tool.⁴

Objective

The goal of this study is to compare the high-tide fracture boot with the air cell stirrup ankle brace in the initial treatment of acute moderate to severe lateral ankle sprains. Outcome measures will include self-reported functional assessments, pain-VAS, days spent crutch-walking, and patient satisfaction. We hypothesize that patients using the high-tide fracture boot will report better function, less pain, less days crutch walking, and better satisfaction after 10-14 days.

Methods

Participants were recruited from the URMU Emergency Department and URMU-University Orthopaedics Foot & Ankle Urgent Care Clinic. Patients with isolated moderate to severe lateral ankle sprains were considered for inclusion in the study. Exclusion criteria included: patients less than 18 years

of age, patients unable to give consent, women who are pregnant or expecting to become pregnant, greater than 48 hours from injury at time of presentation, prior treatment for injury, fracture at time of current ankle injury or previous ankle fracture, deltoid ligament injury, other orthopaedic injuries at time of presentation, intoxication at time of injury, workman's compensation injury, mental illness, dementia, residual symptoms from previous ankle injury, history of neurological disease, non-local residents, history of systemic diseases potentially affecting the foot and ankle (ie diabetes mellitus, rheumatoid arthritis, vasculitides). Inclusion was determined by one of the authors and plain x-ray was used to rule out bony pathology.

Consenting patients were then asked to complete a questionnaire containing the Karlsson Ankle Score, Pain-VAS, and Short Musculoskeletal Function Assessment (SMFA). They were then randomized to receive either an Air Cell Stirrup Ankle Brace (AB) (DonJoy Vista, CA) or a High-Tide Fracture Boot (FB) (DonJoy Vista, CA). Randomization was done in blocks of 4 at both locations of recruitment. Participants were fitted with either orthosis and instructed on appropriate use as described by the manufacturer. Participants were also educated on ice, elevation, NSAID use, activity modification and crutch use if needed. If participants required the use of crutches they were instructed to use the crutches as needed until they could ambulate without pain and to discontinue use after that point.

After 10-14 days participants would follow up with at UPMC-University Orthopaedics Foot & Ankle Clinic. Participants would complete a questionnaire containing the Karlsson Ankle Score, Pain-VAS, SMFA, and questions regarding the number of days missed from school or work, the number of days crutch-walking, the participants' satisfaction with brace they were provided. After completion of the questionnaire participants were examined by the senior author and treated by the conventional standard of care.

Results

Eleven patients consented to participation in the study and were randomized into the 2 groups; however 3 patients, all assigned the FB, were lost to follow up. The FB group contained 3 participants and the AB group contained 5. The mean change in the Karlsson Ankle Score (positive change indicates improvement, ideal score of 90) was 33.5 (19.1) and 26.8 (22.7) for the FB and AB groups respectively. The mean change on the pain-VAS was -2.8 (3.2) and -2 (1.6) for the FB and AB groups respectively. The mean change in the SMFA (negative change indicates improvement, ideal score of 0) was -16.7 (2.4) and -25.7 (11.1). The mean number of days crutch-walking was 1.3 (1.2) and 3.4 (2.3) for the FB and AB groups respectively. The mean number of days lost from work or school was 3.3 (2.5) and 2.6 (5.3) for the FB and AB groups respectively. The mean satisfaction-VAS was 2.5 (0.9) and 2.8 (3.8) for the FB and AB groups respectively. See Table 1 for a summary.

Table 1.

<i>All values are reported as mean change (SD)</i>	High Tide Fracture Boot n=3	Air Cell Stirrup Ankle Brace n=5
Karlsson Score	33.5 (19.1)	26.8 (22.7)
Pain-VAS	-2.8 (3.2)	-2 (1.6)
SMFA	-16.7 (2.4)	-25.7 (11.1)
Days crutch-walking	1.3 (1.2)	3.4 (2.3)
Days without work/school	3.3 (2.5)	2.6 (5.3)
Patient Satisfaction- VAS	2.5 (0.9)	2.8 (3.8)

Conclusion

The results of this pilot study show a trend that supports our stated hypothesis in all outcome measures except for days lost from work or school and patient satisfaction. With the small number of patients recruited for this study we decided that statistical analysis was unwarranted as it is unlikely that any differences would be identified as significant. We have approximated the sample size for the next phase of this study utilizing an $\alpha=0.05$ in two tailed tests and a power of 0.80 (approximately 50 subjects in

each group).

Important changes were made to the study protocol based on our experience with this pilot study and the results. We have decided to expand the inclusion criteria to teenaged patients that exhibit skeletal maturity (i.e. closed physes). This is an important population to include as these typically active patients often present with ankle injuries. Furthermore expanding our inclusion criteria may bolster the recruitment process. We also chose to stratify patients based on their need for crutches after randomization. Often patients would not need crutches to ambulate without pain after the affected ankle was stabilized. This was identified as a potential confounder of one of our secondary outcome measures-number of days crutch-walking.

Other changes were made to our questionnaire. Our method for scoring questionnaires involved scanning the forms and utilizing a computer program that generated a spreadsheet with each participant's responses. These spreadsheets were then easily manipulated for analysis. The original form asked participants to place an X on a VAS scale to mark their level of pain and their satisfaction with the device they were randomized to. This posed potential problem for the scanning software, as there would often be two intersections on the VAS line rather than one. We modified the forms to read, "Please place a single vertical line..."

This pilot study allows us to make pertinent adjustments to our study protocol prior to enrolling a large number of patients. We plan on moving forward with the research after implementing the changes identified by the pilot study.

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Basic Science & Clinical Research

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Early screening tests in the morbidly obese gravida

Introduction:

One quarter of women are obese with a body mass index (BMI) over 30 prior to pregnancy. Maternal obesity is a risk factor for all pregnancy complications, including gestational diabetes (GDM), preeclampsia, cesarean section, fetal macrosomia and shoulder dystocia. Therefore, increased prenatal surveillance including early testing for glucose tolerance (glucola) and baseline liver function testing (LFT) prior to 24 weeks has been recommended by some experts. GDM complicates up to 14% of pregnancies, and among obese women, first trimester glucose tolerance testing (glucola) will identify up to 50% as undiagnosed diabetics. Therefore, in the obese patient, early testing may improve outcomes by giving a longer period of treatment and glycemic control during pregnancy. In addition, morbid obesity is a risk factor for non-alcoholic steatohepatitis (NASH) and thus elevated LFTs. Between 2-5% of all patients and up to 20% of obese patients at autopsy are affected by NASH. Due to the increased risk of preeclampsia with LFT elevations among obese women, early pregnancy baseline LFT testing has been proposed.

Objective:

To determine the rate of baseline glucola and LFTs testing in the morbidly obese gravida, and the positive screen rate. For those patients undergoing early glucola testing, to evaluate maternal and neonatal outcomes based on the timing of a positive glucose screen.

Methods:

We performed a retrospective cohort study in two parts of all women delivered from January 2004 through December 2008 with Class II/III obesity (body mass index $>35\text{kg/m}^2$). Women were divided into three groups based on body mass index (BMI): class II (BMI 35-39.9), class IIIa (BMI 40-44.9) and class IIIb obesity (BMI ≥ 45). For evaluation of glucola testing, patients without a history of diabetes were divided by timing of diagnosis: early (positive glucose screening before 24 weeks), late (positive glucose screening after 24 weeks, with or without early negative screening), and negative (negative early and/or late glucose screening). Rates of gestational diabetes at each testing period, overall compliance with testing, and maternal/fetal outcomes were compared among groups.

For LFT results, records of those patients without a history of diabetes who delivered from January 2004 through December 2008 were reviewed. Women were divided into four groups: under/normal weight (BMI < 25), class II (BMI 35-39.9), class IIIa (BMI 40-44.9) and class IIIb obesity (BMI ≥ 45). Rates of elevations of liver transaminases before 24 weeks gestation were compared among groups.

Results:

For glucose screening, of 1350 morbidly obese women, 991 (II – 567, IIIa – 274, IIIb – 150) underwent glucose screening. The rate of early screening was low, 4.5%, and did not differ between groups (II – 3.7%, IIIa – 4.7%, IIIb – 7.3%). 27% had a positive early screen without differences between groups (II – 28.6%, IIIa – 30.8%, IIIb – 22.2%), and 960 (96%) underwent routine screening (>24 weeks gestation), with 320 (33%) screening positive, 33% in each group. Of positive routine screens, only 84% (257) underwent three hour diagnostic testing, with 107 (42%) testing positive and no differences between groups (39%, 40%, 54%, respectively). 172 (17%) of the morbidly obese women were diagnosed with diabetes at any point in pregnancy, with again no group differences (15%, 16%, 19%). When grouped by timing of diagnosis, 12 early, 155 late, 824 negative, there were no differences in rates of preeclampsia, delivery <34 weeks, chorioamnionitis, or 5 minute APGAR score <7. Early diagnosis did make a significant difference in the rates of neonatal hypoglycemia (early – 25%, late – 6%, and negative – 2.3%, $p<0.0001$). Women with a diagnosis of GDM, regardless of timing, had significantly higher rates of cesarean delivery (early – 66.7%, late – 61.2%, negative – 43.4%, $p<0.0001$), and large for gestational age infants (early – 33.3%, late – 23.9%, negative – 15.4%, $p=0.01$) compared to a negative diagnosis.

In order to examine the utility of LFT screening, 3916 patients without a history of diabetes were reviewed, with 454 (12%) undergoing baseline LFT testing. 22 patients were eliminated for chronic liver disease (hepatitis B or C, cholestasis, alcohol abuse), leaving 432 patients (under/normal weight – 205, class II – 130, class IIIa – 64, class IIIb – 33). The overall rate of elevated LFTs was 5% and was similar among weight groups (4%, 4%, 8% and 3%, respectively, $p=0.8$). Post hoc power analysis indicates an 80% power to detect differences of more than 8% between classes.

Conclusion:

Morbidly obese women are underscreened for underlying diabetes and LFT elevations as recommended by the current guidelines. For glucose testing, few morbidly obese women are undergoing early glucose screening despite recommendations, even though 25% will test positive at early screening. At routine screening 33% of morbidly obese women screened positive, and >40% of those had positive 3 hour testing. Regardless of the timing of diagnosis, morbidly obese gravidas with either early or late diagnosis of GDM have higher rates of cesarean delivery and large for gestational age infants than obese gravidas who screen negative for GDM. The early diagnosis of GDM is associated with higher rates of neonatal hypoglycemia compared to late diagnosis, probably indicative of underlying type II diabetes with positive early testing. Thus, consistent with prior guidelines, early screening for diabetes in the morbidly obese gravida is warranted, yet not routinely done in practice.

However, for LFT testing, the rate of elevation of baseline LFTs was 5% for all women regardless of maternal weight. This did not vary by the degree of obesity, although power to detect variation between the groups was limited. In those patients without risk factors for liver disease other than morbid obesity, baseline LFT testing does not appear to be warranted.

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Basic Science & Clinical Research

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Does hLSD1 Function as an Oncogene in Osteosarcoma?

Introduction: Recent research shows that epigenetics may play an important role in tumorigenesis and metastasis. New findings have discovered several histone demethylases that catalyze the removal of methyl groups from histone H3 lysine residues and thereby influence gene expression.

Objective: The purpose is to establish whether or not human Lysine-specific Demethylase 1 (LSD1) functions as an oncogene in osteosarcoma (OS) cell lines. I predict that hLSD1 expression will be increased in OS cells as compared to normal osteoblasts. I also expect that pharmacologic hLSD1 inhibition will result in inhibited OS cell growth.

Background: The American Cancer Society reports that roughly 900 cases of OS are diagnosed a year in the United States, making OS the most common primary bone cancer. OSs are classified as malignant mesenchymal neoplasms in which the tumor produces immature bone; the primary cell involved in OS is the osteoblast (2). According to a paper by Dahlin, 80% of OSs are undifferentiated. Undifferentiated OS result in a 10-15% decrease in survival at each stage

In a March 2009 article, Schulte et al. find that Lysine-specific demethylase 1 (LSD1) is strongly expressed in poorly differentiated neuroblastoma (5). LSD1 expression is found to be correlated with adverse outcome and inversely correlated with differentiation of cells in neuroblastic tumors. Further, differentiation of the neuroblastoma cells resulted in LSD1 being down-regulated. The authors conclude that histone demethylation, such as by LSD1, reprograms the transcriptome of neurons promoting their transformation. LSD1 allows transcription factors or corepressor complexes to selectively initiate or repress transcription via demethylation of lysine residues 4 or 9 of histone 3 thereby controlling gene expression programmes. Another study found that LSD1 mRNA and protein levels are increased in high risk tumors (7). Expression increases 2 to 3.8 fold in tumors as compared with normal tissue.

It is likely then that targeting histone demethylases may promote neuroblastoma differentiation and inhibit tumor growth. It was found in 2006 that monoamine oxidase inhibitors (MAOI's), such as tranylcypromine (Parnate) inhibit LSD1 (3). The study concludes that tranylcypromine is an effective small molecule inhibitor of histone H3 lysine 4 demethylation. This idea is supported by RNA interference of LSD1 which resulted in decreased cellular growth, induction of differentiation associated genes and increased histone methylation at the promoters of specific target genes (5). Pharmacologic LSD1 inhibition using monoamine oxidase inhibitors resulted in an increase of global H3K4 methylation and growth inhibition of neuroblastoma cells *in vitro*.

Methods: In experiment 1, TE85, MNNG, and 143B cell lines were grown in 8-well plates in DMEM media (10% FBS, 1% P/S, and 1% SP); hFOB cells were grown in non-permissive (34°C) and permissive conditions (39.5°C) in MEM media (10% FBS, 1% P/S, and 1% SP). Cell numbers were counted by a Nanodrop Spectrophotometer. Whole Cell Extracts were then used with BioAssay Systems' QuantiChrom™ Alkaline Phosphatase Assay Kit protocol to determine Alkaline Phosphatase activity in each of the cell lines at non-permissive and permissive conditions. An Adenosine monophosphate buffer

was used with a purine nucleoside phosphorylase buffer.

In experiment 2, a time course osteogenesis assay was set up. hFOB cells were plated at 200,000 cells/ plate in 6 well plates with one plate for each time point of 1 day, 3 days, 5 days and 7 days. 50 mg/ml of AA and 1mM BGP was added at days 1, 3, 5, and 7 to half of the wells, and the other half were non-treated controls. Photomicrographs were taken daily. Alizarin red staining of the desired plate was performed on days 1, 3, 5, and 7 as per protocol in "An Alizarin red-based assay of mineralization by adherent cells in culture: comparison with cetylpyridinium chloride extraction" by Gregory, Gunn, et al. In experiment 3, cell lines hFOB, TE85, MNNG, and 143B, were plated on 10 cm plates with a density of 524,000 cells. hFOB was grown in 5 mL MEM media (10% FBS, 1% P/S, and 1% SP); TE85, MNNG, and 143B cell lines were grown in 5mL DMEM media (10% FBS, 1% P/S, and 1% SP). Five plates of each cell line was prepared, with one plate of each cell line receiving treatment of vehicle (0.02% DMSO), 0.05 mM tranilcypromine, 0.1 mM tranilcypromine, 0.2 mM tranilcypromine and 1.0 mM tranilcypromine. Media and drug were replaced for 3 successive days after plating. RNA collection for qPCR runs were prepared as per protocol in RNeasy kit. Specialized hLSD1 primers were created.

Results/Conclusion: Experiment 1 showed that there was decreased proliferation of hFOB cells at the non-permissive temperature, indicating that this was an adequate cell line with which to compare the osteosarcoma cells. Further, the osteogenesis assay showed that osteosarcoma cells (TE85 and 143B) were more proliferative at baseline. From the alkaline phosphatase assay, increased alkaline phosphatase activity was seen in the permissive temperature cells, relative to the hFOB cells grown at the non-permissive temperature and the OS cells.

Experiment 2 was run to try to make osteoblastic cells as osteoblastic as possible by culturing cells in media enhanced with osteogenic factors (AA and BGP). The Alizarin Red staining and photomicrographs revealed hFOB cells grown in osteogenic media had slower proliferation and morphology consistent with differentiation of the cells.

Experiment 3 showed that the least differentiated hFOB cells exhibited the most amount of hLSD1 in qPCR. This suggests that, as predicted, hLSD1 works most in undifferentiated and proliferating cells such as would be expected in cancer cells. This idea was further evidenced by the findings that hLSD1 was up regulated in the cancer cell lines as compared to hFOB. The cells were treated with tranilcypromine, an inhibitor of hLSD1. The experiment showed that tranilcypromine inhibited the proliferation of OS cell lines, and that the effect was increased with increasing doses of tranilcypromine.

Preliminary data from my experiments suggest that, as in neuroblastoma, hLSD1 is upregulated in more differentiated osteoblasts. Further, hLSD1 is upregulated in osteosarcoma cell lines as compared to hFOB cell lines *in vitro*. Finally, tranilcypromine, an hLSD1 inhibitor, inhibits proliferation, especially in osteosarcoma cells.

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Basic Science & Clinical Research

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Investigation of the Role of the ECM Protein Fibronectin in Heart Failure

Introduction:

The prevalence of heart failure (HF) approximately doubles with each decade of life. It is suspected that by 2020, heart failure will become the leading cause of all disabilities in the US. In addition, the burden on society is enormous, accounting for 2% of all medical costs annually, as high as \$40 billion per year in the US. Pathologic cardiac remodeling results in the deposition of scar tissue in the heart. This complex process involves the loss of myocardial cells, proliferation of fibroblasts, deposition of extracellular matrix (ECM), scar formation and recruitment of inflammatory cells. The role of ECM remodeling in heart failure is poorly understood, however continued ECM remodeling is believed to play a significant role in the pathogenesis of HF.

Objective:

The objective of the experiments is to determine the efficacy of inhibiting fibronectin (FN) in reducing cardiac remodeling and heart failure. In addition, to determine the mechanisms by which FN polymerization regulates cardiomyocyte and fibroblast growth and contractility.

Background:

Data from the Sottile and Blaxall labs indicates that FN plays a role in regulating ECM remodeling. FN is a soluble protein that polymerizes through a cellular dependent mechanism. In addition, FN deposition regulates the deposition of other ECM proteins. FN plays a vital role in the developing heart, however its role in the adult heart has not been well characterized. FN levels are increased in animal model of HF as well as humans with dilated cardiomyopathies. An adhesion-based peptide (pUR4) has been shown to inhibit the deposition of FN in the ECM. Previous work has shown that pUR4 inhibits intima-media thickening, blocks FN and collagen I deposition and reduces inflammation in a flow-induced model of vascular remodeling.

Methods:

In order to study the effects of pUR4 on cardiac remodeling and HF, mice underwent permanent coronary artery ligation, followed by six days of injections with pUR4 or a control peptide (III-11C). 4 weeks post-MI, histologic analysis of the hearts will allow for the determination of infarct size, expansion, FN deposition and cardiac remodeling. In another set of experiments, cardiomyocytes and fibroblasts are isolated from neonatal rats as well as adult mice and are cultured in order to study the effect of FN on fibroblast growth, FN polymerization, cardiomyocyte contractility and cardiomyocyte hypertrophy.

Results:

Initial results have indicated that pUR4 may preserve cardiac function in mice undergoing coronary artery ligation. In addition, histologic analysis of hearts post-MI has demonstrated a pUR4-mediated reduction in cardiac remodeling, infarct size and infarct expansion. The effects of FN on fibroblast growth, cardiomyocyte contractility and hypertrophy have not been fully determined. However, preliminary data

indicates that cardiomyocytes can polymerize FN. The effects of inhibiting the polymerization of FN on cardiomyocyte contractility are not fully characterized. The effects of FN on fibroblast growth are still unclear as well.

Conclusions:

Preliminary data indicates that the inhibition of FN reduced cardiac remodeling and improves heart function. The underlying mechanisms through which this may occur are still unknown, however our work has started to uncover this process. Future research will help to uncover the underlying mechanisms by which FN functions in the normal and damaged heart. Future experiments include the replication of initial cardiomyocyte contractility, fibroblast growth experiments, histologic analysis of cardiomyocyte hypertrophy, collagen deposition and infiltrative inflammation. This research could not have been done without the enormous contributions from Burns Blaxall, Jane Sottile, Dmitriy Migdalovich, Clint Miller, Andrew Serour and all of the members of the Blaxall Lab.

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Basic Science & Clinical Research

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Vertical vs. Horizontal Cesarean Section Incision in the Morbidly Obese Gravida

Introduction:

Morbid obesity is a risk factor for primary cesarean delivery and wound complications. Little data exists on the optimal direction of cesarean section incision, and there is considerable expert debate on the optimal placement of the incision. We sought to determine the rate of wound complications among morbidly obese pregnant women undergoing primary cesarean delivery varied by the direction of skin incision.

Background:

In 2007, approximately 25% of women in the United States were obese, defined as a body mass index of 30 or greater.¹ It is well known that obesity is associated with a number of prenatal complications, including diabetes and hypertension. Obesity is also a risk factor for adverse perinatal outcomes such as shoulder dystocia and higher rates of cesarean delivery.² As such, wound complications are not uncommon in the obese parturient.³ While there are a number of known risk factors for wound complications in obese women, there continues to be mixed reports regarding the type of skin incision.³ Several recent reports comparing Pfannensteil (low transverse) incisions with vertical skin incisions found no difference in wound complications between the two groups.^{4,5} However, the combined sample size in these studies is only 190 women. Another recent study compared wound complication outcomes according to skin incision in women with a body mass index greater than 35. The results showed an increased rate of wound complications in the women who received vertical incisions, however these results were not stratified by obesity class.² As the number of obese women continues to increase, there is a need to identify areas for the prevention of wound complications and possibly identify if certain classes of obesity respond differently to specific interventions.

Objective:

To evaluate the association between type of skin incision at the time of primary cesarean delivery and wound complications in a population of obese women

Methods:

Electronic records were reviewed for all women with class II (BMI 35-39.9) or III obesity (BMI >40) delivering at our institution from January 1994 through December 2008 who underwent primary cesarean section. Diabetes was defined as preexisting or gestation diabetes during pregnancy. Women, who divided by the type of skin incision and wound complications were assessed until their 6 week postpartum visit.

Results:

Of 664 patients, complete data was available on 503 patients. 34 (7%) underwent vertical incisions, while 469 (93%) underwent low transverse skin incisions. Overall complication rates were 15%, and varied significantly by the type of incision (44% vertical vs. 13% low transverse $p<0.0001$). Complication rates

did not vary between BMI class, but did vary between type of incision within each class (Class II 56% vertical, 12% low transverse $p=0.00002$; Class III 40% vertical, 14% low transverse $p=0.0005$). Among only those patients with diabetes and class III obesity, complications were still higher with vertical incisions 58% vertical vs. 9% low transverse ($p=0.0003$).

Conclusion:

After subdivision by BMI and diabetes, patients who underwent vertical skin incisions at the time of primary cesarean section had a higher incidence of both infectious and separation wound complications when compared with low transverse skin incisions. Therefore, vertical incisions should be avoided, if possible, in this population.

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Basic Science & Clinical Research

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Central and Peripheral Corneal Keratocytes Respond Differently to Stimulation by Pro-Fibrotic TGF- β 1

Introduction: In response to wounding stimuli, such as the pro-fibrotic growth factor TGF- β 1, corneal keratocytes become activated into fibroblasts and differentiate into myofibroblasts.¹ Myofibroblast activity is critical to the corneal repair process following trauma and surgery; however, their presence has also been correlated with changes in corneal clarity (haze), ocular aberrations, and refractive shifts^{1,2} – all of which impact upon post-traumatic and post-surgical visual outcomes.

Objective: To determine if cultured primary keratocytes isolated from different regions of the cornea (central vs. peripheral) respond differently to TGF- β 1 stimulation.

Background: Data have accumulated to demonstrate that not all fibroblasts behave in the same manner. Heterogeneity in the phenotypic response of fibroblasts to different growth factors has been identified.³ In response to TGF- β 1, this heterogeneity has been identified as dependant on the tissue of origin.⁴ However, heterogeneity in response to TGF- β 1 has also been exhibited in cells derived from the same tissue.⁵ Proliferation rates of fibroblasts show dependence on quiescent versus fibrotic tissue origin from the same source.⁶ While differences tend to be more remarkable when comparing cells derived from different tissues, they can also occur for cells derived from the same tissue. Hindman et al recently identified a heterogeneous response of anterior and posterior primary keratocytes to TGF- β 1 stimulation.⁷

Methods: Six corneas were removed from eyes of post-mortem cats. Using a 10 mm diameter trephine, the corneas were separated into central regions (central 10 mm diameter area) and peripheral regions (from edge of trephination to the limbus). Primary keratocytes from these regions were isolated and cultured separately in serum-free defined medium. Central and peripheral cells were then stimulated by incubation with 0, 0.1, 1.0, and 2.0 ng/mL TGF- β 1 and their responsiveness in terms of proliferation (Ki-67 staining), protein expression (immunohistochemistry and Western blot for Thy-1, α -SMA, and fibronectin), and ability to close a mechanical wound assessed.

Results: Western blot analyses and immunohistochemistry demonstrated greater sensitivity of peripheral cells to the myofibroblast transforming effects of TGF- β 1. At 0.1 ng/mL TGF- β 1, corneal keratocytes from the peripheral region expressed significantly more Thy-1 ($51.9 \pm 12.6\%$ vs. $14.3 \pm 4.6\%$, $p = 0.0084$), α -SMA ($35.9 \pm 8.2\%$ vs. $16.9 \pm 2.9\%$, $p = 0.0084$), and fibronectin ($52.6 \pm 17.3\%$ vs. $12.9 \pm 2.1\%$, $p = 0.0084$) than central cells. A trend of earlier proliferation amongst peripheral cells was noted at all concentrations of TGF- β 1 concentrations greater than 0.0 ng/mL was noted. At 2.0 ng/mL of TGF- β 1, central corneal cells had significantly greater Ki-67 staining than peripheral cells at early time-points (day 1 to day 6). However, at the same concentration, at later time-points (day 8 to day 13), peripheral cells showed significantly greater Ki-67 staining. In response to a mechanical wound, the peripheral corneal keratocytes closed the wound faster. Peripheral cells showed greater percentage wound closure at 0.1 ng/mL TGF- β 1 at 4 hours ($51.3 \pm 19.0\%$ vs. $15.7 \pm 11.3\%$ $p = 0.049$). Peripheral cells also showed

greater percentage wound closure at 1.0 ng/mL TGF- β 1 at 4 hours ($83.4 \pm 14.4\%$ vs. $17.7 \pm 15.4\%$ $p = 0.0057$), at 8 hours ($100 \pm 0\%$ vs. $38.6 \pm 12.9\%$, $p = 0.0012$) and at 12 hours ($100 \pm 0\%$ vs. $50.2 \pm 21.9\%$, $p = 0.017$) than central cells. At 2.0 ng/mL TGF- β , peripheral cells again showed significantly greater percentage wound closure at 4 hours ($94.1 \pm 10.3\%$ vs. $32.1 \pm 11.3\%$ $p = 0.0022$) and 8 hours ($100 \pm 0\%$ vs. $71.32 \pm 6.4\%$ $p = 0.0015$) than central cells.

Conclusion: Primary keratocytes isolated from central and peripheral regions of the cornea demonstrate a heterogeneous response to TGF- β 1 stimulation in terms of their proliferation, protein expression, and rate of wound closure. This may have important clinical implications in the management of medical and surgical diseases of the cornea.

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Basic Science & Clinical Research

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Angelman's Syndrome in Two Patients Lacking a Deletion in Chromosome 15

Introduction

Angelman syndrome (AS), often characterized by an abnormality occurring in the chromosomal region of 15q11-13, is a neurodevelopmental disorder that presents with severe learning disabilities, little to absent speech, ataxia, and a happy affect with frequent unprovoked laughter. Patients with AS can have common behaviors and/or features such as a love of water, difficulty sleeping through the night, seizures and dysmorphic facies [1-4]. To date, there have been four classes of AS that have been described molecularly: an interstitial deletion within 15q11-13 (class I, 68% of cases), paternal uniparental disomy of chromosome 15 (class II, 7% of cases), a defect in imprinting (class III, 3% of cases), and mutations in the maternally derived ubiquitin protein ligase gene, UBE3A (class IV, 11% of cases). Recently, there has been a fifth class that has been suggested (11% of cases). Class V patients have no known molecular lesion in chromosome 15 and show normal methylation in this area [1, 2, 5, 6].

Objective

To present two unrelated patients with clinically diagnosed AS that show no lesions in chromosome 15 (class V) and to build on the idea that a defect in the ubiquitin pathway may cause AS [1, 2, 6].

Background

The act of breaking a protein is difficult as their stability is a desirable characteristic. Yet, there must be a method of disposing disoriented or mutant proteins for regulation and quality control. Ubiquitin is a 76 amino acid polypeptide that can be joined to a proteolytic substrate with the help of ATP, which aids in protein elimination by labeling proteins for proteasomal degradation [7].

Ubiquitin genes can be E1-like, E2-like, or E3-like. These three subtypes are named for the order in which ubiquitination occurs. First, ubiquitin activation occurs in a two step reaction via the E1 ubiquitin-activating enzyme and ATP as the energy source. Next, the ubiquitin is transferred from E1 to the ubiquitin-conjugating enzyme E2. Finally, the ubiquitin is transferred to the target protein via the connection made by the E3 ubiquitin ligase and additional ubiquitin monomers can be added. This ultimately causes a 26S proteasome to dismantle the substrate while sparing the ubiquitin [7]. When the ubiquitination pathway is disrupted, neuropathologies may result due to signaling abnormalities.

Discussion

Both patients have different results from their respective Chromosomal Microarrays (CMAs) in regards to where their deletions are located, namely, chromosomes 4 and 6. Both deletions, though, have ubiquitin ligases associated: UBE2D3 and UBE2CBP, respectively. While the patients have different phenotypes when looked at as a whole, they both have overlapping characteristics, including unprovoked/inappropriate laughter, motor delays, and psychosocial delays, which are reminiscent of AS. The non-overlapping characteristics can be accounted for by the different regions the patients have deleted.

Clinically, our patients have AS regardless of the fact that their genetic testing for AS was negative. The test results claim that the test is positive in only 80% of cases, thus we believe it is prudent to perform a CMA if AS is suspected and the test is negative. The CMA will show any breaks in a patient's chromosomes and allow the provider to see if there are any deletions in ubiquitin ligase genes. Further research in this area will need to be performed in order to assess the importance of ubiquitin ligase levels throughout the body.

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Basic Science & Clinical Research

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Neurovascular and neuroinflammatory induction of neurogenic intermittent claudication in lumbar spinal stenosis reveals new potential pharmacological targets.

Introduction: As a hallmark of lumbar spinal stenosis (LSS), neurogenic intermittent claudication (NIC) represents a clinical syndrome of high diagnostic value as well as a significant source of disability in its own right. Progressive radicular pain, paresthesias, and numbness – with occasional fatigue and weakness – characterize NIC^{4, 16}. Symptoms typically radiate from the buttocks through the thighs, calves, and sometimes into the feet. Generally, patients experience pain only when ambulating or standing. In contrast, sitting or flexion of the spine provide relief.

Objective: To synthesize the evidence on NIC pathogenesis regarding heightened intraspinal pressure, disturbances in local microcirculation, and resulting inflammation. In the context of these three related processes, the project aims to identify viable pharmacological targets for future clinical trials.

Background: NIC in LSS patients represents the primary indication for the most commonly performed spinal surgery in older Americans. No double-blind, placebo-controlled study of an oral therapy has demonstrated analgesic benefit for this chronic pain syndrome; surgery remains the mainstay of treatment. Given this dearth of effective noninvasive treatments for NIC, development of an oral therapy is a research priority.

Methods: An informal but extensive review of the literature on vascular and inflammatory processes in NIC pathogenesis was conducted. Molecular factors that might participate in these processes were then deduced, and studies investigating their actions were reviewed.

Results: The pathophysiology of NIC has eluded researchers and clinicians for over 50 years. Although some have evoked mechanical compression in LSS as a direct cause of the syndrome, converging lines of evidence point towards a critical role for the neurovasculature as well as CSF flow in induction of NIC^{1-3, 5-15, 17-23}. While increased pressure plays a role, its effects do not appear direct but mediated instead via obstruction of nutritional circulation and alteration of the metabolic environment²⁴⁻³³. In fact, the emerging relationship between increased epidural pressure and compromised circulation suggests a telling metaphor: lumbar intraspinal stenosis as a compartment syndrome of the low back^{5, 33-34}. From this perspective, viable drug targets might include signaling pathways of phosphodiesterase 5, endothelin, adenosine, and calcitonin gene related peptide (CGRP). All of these molecular agents affect vascular tone and have mechanisms of action at the level of the vascular nociceptor.

Conclusion: By focusing on the neurovascular, microcirculatory, and microenvironmental aspects of NIC in LSS, research into the pathogenesis of this syndrome may identify pharmacological targets for oral therapy. Current findings suggest that pharmaceutical trials manipulating the phosphodiesterase 5, endothelin, adenosine, and calcitonin gene related peptide (CGRP) signaling pathways are warranted.

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Community Health Research



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St. Joseph Neighborhood Center

UR-Well at St. Joseph Neighborhood Center 2009 Summer Review

UR-Well at the St. Joseph Neighborhood Center is a free health care clinic run by University of Rochester medical students. The purpose of the clinic is to serve the Rochester community and to provide medical students with the opportunity for early clinical experience. During the summer of 2009 UR-Well medical students and seven volunteer physician preceptors provided health care to a total of 62 patients during twelve Tuesday nights. In addition, two independent projects were conducted at the center to improve UR-Well clinic functioning and the health of UR-Well patients. The first was the Healthy Living and Weight Loss Program which encouraged participants to lose weight and make life style changes to improve their health. The second project was an attempt to improve the functioning of the UR-Well clinic through an information exchange with the well-established MEDiC student run clinic at the University of Wisconsin Medical School at Madison.

Healthy Living and Weight Loss Program

Obesity is a global, national and local problem causing detrimental health effects and increasing health care costs. During the summer of 2009 a pilot weight loss program was created at the St. Joseph Neighborhood center to confront this problem. The 5 week long “Healthy Living and Weight Loss” program consisted of three individual meetings and two phone calls for each participant. The focus of the program was to encourage healthy weight loss and life style changes through education about healthy living. The program was created using resources from the United States Department of Agriculture (USDA), Department of Health and Human Services (DHHS), the Mayo Clinic, the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) and the National Institute of Health (NIH).

The 2009 “Healthy Living and Weight Loss” program consisted of 22 participants. Sixteen participants completed the first meeting, ten participants completed the second meeting and eight participants completed the entire 6 week program. The combined weight loss of the eight participants who completed the program was 29 pounds. All eight participants indicated that they were more aware of the food they were eating and that the overall program was “very helpful” or “extremely helpful”. The weight loss program was a success for these participants, but five weeks of support is not enough for successful long term weight loss. Therefore, the center plans to continue this program by providing continued support through group meetings at the center. Obesity is a critical issue today causing severe health problems, increased mortality and increasing health care costs. The key to

fighting this problem is to create educational programs to encourage healthy living and to provide weight loss support.

MEDiC Information Exchange

During the last week of July, 2009 a student traveled to Madison, Wisconsin in order to observe MEDiC, the student run clinic program at the University of Wisconsin Medical School. The goal of the visit was to interview key faculty and students involved with the program as well as observe normal clinic operations in the hope of improving UR-Well by incorporating new ideas and expertise. The MEDiC program was chosen for observation because of its size and the extensive range of services it offers. MEDiC operates six clinics throughout Madison and offers acute medical care, specialist referrals, medication, and psychiatric care to patients. They also run specialty clinics in dermatology, dentistry and physical therapy.

While in Madison the MEDiC faculty advisor and student president were interviewed about the history, leadership structure and general operations of the program. Additional medical and pharmacy school students were interviewed about their specific responsibilities including three clinic coordinators, a referrals coordinator and a medication supply coordinator. Clinic operations were also observed at three of the six MEDiC clinics. Information obtained from the interviews and direct observation was reviewed to try and determine which elements of MEDiC were most important for its success, and how these techniques could be adapted to improve the functioning of UR-Well. A new volunteer student translator initiative modeled off of a similar MEDiC program has already been created. Additional modifications, including an improved patient census form, are in progress.



Community Health Research



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Study Design: The Deaf Life History Project

Background: The National Center for Deaf Health Research is one of 35 CDC-sponsored Prevention Research Centers nationwide, each of which focuses on addressing the health needs of a particular population. The goal of NCDHR is to promote health in the Deaf and hard-of-hearing populations by conducting community-based participatory research. NCDHR operates on a cultural model, and recognizes that Deaf people who use American Sign Language are a distinct cultural group with their own language and collective identity.

Introduction: Data on the health of the Deaf community has not been collected in a systematic way in the past, so in order to help remedy this problem NCDHR recently administered a survey to gather baseline health information. This was one of the first surveys of its kind, as it used a touch-screen computer interface to present the survey questions in ASL, signed English, or written English. The Center is working on analyzing the data that came out of the survey, and comparing it with health data from the general population in the region to identify disparities between the Deaf population and the hearing population. In doing the analysis, the staff of the center recognized a need for more qualitative data to help contextualize the findings of the survey.

Objective: The Deaf Life History Project was created to use narrative and life history methods to provide a broader framework from which to understand and interpret the quantitative data that was gathered in the Deaf Health Survey.

Methods: An outgrowth of oral history and ethnographic field work, narrative interviewing methods are currently used across disciplines to let research participants tell their own stories in their own words. This method is well-suited to further NCDHR's mission of conducting research in full and equal partnership with the target community.

Results: As an intern at NCDHR working on the Deaf Life History Project, I conducted literature reviews, read textbooks, and collected resources about conducting narrative method studies. I also helped with the initial steps in applying for funding by researching grant application requests from national funding bodies. We laid the groundwork for conducting the interviews by observing videos of ASL life history interviews from the archives at the Rochester School for the Deaf and by contacting the leadership of Deaf Elderly Around Rochester (a branch of the local Deaf Club). In the course of the study design, we learned more about one particular disparity that became apparent in the survey: higher rates of suicidal ideation and attempts. After researching the literature on this topic, I synthesized this information into a paper on how narrative methods could help illuminate context surrounding this disparity.

Conclusion: The initial study design phase of The Deaf Life History Project was conducted over a period of seven weeks. The next steps in preparing this project include completing the specifics of the study design, submitting a grant application, gaining IRB approval, recruiting participants, and training life history interviewers.

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Summer Internship at NCDHR

In addition to working on this project, I also took part in the on-going activities of NCDHR. I helped with logistical support and transcription services for the External Advisory Committee meeting, and attended other events such as Townhall meetings, Deaf Health Community Committee meetings, and Research Committee meetings. I was also a member of the Deaf Strong Hospital planning committee and wrote a new scenario to be used for this event. Deaf Strong Hospital is a role reversal exercise for 1st year medical students to experience what difficulties and barriers members of the Deaf community must face in accessing the healthcare system. I also took part in a weekly course for 4 weeks called Introduction to Clinical/Translational Research, which familiarized me with all the resources available at the University of Rochester for conducting research.



Community Health Research



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ATTITUDES AND UNDERSTANDING OF CHILDHOOD IMMUNIZATIONS AMONG MEDICALLY UNDERSERVED PATIENTS

Introduction: Although the United States makes continual advancements in its health care system, one population that is significantly affected by lack of adequate insurance is children. While underinsured children face numerous health care disparities, one key obstacle is childhood immunizations.

Objective: The objective of this study is to research the attitudes and education about childhood immunizations among the medically underserved patients that attend the Free School /Sports Physical program sponsored by the URM and CACHED office. The goal is to expand the effectiveness of this already successful project even further by offering immunizations and education about these immunizations to students and parents who attend the program.

Background: According to recent research, 8.4 million children aged 0-17 are underinsured¹ and 12,000 children are underinsured just in Monroe County⁵. One issue that the current health care system is trying to combat for children with inadequate insurance is lack of proper immunizations. In addition to lack of adequate insurance, this trend of under-immunization has been attributed to lack of knowledge regarding vaccines and concerns for the safety of vaccines⁶. In attempts to address this issue, New York recently instituted a requirement for the Tdap (Tetanus, Diphtheria, Pertussis) booster vaccine for all students entering the 6th grade who are born on or after 1/1/94⁴. This new requirement has added even more weight to the importance of providing necessary vaccination and education about immunizations in our local community. The Free School/Sports Physical program was created in 2002 by the collaboration of University of Rochester School of Medicine and Dentistry, the Department of Family Medicine, and the Rochester City School District to address the needs of underinsured and medically underserved students in the inner-city Rochester area. In hopes to expand this project's effectiveness by providing for the need for immunizations and education regarding these immunizations, this project was established to first understand the existing attitudes and education barriers that need to be addressed.

Methods: Participants completed a 10 question survey intended to research the attitudes and understanding of childhood immunizations, specifically addressing the student's immunization status, parent's and student's understanding of immunizations and possible influences on parent's attitude towards immunizations. Surveys were given to all parents who attended the Free School/Sports Physical program, and they were completely anonymous.

Results: 175 participants completed the survey. Results showed that 80% of parents both knew with certainty their child was up-to-date on immunizations and had a record of these immunizations and when they were administered. Of the remaining 20%, 18% were unsure of their child's immunization status while 2% knew their child was not adequately immunized. 25% of parents felt their child did not know what immunizations he/she had received or what these immunizations were for. The recent New York

State law mandating the Tdap booster influenced 34% of parents who took the survey, as they reported that they would probably not have vaccinated their children if this law were not in place. 60% of parents stated that insurance and health care benefits have influenced their children's vaccination, whereas religious views and media were reported to be influences for only 19% and 28%, respectively.

Conclusion: From this study, we can see that a great majority of students who come to the Free School/Sports Physical program are adequately vaccinated (80%). Trends also point toward parents having both an understanding and up-to-date record of their children's vaccinations. Whereas parental religious views and media appeared to not influence whether or not children received immunizations, insurance/health care benefits and the New York State law did appear to play a role.

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International Medicine Research



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Understanding the Educational Experiences of Street Children in Bolivia: An Introduction to the Population of Surveyed Children

INTRODUCTION:

The 1989 *Convention on the Rights of a Child*, defines children as “human beings below the age of eighteen years unless under the law applicable to the child, majority is attained earlier.” While the beginning of childhood remains controversial, the period uniquely characterizes a phase of innocence, vulnerability, curiosity, and a sense of newness or renewal. Regrettably, countless children of the world lack adequate protection. This in turn fosters the development of practices and beliefs that permit abuse and neglect of this vulnerable group. The population of street children found around the world most aptly illustrates this concept. UNICEF separates street children into three categories; *children at risk*, *children on the street*, and *children of the street*. *Children at risk* are poor children with risk factors (i.e. poverty) that may result in a “partial expulsion” from their homes, leaving them to spend some amount of time on the street. *Children on the street* work menial jobs on the street during the day; however, they are able to return to their homes at night. *Children of the street* have little to no family contact and live full-time on the street. Children with no familial contact may also be referred to as *abandoned street children*, a title that includes children of street children. (UNICEF). The United Nations currently estimates that as many as 150 million street children exist in the world today. (UN as cited by UNESCO). In the Western hemisphere, Bolivia ranks top amongst countries with the highest populations of street children. Estimates suggest that some 3,700 children live on the streets of its major cities: La Paz, Cochabamba, Sucre, El Alto, Santa Cruz, and Tarija (UNICEF) and some 9,200 children live in orphanages or similar institutions for abandoned children. Abuse in these institutions has been reported, in addition to the absence of sufficient funds to sustain many of the institutions’ respective infrastructures. Unfortunately, mistreatment also presents itself in the Bolivian school system. Street children exemplify an especially defenseless population due to the absence or decreased presence of protective factors such as health care, education, parental guidance/care, suitable physical shelter, and consistent/healthful food options.

OBJECTIVE:

This project is geared toward understanding the school experience of local street children in Bolivia in order to explore the potential role that Bolivian school systems can play in mitigating their life ordeals. Responses generated from these interviews will more clearly elucidate some of the problems experienced by street children in Bolivia revealing patterns of shared characteristic experiences that negatively affect their school attendance.

BACKGROUND:

A variety of initiatives aim to improve the lives of street children by focusing on varying immediate targets (reintegration with families, food and housing, surrogate families) such that street children stabilize and progress to eventually become fully integrated members of society. Surprisingly, school-based initiatives are not commonly seen among these programs. UNICEF notes that only 39% of working children in Bolivia continue to attend school and some 3.4% have never attended school to begin with. There is a general absence in the literature surrounding street children that focuses directly on the

impact of schooling or on school-based interventions that might help populations of street children. Yet, schools may provide great avenues for intervention because their purpose and infrastructure are founded upon unique elements which are crucial for the rehabilitation of street children. In the event that school intervention does not prevent children from moving to the streets, it may provide an avenue that will foster positive persisting relationships. These bonds may mitigate some of the most detrimental factors to street children (vagrancy, distrust of authorities, drug use) and make the transition off the streets an easier process. Research by Huang (2008) may lend support to this theory. Among the 10 children studied in her dissertation, only one child was enrolled in school throughout his time as a street child. He himself took responsibility for his attendance and enrolled himself in school yearly. Among the factors that distinguished this boy from his peers was a relationship that he had with one of his teachers early on in his school career. In her, he found an advocate. He notes that she would tutor him, check in on his well-being, and give him general counsel. With consistent school attendance, he remained on track to graduate with his peers and thus was spared the frustration and embarrassment that can prove to be an obstacle for children being reintroduced to school after years on the street.

METHODS:

We conducted a face-to-face, semi-structured, 42 question survey with Bolivian street children concerning their life on the streets and their experiences with education. Survey items included the subject's personal and family characteristics, employment status, and educational experiences. An initial survey was constructed with the support of the Kaya organization and later piloted with children living in the Kaya group homes. Changes were made to accommodate local dialect. From June to July of 2009, the final version of the survey was administered to children living or working on the streets of El Alto, Bolivia. A representative from the Kaya organization identified prospective study subjects and along one of with three URSMD student interviewers, completed the 20 minute survey. A second optional survey opportunity was also available for those subjects who elected to participate. This was also administered in the same face-to-face oral format and provided subjects a free response structure where they could answer six open-ended questions about their views on the role education has played in their lives. These interviews were tape recorded and transcribed. All interview data was entered into an excel spreadsheet for data analysis with SPSS. Only data from the first survey are presented here.

RESULTS:

A total of 96 surveys were conducted. Six were eliminated from analysis due to problems with the original transcripts. Of the 90 surveys remaining, the average age of survey participants was 15.6 years, average years living or working on the street was 3.6 years, and the average income per week was 45-98 Bolivianos (\$6-14 USD). Forty-four percent of participants reported working on the street only, while 51% lived and worked on the street. Analysis of these two groups revealed notable differences between the two. Using chi-square analyses, when compared with children who only worked on the street, those children who lived on the street were statistically more likely to 1) be former rather than current students, 2) have failed a year of school and 3) steal (as compared to performing other jobs like announcing or shoe shining) to earn money. Other differences, although not statistically significant, were that children living on the street were more likely to have been taken care of by parents rather than siblings or other family members. These children were also more likely to spend their time on the street alone or with close street friends when compared to children working on the street.

CONCLUSION:

Many preliminary conclusions can be made from these data. Children living on the street continuously appear to be entrenched in activities and social circles that reinforce their current lifestyles (e.g. not attending school, stealing). Although contrary to expectations, the fact that children only working on the street are cared for by siblings or other family members to a greater degree than children living on the street, may indicate that there is a protective role played by siblings or the social environment that they provide for at risk children. There is also a difference in academic performance between the two groups.

Children living on the street were more likely to have lower grades, failed a grade level, and not be current students, indicating that the life stressors that precipitated street life may have manifested themselves in quantifiable changes in student performance and behavior beforehand. Since these data were not collected longitudinally causal inference is not possible. In returning to the objectives of the study, there may be a role for school systems/charitable organizations to potentially change or become a part of the sphere of influence of children at risk to prevent an immersion into and adoption of behaviors commonly practiced by street children, which may reduce the potential dangers confronting street children.

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Why Peruvian Medical Students Choose to Practice Outside of Peru

Introduction: The state of New York, like many across the United States, is facing a doctor shortage, particularly in primary care. As a way of tempering the shortage of providers, foreign trained doctors now make up an estimated 27% of all physicians practicing in the US.ⁱ This problem, commonly referred to as brain-drain, is widely recognized and its effect is felt around the globe.ⁱⁱ Countries like India and China are frequently associated with suppliers of the foreign trained physician; however the problem has long existed in South America and threatens to become significantly worse as the US and UK demand for foreign trained providers increases and key South American industries such as gold and oil slow.ⁱⁱⁱ Peru is a hot spot where physician migration has more than doubled in recent years.

Objective: The objective of this study was to identify the reasons why physician migration has significantly increased in Peru over the last decade.

Background: The issue of physician migration is highly complex because of the number of stakeholders it concerns. Governments, both national and local; Communities, both national and local; Populations, families and individuals. Peru, like many other countries is facing a serious challenge of supplying healthcare to its rural communities. Its long standing strategy of requiring a year of internship of all graduates in a location designated by the government is no longer working as recent graduates opt to go abroad to practice. In addition to the geography issue, Peru also faces a reimbursement challenge. Peru is recognized as the most underfunded healthcare system in South America.^{iv, v, vi}

The literature suggests there are important motivators beside income that governments and policy makers should recognize. One study reported that 10% of those who left Peru (primarily to work in the United States) were also members of the highly educated work force. Interestingly, these people did not cite economic reasons for leaving but were more concerned about political environment or better opportunities to pursue scientific and technical careers abroad.^{vii} The motivating factors behind the physician migration from Peru to date is unclear.

Methods: This study was conducted with Peruvian medical students at four different universities: Universidad Nacional Mayor de San Marcos, Universidad Peruana Cayetano, Universidad Catolica de Santa Maria and Universidad Nacional de Trujillo. Participants were in their first, second, third or fifth year of medical school. Students in their fourth, sixth or seventh years were not surveyed due to time and logistical constraints. Survey structure and language was finalized with the aid of native Peruvians and feedback from a test group. Surveys were administered either at the beginning or end of class, with the approval of the professor. The voluntary nature of the study, the purpose of the study and specific instructions concerning completion of the study were explained to the students prior to completion. After completion, the surveys were collected and filed to be analyzed later.

In total, 984 surveys were collected. The number completed at each institution varied with class attendance and total class size. The number of students surveyed at each school were: San Marcos 280,

Cayetano 117, La Catolica 357, Trujillo 230. The distribution of students in each year was roughly equal with 270 (27%) 1st year, 256 (26%) 2nd year, 234 (24%) 3rd year and 222 (23%) 5th year. The average age of the participants was 20.5 and 54% were male.

Results: Of the 984 surveyed Peruvian medical students, 82.2% planned on leaving Peru after their training. Of those students, the most common desired country was the United States (25.3%), followed by Spain (16.0%), and France (5.8%). Fewer than 5% of responders believed they would go to another South American country. Of those that wanted to leave, 82.8% planned on returning within 10 years and 6.9% did not plan on returning.

Among students that planned on staying in Peru, 32.2% stated that family/partner and 24.6% stated that Peruvian culture was an extremely important factor in making their decision. For those students that planned on leaving, access to adequate technology and opportunities to specialize in Peru were listed as extremely important factors 41.1% and 39.0% of the time, respectively. Salary was marked as an extremely important factor for the fewest number of responders leaving Peru (7.9%). When asked to rank factors that influenced their decision, 70.4% of students that planned to leave listed access to advanced training in Peru as the most important factor. Salary was listed as most important 8.3% of the time.

Conclusion: In this study, it was shown that a large majority (82.2%) of Peruvian medical students surveyed, planned on leaving Peru, but most (82.8%) planned on returning within 10 years. Adequate technology, opportunities to specialize, and access to advanced training were listed as the most important reasons for leaving. Salary, the main focus of most papers, was shown to be one of the least influential factors.

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Child Survival and the Role of Maternal Grandmothers in Ladakh, India

Introduction:

While under-5 child mortality rates have generally declined worldwide over the past 30 years, rates remains high in Himalayan regions at 72 per 1000 in India (1). Previous work by Chin et al. suggests a positive association between the presence of maternal grandmothers and improved under-5 child survival (2). A further exploration of this bond and its implications for children's health may provide information to enhance child survival efforts in Ladakh.

Objective:

Our goal was to explore the role of the Ladakhi maternal grandmother and to identify how her presence contributes to positive deviants of child survival. The long-term goal of our research is to identify and implement solutions already present within the community that can improve child survival and be inherently sustained in a resource poor environment.

Background:

Child mortality in Ladakh is a significant problem that is not well-understood. A 1994 study of 2 villages in Ladakh found that 20-30% of births ended in death before reproductive age (3). However, current research as to why Himalayan communities such as Ladakh have higher mortality rates is not conclusive (3, 4). The World Health Organization has issued a bulletin on child mortality emphasizing that classically used strategies, including strengthening health systems and training health care providers in technologies, are not sufficient to combat child mortality. Instead, a new concentrated effort must be made in promoting household practices that are linked to prevention and curing of common childhood illnesses (5). What these practices should be and how they may be carried out in the remote, resource-poor environment of Ladakhi villages is unclear. In order to identify such household practices, we used a positive deviant approach that has been used successfully in developing country child nutrition projects (6). We used this approach to identify how the presence of the maternal grandmother may contribute to practices that improve child survival.

Methods:

To identify how maternal grandmothers may create positive deviants of child survival, we used a two-phase mixed method study design. Phase 1 was a modified-WHO survey of quantitative demographic data collected from Ladakhi women, including a child survival rate for children surviving past the age of 5. This population was divided into three groups to better assess the impact of the presence of a maternal

grandmother. Group 1 included those women whose mothers lived past the woman's 21st birthday and group 2 included those whose mothers died when they were 21 or younger. Group 3 consisted of grandmothers who have grandchildren born at least five years ago (ie the children survived to 5 yrs or would have been 5yrs had they survived.)

Phase 2 was an interview with women and maternal grandmothers about what factors influence child survival and the potential role of the maternal grandmother in grandchild survival. We used a convenience sample population of married, Buddhist, Ladakhi women from rural villages around Leh, India. Women were enrolled after IRB approval and support from the Jammu & Kashmir government from July through August. During the entire study, we used 2 female translators: one from The Students' Educational and Cultural Movement of Ladakh and one from the Women's Alliance of Ladakh. A total of 100 females participated in the project, but 19 were excluded for a variety of reasons: not married, no children over 5, no grandchildren, not Buddhist. Out of the 81 included women, 50 women had mothers living past the woman's 21st birthday (group 1) and 11 women had mothers dying before the woman's 21st birthday (group 2) and 20 were grandmothers (group 3). The 61 women from groups 1 and 2 participated in Phase 1, completing the demographic survey. For the Phase 2 qualitative survey, 22 women from group 1, 10 women from group 2, and 20 grandmothers from group 3 participated.

Results:

The under-5 survival rate for group 1 was 94.4%, and 85.4% for group 2 (see table 1). The average ages were 38.3 for group 1, and 43.5 for group 2. Over half the women in group 1 had some education, among which the average number of years was about 10. About half the women in group 2 were educated past secondary school, but none past the 10th standard. The average number of live births was 2.7 for group 1 and 3.8 for group 2. While our survey data demonstrated a trend of higher child survival among women whose mothers survived past the woman's 21st birthday (94.4% vs 85.4%), this trend was not statistically significant.

Parameter	Group 1	Group 2
number of women	50	11
under 5 survival rate	94.4%	85.4%
average age	38.32	43.5
average years of schooling	5.8	4.7
currently self-employed	22%	9%
currently employed (not self)	10%	9%
currently unemployed	68%	82%

However, our Phase 2 interviews revealed the presence of a strong mother-daughter bond which both the women and their mothers believe contributed to care of the grandchildren. Recurrent themes included education/passing of knowledge from mother to daughter, direct child care by maternal grandmothers, support by other means from the maternal grandmothers, as well as a close, enjoyable relationship between mother and daughter. Many of the women attributed their knowledge of how to care for children and family, as well as how to recognize illness, to their mother. All groups interviewed emphasized the role the maternal grandmothers have in taking care of grandchildren, which included such tasks as helping with homework, getting them to school on time and taking care of children. In addition to direct childcare and advice, the grandmothers also helped with field work, housework, and material support, easing difficulties for the women. Both direct child care and help with work was dependent upon frequent visiting which wasn't always the case, as women generally live with their husband's family after marriage

and may move up to 100 kilometers away. Occasionally a woman would name her mother-in-law as a larger source of child care information than her mother. Even among those separated by distance, the relationship often remained strong. The mother would stay for a month or visit during late pregnancy and help after delivery. The mother-daughter relationship was often described as a positive one with much emphasis on talking, discussing life, sharing problems, and humor. Thus there were many facets by which this relationship affects child care and health.

Prominent themes that arose in discussing how to keep children healthy and improve child survival included diet, hygiene, education (of children as well as parents), traditional practices, community improvement, and doctors/medical infrastructure. Diet and hygiene in particular were brought up frequently. Many women and their mothers were concerned about "junk food" that has come into the area and emphasized the importance of traditional food. Other concerns included getting clean water, feeding children on time, and the lack of fruits and vegetables in the long winter. Good hygiene and clothing were also a widespread concern with great weight placed on keeping the body and surroundings clean, as well as having warm clothes for the children in the winter. Education of both children and parents also frequently arose in interviews. Some examples included raising awareness over infant health, vaccines, prenatal health, as well as teaching children good habits. Local women's groups have already started some related educational projects in villages and were favorably spoken of in interviews.

Conclusion:

The mother-daughter bond in rural Ladakhi culture contributes to the care of children in the area. Mothers pass knowledge to their daughters on how to raise a family and recognize illness, in addition to caring for grandchildren and providing other means of support. The lack of a statistical difference between under-5 child survival rates of women whose mothers lived past the women's 21st birthdays and those whose mothers did not could be due to our small survey population size or the possibility that women without mothers are supplied with similar information and aid from other sources, such as their mother-in-law. Women brought up recurrent themes, such as diet, hygiene and education, when asked how to improve child health and survival. Local women's groups are already undertaking some of this education and are being met with a favorable reception. These groups represent one avenue to expand local education on desired health and child care topics. Further research is warranted to more fully elucidate factors underlying child survival in Ladakh.

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International Medicine Research



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HIV Knowledge and Risky Behaviors in Rural Malawi: How Cultural Factors May Limit the Effectiveness of a Gender Focused Educational Intervention

Background: The rate of HIV infection continues to increase in sub-Saharan Africa despite interventional efforts by governmental and non-governmental organizations. Malawi has been a focus for many of these efforts due to high infection rates and limited resources. However, there has been limited success targeting the rural villages. One of the few efforts extending into the rural population is a government sponsored health education program run through health clinics to provide women with basic health education, including HIV. Little research has looked at the relationship between the introduction of this program and basic HIV knowledge and risky behaviors among targeted populations.

Objective: The purpose of this project was to assess the level of basic HIV knowledge and attitudes towards risky behaviors among adults and adolescents in rural Malawi.

Methods: Surveys were given to 85 individuals varying in age and sex to assess basic HIV knowledge that reflects information recommended by the World Health Organization to be taught in basic health education classes. In addition, fifteen in-depth interviews and 5 focus groups with various role players were conducted in 9 rural villages to assess general understanding and practice of behaviors that increase the risk of transmitting HIV.

Results: The surveys demonstrated that adult women had a significantly better understanding of HIV than adult men and adolescents, while no difference was found between the men and adolescents. Interviews and focus groups complemented this data by showing that adult women had a better understanding for risky behaviors. Despite this, the data also illustrated that all groups readily practiced behaviors that increase the risk of transmitting HIV. The primary factors identified that promote these behaviors are gender inequality, cultural stigmas, and lack of education among men and adolescents.

Conclusions: While this educational intervention appears to be improving HIV knowledge and attitude toward risky behaviors in adult women, its success has not translated into a reduction in risky behaviors. Addressing the cultural factors identified as the primary barriers to translation may improve the effectiveness of similar interventions.

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Role of Socioeconomic Status and Structural Barriers on Malaria During Pregnancy in Primigravidas and Multigravidas in Assam, India

Background: Malarial infection during pregnancy is a major public health concern in tropical regions worldwide. It can have adverse health consequences for both mother and fetus, increasing the probability of intrauterine growth restriction, prematurity, low birth weight, fetal death, and maternal anemia. With the vast majority of investigative work done in Africa, little is known about malaria in pregnancy in Southeast Asia, particularly in Assam, India where there is seasonal transmission. Three years ago, Assam had an epidemic that claimed the lives of many individuals primarily affecting more first time pregnant mothers (primigravida) than experienced pregnant mothers (multigravida).

Objectives: The purpose of this study is to identify and describe socio-economic and structural factors that may predispose women to malaria infection during pregnancy. The study examines differences between primigravida and multigravida and how these factors may influence malaria risk.

Methods: A qualitative study was done to compare primigravida and multigravida. Demographic data was collected to ensure that information was obtained from a wide range of backgrounds for determination of socio-economic status (SES) and structural barriers. Direct observation, participant observation, and structural interviews were used to gather information on barriers to malaria prevention in pregnant women.

Results: Primigravida were more likely to have husbands with jobs that required more training and higher education than Multigravida and were more likely to be more educated than their counterpart. Fifteen of 16 women interviewed reported having had malaria at some point in their life, suggesting that malaria is endemic. Six of 9 Multigravida had history of miscarriage. Of the 6, two were reported to be malaria-related. More Primigravida used bed nets than Multigravida; however, of the 5 Primigravida that used bed nets, only 1 reported using medicated bed nets.

Conclusion: Malaria is a serious and common problem among pregnant women in Assam and medicated bed net usage is low. There is a need for healthcare workers to increase discussion of malaria prevention. Educational level and SES effects on malaria risk in pregnancy could not be adequately assessed. A larger cohort of pregnant women including grand multiparous (more than 2) are needed to discern the effects of education and SES on malaria risk during pregnancy.



International Medicine Research



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Assessing if a Telemedicine Network can be used to Meet Continuing Medical Education Needs of Health Professionals in Belize

Background: Telemedicine uses communication networks for the delivery of medical services and education between locations. It overcomes shortages of infrastructure and resources, and it has been identified by the WHO as an effective means for educating professionals and communities in developing countries (1). Telemedicine has already been successfully employed in the education of rural U.S. health providers in Hepatitis C virus (2), physicians in 10 French-speaking African nations (3), and doctors in India to reinforce endocrine surgery training (4). A telemedicine unit was installed at Southern Regional Hospital (SRH) in Dangriga, Belize with the capability of connecting physicians in the US and Belize. However, the unit is not being used.

Objective: The purpose of this research was to gain a better understanding of the barriers preventing Belizean health professionals from using telemedicine for continuing medical education (CME), either for consults or broadcast lectures.

Methods: Direct observations and 16 in-depth interviews with health professionals at SRH were performed to assess the barriers to CME and to telemedicine use for education. Using qualitative research analysis, interview responses were coded for themes associated with barriers and were compared with direct observations.

Results: Identified barriers to CME stem from resource limitations. These included lack of time, staff shortage, cost of journal subscriptions and travel, and slow Internet connection. Of these, lack of time and staff shortage were also recognized as factors hindering telemedicine use. Barriers unique to telemedicine consist of lack of incentive and structural support, as well as fundamental differences between the U.S. and Belize. These were differences in available resources, language, time zones, and perception of punctuality. Marked differences in resources created an applicability problem in which U.S. physicians were recommending medications and diagnostic tests not available to Belizeans. Many of the doctors at SRH were from Cuba and spoke mainly Spanish, creating communication difficulties when consulting with or viewing a lecture from U.S. physicians. The two-hour time difference created scheduling conflicts, especially since most Belizean health care workers were very resistant to arriving before 9am. Finally, the fact that meetings in Belize regularly started half an hour late also created scheduling difficulties.

Conclusions: The telemedicine unit in Belize has a separate high-speed Internet connection that is free for the hospital, thereby overcoming two of four barriers to CME (cost and slow Internet connection). However, the lack of time, staff, structural support, basic necessities, and incentive as well as economic and cultural differences still hinder telemedicine use. In order for the telemedicine unit to be utilized,

these barriers must be addressed. Educating US physicians about resource constraints in health care delivery in Belize, making Spanish lectures and consults available, recording lectures and consults for later viewing, creating incentive by providing food for lectures, recruiting a hospital staff member for promotion and oversight of telemedicine, and placing a medical student at Southern Regional Hospital for long term facilitation of telemedicine are some suggestions for increasing the use and applicability of telemedicine for continuing medical education in Dangriga, Belize. Some of these barriers are currently being addressed (a medical student from URMU is in Belize supervising telemedicine and U.S. physicians are being educated on Belizean conditions), already increasing telemedicine use and creating the potential for even more improvement in the future.

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International Medicine Research



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Assessing the traditional healers' cultural views and understanding of HIV vaccine trials in Nyanga district in Cape Town, South Africa.

Introduction: The human immunodeficiency virus (HIV) is the most important infectious disease globally and the principal cause of death in Africa [2]. By the end of 2007, it was estimated that around 33.2 million people worldwide are living with (HIV) [1]. Each year, approximately 2.5 million people become infected with HIV while 2.1 million die from AIDS.

As of 2005, 18.8% of the adult population in South Africa were living with HIV/AIDS 1200 children (0-17 ages) orphaned by AIDS. [6] The prevalence rate of HIV varies in different regions of South Africa; Nyanga district of Cape Town Province continues to be one of the severely affected regions. Nyanga district is a predominately black, Xhosa speaking community with approximately 400,000 population size. With antenatal HIV prevalence of 29%, HIV/AIDS is a major concern in the community [7]

Objective: The main purpose of this study will be to assess the traditional healers' cultural views and their understanding of vaccine and HIV vaccine trials in Nyanga district. Based on the results, we will be able to understand their impact on the community's consensus about HIV/AIDS and the vaccine trials.

Background: Traditional healers play important roles in the healthcare of many African communities, including the Nyanga district. It is estimated approximately 70% of sub-Saharan Africans consult traditional healers [4]. Healers can be described as *sangoma*, primarily diviner-mediums who consult ancestral spirits on behalf of a patient to determine the cause of the illness and the remedy. They are forbidden by their ancestors' spirits to reject patients. *Inyanga* are herbalists who routinely work together with *sangomas* in order to include divination in the treatment of their clients. [8]

South Africans generally consult traditional healers in preference or in conjunction with hospital/clinical professionals [5]. Unfortunately, there is little collaboration between traditional healers and biomedical health providers [4]. Nonetheless, it is imperative to have collaboration between these two modes of health care in order to succeed in HIV preventive measures.

Methods: A questionnaire was administered to 20 traditional healers of the Nyanga community. It contained 30 questions in total divided into several components. The first component focuses on HIV knowledge and attitudes. These include HIV transmission, treatment, and prevention. The second component of the questionnaire focuses on vaccine and HIV vaccine trial. The last component is questioning how traditional healers gain their knowledge of HIV/AIDS and how they continually learn about its progression. The traditional healers were visited at their homes. The questionnaire was presented

in both English and Xhosa. Our research population included both male and female age 18 years or older.

Results: We interviewed 20 traditional healers in the Nyanga District of Cape Town, South Africa. Of these 20, 15 of the healers were women. The median number of clients seen per week by the healers was 5, with some healers seeing only 2 clients a week and other healers seeing 140 (mean 20.25, SD 41.24). The mean percent of HIV positive clients seen in a week was 57.4% (SD 46.1).

All healers interviewed report having heard of HIV and 85% (17 healers) believe HIV causes AIDS. 85% (17 healers) were able to correctly identify the major methods of transmission of HIV. Incorrect methods of transmission (such as via mosquitoes, drinking dirty water, kissing, contact with urine or feces) were also identified by the majority of subjects. 80% (16 healers) believe HIV transmission is preventable, with abstinence and condoms correctly identified as methods of prevention by 14 of the 16 healers. Prayer and herbal treatments were also identified as methods of prevention by 4 and 7 healers, respectively. 80% (16 healers) of subjects had heard of vaccines and 75% (15 healers) had heard of an HIV vaccine. We found that the healers' understanding of the role of an HIV vaccine was variable, with 7 healers identifying an HIV vaccine as a treatment for HIV infection/AIDS, 8 healers identifying an HIV vaccine as a cure for HIV infection/AIDS, and 15 healers correctly identifying an HIV vaccine as a way to prevent HIV infection/AIDS (healers were able to select more than one response). Encouragingly, 100% of healers stated that they somewhat support or strongly support HIV/AIDS vaccine trials, and 95% (19 healers) would encourage their clients to be vaccinated were an effective HIV vaccine to be developed.

Conclusion: This study enabled us to look at the knowledge base and opinions that traditional healers of the Xhosa community have on HIV and HIV vaccines. The healers were very helpful and cooperative, so we attained the information with relative ease. We found the healers to have limited to moderate knowledge of HIV and vaccines. This warrants further education in the community targeted specifically at this population. The healers touch the lives of many in the community, so knowledge and awareness of HIV/AIDS could be spread with greater efficacy with the healers as allies. As a group, the healers also seem to be supportive of further vaccine trials. Despite this promising information, we believe our data was subject to a number of biases. Firstly, the number of healers we interviewed was limited due to time and protocol. Secondly, our subject pool was from limited regions of the township and had a skewed proportion of women to men.

This may have been due to recruiting factors. Thirdly, the participants may have answered questions, such as the one regarding their opinion on future HIV vaccine trials, according to the way they believe we wanted them to answer it. Future studies should include larger number of participants from more diverse regions of the township.

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International Medicine Research



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Can educational materials distributed at the time of CPR instruction improve retention of CPR knowledge and skills?

Introduction:

The 2005 epidemiological data for the country of Belize, hypertension, diabetes, and ischemia heart disease are the three leading causes of mortality [4]. More recent global epidemiological data suggest that heart disease is rapidly becoming the leading cause of death in a large number of developing countries [3]. This data is confirmed in Belize as ischemic heart disease went from the seventh leading cause of death in 2004 to the third leading cause of death in 2005 [4]. Sudden cardiac death is a lethal sequelae of cardiac disease. Cardiopulmonary resuscitation (CPR) and early defibrillation are useful tools in improving outcome for victims of sudden cardiac arrest (SCA). [5]. As a small developing country Belize has only 8.5 doctors and 15.1 nurses per 10,000 people. With limited medical recourses it is imperative that continuing education is provided to its healthcare providers in order to prepare for the expected increase in SCA.

Objective:

The purpose of this study is to assess whether providing supplementary educational materials, in the form of a laminated pocket flowchart, can improve the retention of CPR knowledge and skills in healthcare providers after attending an AHA(American Heart Associations) 4.5-hour BLS(Basic Life Support) for the HCP(Healthcare Provider) CPR course. This study also seeks to establish a resuscitation training facility at Southern Regional Hospital in Dangriga, Belize to allow for continuing resuscitation skills training in a resource poor area.

Background:

With the support of the Rochester Non-profit InterVol, a connection was made with Dra. Melissa Espat, Chief Medical Officer at Southern Regional Hospital in Dangriga, Belize, Central America. Plans for a resuscitation training program were established and a study to potentially improve the retention of participants' CPR knowledge and skills were designed with the help of the University of Rochester Emergency Medicine study review committee. Equipment necessary to establish a resuscitation training center at Southern Regional Hospital, was generously donated by Rural Metro Medical Services of Rochester, New York, Rochester General Hospital, InterVol, Laerdal Medical AS, and the University of Rochester Medical Center. Additional support was provided by the Offices for Medical Education, the Center for Advocacy, Community Health, Education and Diversity and an anonymous donor. The study was approved by the University's Research Subjects Review Safety Board.

Methods:

Health Professionals at Southern Regional Hospital in Dangriga, Belize voluntarily enrolled in a

free-of-charge AHA 4.5-hour BLS for the HCP CPR course. Courses were offered by an AHA Instructor at Southern Regional Hospital during June and July of 2009. Reasonable efforts to maintain the AHA BLS course guidelines [5] included: distributing student course manuals two weeks prior to training, maintaining a student to instructor ratio of 6:1, providing a student to mannequin ratio of 3:1, providing each student with a pocket mask, utilization of a large video monitor for viewing the training video, and displaying the AHA training posters at time of training.

On the first day of the CPR course students were offered to voluntarily participate in this CPR study. If the student verbally consented to participate, a survey on previous CPR experiences was administered. Based on the current day of the study, participants would either receive no additional training materials (control) or a two-sided pocket-sized, laminated flashcard (experimental). This flashcard was provided prior to training, and contained the AHA Adult and Pediatric BLS CPR Algorithms in flow chart form (See Figures#7 and Figure #11 in AHA Student Manual [6]). After completion of the course, participants' CPR skills were assessed with the AHA's adult 1-rescuer CPR Skills test and CPR knowledge was assessed with the February 2006 AHA's written exam A or exam B. Selection of the multiple choice exam version was based on the number of CPR courses that had been offered in the study. The permutation of exam versions and flashcards allowed for block randomization of study participants. Participants were provided with remediation for all missed written questions and didactic skills.

Approximately four weeks later, healthcare providers were then offered, free-of-charge, one of the AHA advanced resuscitation training courses. When the study participants returned for the advanced training, voluntary participation in conclusion of the study was offered. If participants provided oral consent prior to advance training, a post-CPR course CPR experiences survey was conducted. The skills retention of the participants was re-evaluated using the AHA's adult 1-rescuer CPR skills test and their knowledge retention was evaluated using the alternative AHA multiple choice exam.

Data was compiled in a Microsoft excel database and all participants' identifying information was removed. Standard Excel statistics functions were used for data analysis. P-values were calculated using a two-tailed homoscedastic Student's T-test comparing the means of the experimental vs. the means of the control. The percentage of correct responses to a question were averaged between the groups and the odds of correctly responding was calculated (Experimental:Control).

Results:

Between June 16 and July 30, 2009, 82 students participated in the 4.5-hour AHA BLS for HCP CPR course. Of these 82 students, 49 participated (59.7% response) in the initial phase of the study. Study participants included 9 Doctors, 38 Nurses, and 2 Nurses Aids. 31% of participants had never taken a CPR course previously and 41% had only taken one pervious CPR course. The average time since the previous CPR course was 3.96 years. 73% of participants on average had witness CPR being performed on a patient 1.6 years previously.

The initial 49 participants average score on the first exam was an 81% ($\sigma=14\%$) giving a 55% pass rate using AHA criteria. 27 participants were randomized to exam A with an average 81% ($\sigma=13\%$) and 22 to exam B with an average 79% ($\sigma=16\%$, T-test $\mu_{\text{Exam A}}$ vs. $\mu_{\text{Exam B}}$ $p=0.55$). The 24 participants in the experimental group averaged 85% ($\sigma=11\%$) and 25 participants in the control group averaged 75% ($\sigma=15\%$, T-test μ_{Control} vs. $\mu_{\text{Experimental}}$ $p=0.01$).

There were 28 participants (57% returning on average 30 days later) who consented to the final phase of the study, which included 5 doctors, 22 nurses, and 1 nurse's aid. Of the returning participants 16 were in the experimental group (67% returning, 75% first exam pass rate) with an average first test score of 86% ($\sigma=10\%$) and 12 participants from the controls (48% returning, 42% first exam pass rate) with a first test score of 80% ($\sigma=12\%$, $p=0.11$). Participants from both groups had performed similarly on the first skills exam. In both groups the least correctly preformed skill ($\mu_{\text{correct preformed}}=46\%$) was to activate the emergency response system after verifying unresponsiveness in the victim.

On reevaluation, the experimental group scored an average of 72% with a 25% pass rate ($\sigma=19\%$)

and had average decrease in score of 15% ($\sigma=18\%$). The control group scored an average of 77% with a 42% pass rate ($\sigma=13\%$, $p=0.43$) and had an average decrease in score of 4% ($\sigma=14\%$, $p=0.05$). The least frequent, correctly answered questions were the same between the two groups. One exception was that the same questions were missed on the 1st exam. The least frequent, correctly answered questions concerned infant CPR sequencing ($\mu_{\text{correct}} = 29\%$, $OR=1.25$), defibrillation science ($\mu_{\text{correct}} = 32\%$, $OR=0.6$), ventilation sequencing ($\mu_{\text{correct}} = 43\%$, $OR= 1.05$), chest compression techniques ($\mu_{\text{correct}} = 61\%$, $OR=1.38$), airway assessment ($\mu_{\text{correct}} = 61\%$, $OR=1.05$), and AED sequencing ($\mu_{\text{correct}} = 68\%$, 1.03).

The skills least correctly performed or performed out of sequence were checking for a pulse ($\mu_{\text{correct}} = 32\%$, $OR= 1.5$), activating the emergency responses system ($\mu_{\text{correct}} = 36\%$, $OR=1.1$), opening the airway using a head tilt-chin lift ($\mu_{\text{correct}} = 61\%$, $OR=1.29$), and checking for breathing ($\mu_{\text{correct}} = 68\%$, 2.1). It should be noted for the remaining skills the experimental group was more likely to incorrectly perform a skill (0.75-0.9).

Conclusion:

Providing a laminated flashcard with the steps of adult and child CPR did not sufficiently maintain the retention of CPR knowledge (72% vs. 77% $p=0.43$) or skills 30 days after initial testing. Initial data suggest the experimental group had a statistically improved first exam scores of 85% vs. 75% $p=0.01$. On reevaluation, the experimental group had a decrease in exam score of 15% as compared to the 4% ($p=0.05$) decrease in the controls scores, yielding no improvement in CPR knowledge. Data also suggested that the most frequently missed exam questions and miss performed skills were less frequently missed in the experimental group as compared to the controls. This study also suggested that providing a laminated flashcard improved participant's willingness to participate in research 67% returning vs. 48% returning.

Perhaps the most powerful data collected was the sense of confidence provided to those that utilized CPR after training. In the pre-course survey participants were asked to describe feelings they had experienced while witnessing a resuscitation attempt of a patient. One participant responded "I felt unhappy with myself as I could not help the patient." After this participant completed the original course they performed CPR on a neonatal patient. In the post-course survey when asked about feelings experienced during CPR the participant replied "I feel great because the CPR I performed was effective on the patient." Future studies with greater power may be able to couple the improvement in exam score provided with a pocket laminated CPR flowchart with another technique to improve CPR knowledge and skills retention.

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International Medicine Research



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Studying the Impact of the Nutrition Transition and Globalization on Diabetes Management in South Korean Diabetics (Seoul, Korea)

Introduction and Background:

Diabetes is a significant health concern for Koreans. The prevalence of diabetes and obesity in Korea has been increasing rapidly over the past 30 years, with the recent KNHANES (Korean National Health and Nutrition Examination Survey) reporting an increase in diabetes prevalence from less than 1% in 1970s to 7.6% in 2001, and in rate of obesity from 26.3% in 1998 to 31.7% in 2005 (3,5). In addition, studies have shown that Asians develop diabetes at a lower BMI and at a younger age, and suffer longer from complications than those of the European descent, drawing more attention to Korean diabetes epidemic (1,2)

The rise in the prevalence of obesity and other nutrition-related diseases correlate highly with the rapid globalization and economic growth that has occurred in Korea since the 1970s (4). These phenomena have led to a shift in the infrastructure, food supply, and technology. Koreans now consume less complex carbohydrates and eat high density diet, with fat derived energy intake increasing from 6.2% to 18.8% from 1940 to 1995 (4). People have also adopted more sedentary lifestyle.

Furthermore, studies conducted in Japan, Finland, and India show that programs aimed at adjusting lifestyle and diet can lower the development of diabetes in high risk individuals and reduce the mortality rate (2). Therefore, understanding the nutrition transition and culture can help reduce the rising rates of diabetes and obesity in Korea.

Objective:

This study looks at how the nutrition transition and changes thereafter have shifted the way people approach and manage diabetes, especially focusing on the challenges diabetics face. The results from this study can be used to help clinicians develop methods to effectively manage diabetes in Korea, raise public awareness of western influences on Korean diet, and translate the findings to managing diabetes in Korean American diabetics in the US.

Methods:

A total of 13 diabetic (7 men, 6 women) between ages 55-80 were recruited from Gangnam community clinic in Seoul, Korea. In-depth, individual interviews were conducted in order to assess their lifestyle, diet, management and treatment of diabetes, as well as changes in these aspects over time. A semi-structure interview guide and dietary recall were utilized.

Results:

Data was organized into three categories:

- 1) **Demographic and social characteristics:** Living situation, employment, social habits and culture play a significant role in determining the diet and exercise patterns of Korean diabetics. Women living away from children cooked infrequently and consumed more processed high carbohydrate items. Patients who were employed dined out and consumed alcohol more frequently than those unemployed.
- 2) **Diagnosis and management of diabetes:** Despite the different demography and history of illness, the subjects shared a common approach to their diabetes management. Most patients took diabetes medications, many without the knowledge of drug functions or the correct regimens. Majority of the patients focused on decreasing food intake as the main form of diet management, and many increased their vegetable intake. Almost everyone included exercise in their diabetes management, with almost half of the patients exercising 1-2hrs/day.
- 3) **Changes and barriers in diabetes control over time:** The amount of fast food consumption, as well as the frequency of dining out, has decreased over the decades in these patients, despite the increasing availability of western foods and number of restaurants in Korea. Patients report increased consumption of vegetables and traditional meals over the past few decades. Most people have indicated that managing appetite and portion size as major difficulty, and several report it as their biggest barrier. Other barriers include alcohol consumption, low income, and fatigue.

Conclusion:

Despite the numerous studies indicating the impact globalization and westernization have on Korean diabetes epidemic, these phenomena minimally influence the diet and diabetes management of Korean diabetics over age 55. In fact, this study shows that the consumption of traditional Korean food has increased within the past few decades, and the living situation, employment, social and drinking culture play a greater role in people's diet than the influx of fast food restaurants and western foods.

However, most diabetics do not have an accurate knowledge about the disease, drugs or nutrition. Many are consuming high carbohydrate foods and alcohol, without regular monitoring of their blood glucose levels. Therefore, patient education about disease pathogenesis and nutrition that is sensitive to age, eating and work culture, socioeconomic status and social habits, is needed to improve diabetic care in Korea.

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International Medicine Research



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Nosocomial tuberculosis in Lima, Peru: an assessment of health care workers' knowledge of pulmonary tuberculosis transmission and prevention

Introduction

Mycobacterium tuberculosis causes an airborne disease that killed 1.5 million people globally in 2006. While it is a disease that is less familiar to the United States, tuberculosis continues to plague less-developed countries. In particular, in 2003, Peru was one of the thirty countries most burdened by tuberculosis and one of the eight most burdened by multi-drug resistant tuberculosis (MDR-TB). Peru's incidence rate of tuberculosis was 162 per 100,000 population per year and mortality rate was 16 per 100,000 population per year in 2006. Despite measures that have been taken to reduce the transmission of tuberculosis in the community, one sector of society continues to be at higher risk of contracting it: health care workers. Nurses, physicians in internal medicine and specialists in respiratory medicine, pathologists and lab workers were found to be at greatest risk because of their prolonged and frequent exposure to either infected patients or the active bacterial culture.

Objective

To assess the level of knowledge various health care workers at a Peruvian hospital have regarding the proper preventative measures they should be taking when interacting with a patient suspected or confirmed to have tuberculosis.

Background

To reduce and ultimately prevent nosocomial transmission of tuberculosis to health care workers and the patient population there are three distinct principles that must be met. The first is that there exist policies and regulations outlined by federal and local governments that are then tailored by each hospital. These policies address the prevention measures shown by several studies to be important in reducing tuberculosis transmission in hospitals. The second principle is that health care workers must be knowledgeable of these policies in place. Thirdly, all parties must adhere to the hospital policies outlined. In order for the policies put in place to be effective, employees must not only be knowledgeable of them but also follow them. Knowing that regulations are in place in Peru as outlined by the Peruvian Ministry of Health, we will focus on the second principal. In studying health care worker awareness at the Hospital Nacional Dos de Mayo, a hospital in Lima, Peru with a large tuberculosis-infected patient population, we will identify health care workers' level of knowledge of hospital policies.

Methods

This was a cross-sectional study performed at the Hospital Nacional Dos de Mayo in Lima, Peru. Health care workers (HCWs) surveyed include attending physicians, residents, interns, nurses and technicians. The PASS 2008 software program was used to randomly select a proportionate number of each category of HCWs to be surveyed. A total of 190 HCWs were surveyed: 34 attendings, 24 residents, 19 interns, 40

nurses, and 73 technicians, and 177 questionnaires had all questions completed. Surveys were in the form of a multiple choice questionnaire in Spanish consisting of 10 questions prepared based on regulations and guidelines outlined by the Peruvian Ministry of Health. Descriptive statistics and odds ratio with 95% confidence intervals were calculated to determine preliminary trends and significance of data.

Results:

The questionnaire was graded out of a total of 50 points, with each correct answer being worth one point and zero points awarded for incorrect answers. Because the questionnaire had never been used in previous studies or standardized to assess what the cut-off mark should be for an “adequate” level of knowledge of tuberculosis, the authors arbitrarily decided to consider scores above 35/50, or 70%, an adequate level. Of the males who completed the entire questionnaire, 72% scored greater than 35 and 48% of the females who completed the entire questionnaire). Males had 2.5 times the odds as females of scoring above 35 on the questionnaire (odds ratio, OR= 2.5 (95% confidence interval (CI) 1.31 to 4.94]. We also looked at how levels of knowledge varied according to occupation; an adequate level was shown by 71% of attending physicians, 83% of residents, 68% of interns, 57% of nurses, and 33% of technicians. There were greater odds that attendings (OR=4.9, 95% CI: 1.99 to 12.1), residents (OR=9.7, 95% CI: 2.9 to 32.2), interns (OR=4.4, 95% CI: 1.5 to 13.3) and nurses (OR=2.7, 95% CI: 1.2 to 6.2) would have an adequate level of tuberculosis knowledge compared to technicians. An association was also found between receiving tuberculosis-related training workshops and having an adequate level of knowledge of tuberculosis prevention and transmission (OR=2.0 95% CI: 1.07 to 3.71). We found that 64% of participants received some sort of training outside of their technical school or university education, and 61% of them had an adequate level of knowledge while 44% of those who did not receive training also showed an adequate level of tuberculosis knowledge.

Conclusion

Mycobacterium tuberculosis causes the infectious disease, tuberculosis that has continued to spread in less developed countries such as Peru. The particular phenomenon of tuberculosis transmission to health care workers has several implications regarding the preventative measures that need to be taken by the general population and health care workers so that tuberculosis does not reach epidemic proportions. Overall, technicians had the lowest percentage of workers with an adequate fund of tuberculosis knowledge; the odds were greater that all other groups of HCWs would have adequate levels of knowledge compared to the technicians. The association that existed between receiving training or attending tuberculosis-related workshops and having an adequate level of knowledge leads us to believe that the Hospital Nacional Dos de Mayo needs to have a greater emphasis in training all HCWs about tuberculosis, its transmission, and preventive measures. To find what the most significant factors are in preventing the nosocomial transmission of tuberculosis we see it beneficial to perform future studies that include assessment of the actual training programs that the hospital provides and an evaluation of health care worker adherence to federal, state and hospital regulations and recommendations.

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International Medicine Research



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The decision to become a doctor: Graduate entry vs. student leaver programs

Introduction:

This study was designed to explore differences among medical students who have previously completed a university degree compared to those who entered medical school as student leavers (straight from high school).

Objective:

We examined student satisfaction of attending medical school as well as student confidence in their career path choice. We hope to gain insight into the different experiences of both subsets of students and the unique challenges they face in their pre-clinical careers. In addition, we aim to identify whether one group is more confident in their career choice, and perhaps was more prepared to make that decision when they did.

Background:

Multiple medical schools in Australia are in the midst of a fundamental change, moving from student leaver to graduate entry programs. There are questions as to whether older students who have completed a university degree are better prepared than high school students to make the decision to enter medicine, and whether they are more satisfied with their choice as a result.

Methods:

Five group interviews were arranged with students from four different medical schools: the University of Melbourne, Deakin University, and Monash University. Interviewed were both graduate entry and student leavers from the University of Melbourne, graduate entry students from Deakin University, and both graduate entry and student leavers from Monash University. Students were questioned on their motivations for entering medical school, how prepared they have felt during their current coursework, what other options they explored before matriculating, and whether they have ever regretted their decision to enter medical school.

Results:

Graduate entry students were more likely to state that they had always wanted to go into medicine, or

followed a science pathway through their undergraduate years which led them to medicine. They consistently expressed that if they had not been accepted into medical school, they would have tried again. Student leavers were more likely to have applied to medical schools due to medicine being the best opportunity at the time or due to influences of family members. This group was more likely to state that if they had not been accepted into medical school, they would have pursued a different career choice. Both groups of students expressed feelings of preparedness for their medical careers citing different reasons. Also, a much higher ratio of graduate entry students had exposure to medicine before making their decision.

Conclusion:

Graduate entry students and student leavers show many differences in what led them to a medical career. Student leavers were more likely to express interest in other career paths, which leads us to question their level of confidence in their choice. Further research should be carried out to quantitatively define differences among these groups, and to examine how they affect each group's decision to enter medical school and their educational experiences thereafter.



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Assessment on the preferred method for point of use intervention for improving water quality and community health in Cacha, Ecuador

BACKGROUND: Worldwide, 88 percent of diarrheal disease is attributed to unsafe water supply and inadequate sanitation and hygiene [1]. In Ecuador, diarrhea is one of the top reasons to seek ambulatory care. Diarrheal disease is more prevalent in rural indigenous communities than urban areas [2]. Conclusive evidence shows that low-technology, low-cost, household-level interventions can reduce the incidence of diarrhea [3]. To be successful, water treatment programs need to address barriers posed by cultural, behavioral and health-belief factors [4].

INTRODUCTION: Cacha is a rural, impoverished area in the Andean highlands that includes 23 communities and about 3,000 people, almost exclusively of indigenous ethnicities. Ground water is filtered through sand at a central distribution center before being delivered to communities and households, where it is often stored. Water is delivered to houses through outdoor spigots as houses lack indoor plumbing.

Problems with filtration, distribution, and handling of potable water all contribute to contaminations. Cacha residents are concerned about water-borne illnesses, as 69 – 80% of households expressed diarrhea as a concern [5, 6]. There are two communities which do not receive filtered water. Microbiology testing showed a significant coliform count (Mean \pm 95% CI = 4010 \pm 1117 / 100 mL)^{vii} at the source for one of these communities [5]. While the distribution center had non-significant coliform counts, slow-sand filtration does not filter out viruses. A significant coliform count (864.82 \pm 689.89) does exist at household spigots, suggesting that contaminations are introduced in the distribution pipes. Therefore, water treatment is necessary before consumption. Furthermore, mean coliform counts increase as water moves further from the source, with the biggest jump occurring between the spigot and storage containers [5]. Past studies in Cacha and recent systematic reviews suggest that point of use (POU) interventions are more effective methods for reducing morbidity due to water borne illnesses than interventions at the source [5, 6, 7].

OBJECTIVE: To assess feasibility of various POU interventions and develop a framework for implementing the most efficacious intervention.

METHODS: Brief oral surveys were administered in Quichua to respondents of at least 18 years of age at their homes via a translator. Questions were asked regarding their water supply, usage, transport, and storage, treatment methods, cleaning and hygiene habits, incidences of diarrhea, number of children in the household, cost of water and fuel, and willingness to spend more for cleaner water. Qualitative responses were analyzed and grouped into pre-determined categories. Households were chosen based on availability

of the residents and on recommendations by local leaders. In total, 32 households were chosen. In addition, four doctors providing healthcare to the Cacha were interviewed regarding perceived incidence of diarrheal disease, past water contaminations, and local attitudes towards water sanitation.

RESULTS: Food and water borne illnesses are prevalent in Cacha, with 27% of adults reporting acute stomach cramps, diarrhea, or vomiting twice or more on an average month. Children are also affected, as 38% of adults reported their children having the aforementioned acute symptoms twice or more on an average month. Doctors interviewed reported two instances of water source contamination in the past year that sent over hundred people to the hospital in the nearby town.

Because of significant coliform counts at the spigots, water treatment is necessary prior to consumption. However, 31% reported consistently boiling their water. No other water treatment methods were cited. Change in taste and inconvenience were two common reasons for not boiling. No one expressed the cost of fuel as a concern.

Improper hygiene habits may contribute to the large jump in coliform count from spigot to POU. From the outdoor spigot, 87.5% of respondents used a bucket or other large opening containers to transport water. From there, 56% of them put their hand directly in the container to obtain water for drinking or cooking. Only 19% used bleach to wash their containers, and 25% did not consistently report washing their hands with soap prior to contact with water. The usage of storage containers is common (37% stored outside their homes, and 26% stored inside their homes) because water is not always delivered due to problems in the distribution system. Only 10% of these containers are cleaned with bleach. Storing contaminated water leads to microorganism growth, and may contribute to the large jump in coliform count from spigot to POU.

POU interventions we initially proposed included the use of ceramic filters, slow-sand filters, and storage containers with narrow openings, all to be implemented at the household level. However, with the high risk of recontamination and sufficient resources in each household to boil water, we feel that education is the best intervention. A majority of respondents (77.1%) reported learning about water sanitation from healthcare worker or organization [6]. Two forums are community based health lessons given by doctors and doctor visits. We prepared a summary of our data and guidelines for the doctors. Furthermore, a community based change is needed. Not every community is affected equally. Doctors in different clinics the reported the percentage of visits related to diarrheal disease to be as low as 10% and as high as 40%. Individual communities can help reduce contamination by cleaning community tanks and flushing distribution lines with bleach. We were able to present our data to a group of community leaders. Ideally, in the future, improvements can be made in the filtration and delivery system to make sure clean water is delivered inside everyone's homes.

CONCLUSION: Based on the studies conducted by our group and two other student groups from the University of Rochester School of Medicine, we suggest that interventions to reduce the incidence of water-borne illnesses in Cacha, Ecuador should focus on education on boiling water prior to consumption and proper hygiene practices to prevent recontamination. We believe that these simple and common sense point of use (POU) interventions will be more efficacious than more technologically based interventions. Further studies can focus on the efficacy of proper education.

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Year-Out Research

Haggerty-Friedman Fellowship in Developmental and Behavioral Pediatrics

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The Burden of Cancer in Children: The Impact and Content of Video Illness Narratives

AIM: In order to gain a greater understanding of the full experience of children with life-threatening illness, this study provided video cameras to 10-18 year olds in active treatment for cancer, and instructed them to make video illness narratives over the course of 1-3 months. We hypothesized that these narratives would provide insight into the lives of children with cancer, increase their self esteem, decrease symptoms of distress, and improve communication between patients and their doctors.

METHODS: Six children and adolescents with cancer in treatment at Galisano Children's Hospital at Strong were recruited and provided with video cameras to make video illness narratives. The narratives were studied as an intervention; each of the participants were administered a measure of physical symptoms (The Memorial Symptom Assessment Scale 10-18) and a measure of self-esteem (the Rosenberg Self-Esteem Scale). The video narratives were also analyzed for content by theme in order to understand the participants' experiences in their own words.

RESULTS: Of the 6 participants, 2 ended their narratives before they were completed. All participants did not complete all recommended tasks. There was a decrease in symptoms, and a decrease in distress from these symptoms after participation. Changes in self esteem were small, but present in the majority of participants. Themes addressed were diverse and included medical knowledge and self care, hospitalization, family dynamics, body image, developmental issues of adolescence, and schoolwork, among many others.

CONCLUSION: Participation by children with cancer in active treatment in a video illness narrative project showed improvement in objective measures of symptom distress and self esteem, and the narratives conveyed both their enjoyment of participation, and revealed their experiences. The themes that emerged represented both normal adolescent development, and how illness affects the psychosocial milieu of children with cancer.



Year-Out Research

Offices for Medical Education Student Research Fellowship

Brian Jones, MS2 Preceptor:
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Tau pathology is a well-established characteristic of Alzheimer's disease. The role of Tau in initiation and progression of Alzheimer's disease however, remains an area of intensive scientific investigation. To date, animal models of Tau's role in the disease have used standard molecular biology techniques resulting in hyperphysiological levels of Tau protein expression. Using a newly developed system for single copy genomic integration of a transgene in *C. elegans*¹, we were able to create a model in which Tau is expressed at physiologic levels under the control of the *mec-7* promoter in touch cells. The well defined morphology and behavioral output of these neurons make them ideal candidates for the investigation of a role for Tau prior to the appearance of major structural abnormalities such as neurofibrillary tangles (NFTs).

Our results indicate that physiologic levels of wildtype Tau expression do not cause functional deficits in the *C. elegans* gentle touch response. However, expression of a Tau mutant that is truncated at the C-terminus to mimic the caspase-cleaved form is sufficient to cause a progressive, age-related touch deficit despite the apparent lack of NFTs or concurrent cell death. This result suggests that soluble forms of mutant Tau play a significant role in the emergence of cellular dysfunction and that continued insult from soluble Tau over time exacerbates the problem. Interestingly, the touch deficit seems to be significantly worse in anatomical regions innervated by long axonal projections versus those innervated by short projections. This observation suggests that longer neuronal projections are more vulnerable to the aberrant effects of mutant Tau. The mechanism underlying this apparent susceptibility however, needs further elucidation.

This genetic model will allow us to test how physiologic events such as protein processing influence Tau toxicity without the confounding detrimental effects of protein overexpression, and to assay the early contributions of Tau to neuronal dysfunction prior to cell death. Adding to the power of our system is the presence of a photoconvertible fluorescent protein tag (Dendra) that will allow us to explore differences in cellular turnover of our Tau constructs in various processing mutants (ie ubiquitin protease system vs. autophagy). Our ultimate aim is to define the mechanisms contributing to Tau turnover in neurons and to identify the functional consequences that occur as a result of aberrant Tau processing.

Frøkjær-Jensen et al. Nat Genet. 2008 Nov;40(11):1375-83



Year-Out Research

Offices for Medical Education Student Research Fellowship

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Howard N. Langstein, MD

Chief of the Division of Plastic Surgery University of Rochester Medical Center

A Novel Animal Model to Study Capsular Contracture Utilizing Gamma Radiation and Livescan μ CT Technology.

Background

Capsular contracture remains one of the major problems following prosthetic implantation of the breast, especially in post-mastectomy breast reconstruction patients receiving radiation therapy. Advances in this area have been hampered by the absence of an acceptable animal model. This study evaluates a new murine model in order to facilitate research into the cellular and molecular pathways underlying capsular contracture and provide a surrogate to evaluate potential therapies. *Methods*

On day 0, mice were implanted with bilateral silicone gel implants (Mentor, Inc.). Postoperatively, animals were imaged using livescan μ CT. Animals in the irradiation group then received a 10 gray directed radiation dose from a slit beam cesium source. On days 21, 28, 35, and 42 both irradiated and non-irradiated animals were imaged again. Animals were sacrificed for histological evaluation of day 21, 28, 35 and 42.

Results

Implants from the non-irradiated group demonstrated very little change in contour from day 0 through day 42 on μ CT. In contrast, irradiated implants demonstrated consistent shape deformation and irregularities in contour beginning at day 21 and continuing through day 42. Non-irradiated histological specimens showed thin, uniform, and well organized collagen capsule surrounding the implants that was a consistent thickness from day 21 through day 42. Irradiated specimens had irregular capsules composed of disorganized collagen fibers with inflammatory infiltrates that grew in thickness at each time point from day 21 to day 42.

Conclusions

Here, we introduce a novel animal model to study capsular contracture. This model is the first of its kind to use radiation to induce and livescan μ CT to evaluate capsular contracture. Radiation was shown to cause reproducible changes that can be consistently evaluated with μ CT and histology. Future studies with this model will study the cellular and molecular mechanisms underlying capsular contracture using knockout and transgenic mouse strains.



Year-Out Research

Offices for Medical Education Student Research Fellowship

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Longitudinal Variation in Group B Streptococcal Status in Preterm Patients

Background: Prior studies of term gestations revealed 96% concordance between a negative Group B Streptococcus (GBS) culture obtained within 4 weeks of delivery and culture status at the time of delivery. However, the concordance of GBS cultures for patients at risk of preterm birth has not been established. A pilot study at our institution revealed 4 of 19 patients (21%) with symptomatic preterm labor (PTL) or preterm rupture of membranes (PPROM) converted from negative GBS status to positive GBS status within 2 weeks. Additionally, we observed a non-significant but marked decrease in the period of latency for subjects that converted. **Objective:** The purpose of this study was to establish the longitudinal concordance of Group B Streptococcus (GBS) cultures in patients with PTL/PPROM compared to term and preterm controls. Our secondary aim was to quantify the impact of conversion on the period of latency. **Study Design:** This was a prospective observational study of the results of weekly rectovaginal GBS cultures obtained from patients admitted for PTL or PPROM. Conversions to positive were compared to asymptomatic preterm and term controls concurrently enrolled.

Results: Conversion from a negative to positive GBS culture within 4 weeks occurred in 6 of 50 PTL/PPROM patients (12.0%), 10 of 52 (19.2%) term controls and 4 of 26 (15.4%) preterm controls. There was no significant difference in conversion rate for the three groups (P value= 0.603). Mean interval to conversion was 12.8 days for PTL/PPROM cases, 10.4 days for term controls and 24.0 days for preterm controls. There was no difference in the latency between converters and non-converters in the PTL/PPROM cases.

Conclusion: There was no difference in conversion to positive GBS culture between PTL/PPROM patients and term and preterm controls. However, the conversion rate is approximately 5 times higher than prior reports. Conversion to GBS positive status did not affect latency. These results call into question the reliability of GBS cultures obtained even 2 weeks prior to delivery.



Year-Out Research

Offices for Medical Education Student Research Fellowship

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Colleen Fogarty, MD, MSc

Assistant Residency Director, Director of Community Medicine, & Assistant Professor of Family Medicine

Department of Family Medicine

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Doctors for Global Health: A Model for Sustainable Grass Roots International Medicine

Introduction: International medicine is a diverse field, encompassing various methods of improving health in developing countries. Many people are familiar with Doctors without Borders and their model of providing medical relief in situations of conflict or acute need. Another common model is the ‘medical mission,’ or a short venture into a country to provide acute care, either surgical or medical, once per year. Although these interventions provide some clear benefits, especially in situations of acute need, the downside of what some consider to be ‘medical tourism’ is often overlooked. For example, what happens when a large group of patients received treatment for which they have no long-term follow-up? Will one month of anti-hypertensives change a patient’s outcomes when he may not be able to fill the next month’s prescription? Even if follow-up is available, many patients do not understand the treatment given to them or their diagnosis, so their treatment may end once the medical mission has left. This cohort of only partially treated patients becomes an additional burden on their already over-stretched, low resource, local health care system. Are these situations the best use of our philanthropy, and more importantly, are we thinking practically about the communities we visit? How can we change the structure of how we provide medical care in international settings?

Objective: Given my interest in international health, specifically in working with underserved Latino populations in the US and abroad, I spent half of my year-out volunteering for the international non-profit organization, Doctors for Global Health (DGH). My main objective was to gain experience working for an aid organization whose goals are to provide sustainable, long-term, grass roots solutions to improve not only health but basic human rights in the developing world. DGH believes that change must come from within, and thus they only become involved in communities they have been invited to work with, working alongside locals toward the goals established by their communities. It seems that each community DGH accompanies tends to share a common thread: the health inequities they face are symptoms of larger social, economic and political injustices. Thus DGH works to improve community health not only by improving access to quality health care, but also by developing educational opportunities and avenues for artistic expression, as well as raising awareness of health and other human rights.

Background: The organization DGH was born out of work that began in the communities of Estancia, El Salvador, a remote mountainous area that was devastated by the country’s twelve-year civil war. To this day Estancia and the rural residents of Morazán struggle with little infrastructure, including poorly maintained roads, and a lack of running water, electricity, and basic education. Ever since the end of the war in 1992, DGH has been accompanying the people of Estancia, first by helping to build a bridge that connects these remote villages with the rest of urban El Salvador, and by training community health care promoters. Since then they have taken part in projects in the areas of health, education, environment,

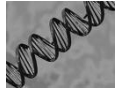
agriculture, income generation and community development. In 2001 members of the Estancia community, who were formerly largely illiterate, uneducated, and from their country's lowest socioeconomic class, joined together to form their own nonprofit organization, La Asociación de Campesinos para el Desarrollo Humano (CDH). Their 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." DGH supports CDH as it runs the local community health center, Clínica CAIPES, and six childhood development centers (CIDs or kinders), as well as broader community health and development projects.

Methods: As a medical volunteer, I worked alongside community health promoters to provide clinical and ancillary services in the Clínica CAIPES. We attended to 11-25 patients per day, including women, children, and adults, with both acute and chronic problems, as well as attended to clinic maintenance, including stocking the pharmacy, dispensing medications, sterilizing equipment, etc. We were also in charge of a specialist referral assistance program to aid local patients in accessing specialist care. To do this we set patients up with appointments, taught them how to navigate the transportation system, and ensured their follow up care, providing any necessary financial support along the way. We also did monthly public health talks, events for the elderly, made home visits, lead a youth group, and taught yoga to women who suffered from anxiety, depression, and PTSD. I was also exposed to and able to take part in some of the other CDH activities, such as the annual dental campaign, a pediatric malnutrition tracking and supplementation program including maternal education and home visits, and improving environmental health through building latrines, roofs, and vaccinating animals.

Results: The combined success of CDH and DGH in improving the health of the Estancia community has been profound. Over the years childhood nutrition has improved dramatically, and many preventable diseases have all but been eliminated through these comprehensive, community-based efforts. The clinic's success is clear, as our patient base has nearly tripled over the past year, and we have started to draw patients from distant geographic areas. During my time there I was blessed to experience the fulfillment of being a community physician-in-training, as well as help many individual patients receive appropriate treatment for their complex medical problems.

Conclusion: Comprehensive grass roots efforts supported by international aid organizations can be successful in improving the health of their local community. Although this model requires greater resources and long-term commitment, it merits more ideological and financial support from the international community.

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Year-Out Research

Offices for Medical Education Student Research Fellowship

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Community Health Worker Follow-Up and Compliance with In-Home Ceramic Water Filters: A Randomized, Controlled Trial in Rural Honduras

BACKGROUND: Simple, low-cost household-level water treatment technologies effectively reduce diarrheal disease burden.^{1,2,3} Such interventions achieve greater disease reduction when a larger proportion of participants continue using the device properly, that is, they remain compliant.² While it is known that static factors such as monetary investment, unimproved water source, less time since procurement and prior sanitation and hygiene knowledge are all related to higher compliance, no research has explored how changeable factors, such as the implementation program, affect compliance.⁴

OBJECTIVES: This study sought to elucidate whether or not household-level follow-up improves compliance with an in-home ceramic water filter, as compared to the standard practice of a single educational session.

METHODS: All households in a poor, rural community in Honduras were offered the opportunity to buy a “Potters for Peace” style filter for a nominal cost. Participating households were randomly assigned to one of two groups: Control group households received a single educational session emphasizing proper filter maintenance and drinking water health knowledge, while follow-up households received the educational session as well as three monthly educational home visits by a community health worker. At three and six months post-distribution, household drinking water was sampled and filter and water-related health knowledge were assessed. General coliform colonies per 100ml and *Escherichia Coli* colonies per 100ml were used as surrogate measures of compliance in order to capture both improper usage and complete non-compliance. An internal control for intervention efficacy was obtained by sampling source water at each follow-up point. The study was powered to detect an 85% reduction in non-compliance in the follow-up group.

RESULTS: The 37 control households were not different in any baseline measure from the 35 follow-up households, including bacterial contamination of drinking water (geometric mean, *E. Coli* 14.9 versus 22.4; $P=.23$ and general coliform, 1454.4 versus 1695.6; $P=.37$). Geometric mean *E. Coli* counts for follow-up and control groups were not statistically different at three months post-distribution (1.4 [95% CI: 0.0-2.8] versus 1.4; 95% CI: 0.1-2.8; $P=.46$) nor at six months (2.5 [95% CI: 0.6-4.3] versus 3.0 [95% CI: 1.2-4.9]; $P=.33$). General coliform count geometric means also did not differ between follow-up and control groups at three months (1.4 [95% CI: -0.1-2.8] versus 1.7 [95% CI: 0.1-3.4]; $P=.24$) or six months (5.5 [95% CI: 3.3-7.6] versus 5.5 [95% CI: 3.4-7.7]; $P=.49$). At both three and six months, actual drinking water from both groups had significantly fewer *E. coli* and general coliforms compared to pre-filtered water ($P < .01$). Both groups had equal and high levels of filter and health related knowledge.

CONCLUSION: While in-home ceramic filters are effective at reducing the bacterial contamination of drinking water, educational monthly follow-up does not appear to improve compliance compared to the standard single educational session. Possible reasons for this apparent lack of benefit include: a single educational session may be sufficient to teach the needed health messages, cross-talk between control and follow-up households may distribute the knowledge among all participants, a smaller benefit not detectable by the power of this study may exist, or equally-distributed benefits of filtration, such as improved water flavor and temperature, may actually provide the most powerful motivator for continued usage. Since this study gives the first evidence that the common practice of educational follow-up does not improve compliance, further investigation should replicate these findings with the aforementioned issues in mind.

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Year-Out Research

Offices for Medical Education Student Research Fellowship

Rebecca Ryan, MS4 Preceptor:

Dr. Rachael Phelps

Director of Medical Services Planned Parenthood

Community Health Workers: Bridging the Gap

Introduction: Community health workers (CHWs) are a powerful means of addressing health disparities in underserved communities (1). They are trusted lay members of the community they serve and therefore share language, culture, socioeconomic, and experiential characteristics with their target population (2,3). They are a growing entity in the American healthcare system in large part because of their ability to “bridge the gap” between medical providers and communities (4).

Objectives: To explore the utilization of CHWs by the medical system in diverse settings and populations as well as to develop a functional knowledge of CHW roles and how they can be incorporated into medical practice.

Methods: I rotated through health centers that employ CHWs in rural Alaska, rural India, inner-city India, and along the Texas/Mexico border. During these rotations I worked directly with CHWs and physicians. I did multiple key informant interviews with CHWs, providers, and community members to learn about their CHW programs.

Results:

- Nome, Alaska-Community health workers live and work in isolated communities providing basic patient care. They communicate daily with providers at the central hospital via telemedicine to discuss patient encounters, prescriptions, and follow-up. They primarily provide direct patient services in addition to some educational outreach work.
- India-CHWs are utilized particularly in rural centers, but also in urban “slums.” One of the primary goals of CHWs are to reduce the birth rate and maternal mortality through direct family planning services. They also perform extensive educational work in sanitation, malaria, tuberculosis, HIV, and malnutrition. They link people with needed medical services.
- Texas (Texas/Mexico border)-CHWs work with recent Mexican immigrants in economically disadvantaged neighborhoods. They primarily provide disease-focused educational outreach, as well as information about accessing medical services. They work closely with diabetic patients making regular house-calls to do glucose checks and provide diabetic counseling

Conclusion: CHWs are valuable outreach agents in underserved communities where they are able to improve access to medical care and provide culturally appropriate health education. The exact services they provide and the training they receive differs greatly amongst different programs lending to increased flexibility to meet the specific needs of the community. CHWs have insight into and functional knowledge about their community that providers are rarely able to duplicate. As a result, CHWs can and are used by some primary care institutions as a means of learning about the communities they work, performing needs assessments, raising health literacy and empowerment, and facilitating improved access to care.

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Year-Out Research

Fellowship in Medical Humanities

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Department of Family Medicine

Cecile Carson MD Adjunct faculty
Department of Medical Humanities

Michael Milano MD University of Rochester
Department of Radiation Oncology

Impact of existential well-being and disease stage on quality of life among patients receiving radiation therapy for cancer

Background: People who are living with cancer often have compromised quality of life due to a variety of bio-psycho-socio-spiritual factors. Previous studies that explore existential issues focus primarily on patients at the end of life. The impact of existential issues on quality of life across all stages of disease has not been well described.

Objectives: To compare existential well-being to other domains which contribute to self-assessed quality of life (QOL), and to explore the interaction between existential well-being and disease stage on QOL.

Methods: We surveyed 101 people in radiation treatment for cancer at the University of Rochester with the SF-12 Health Survey and the McGill Quality of Life Questionnaire (MQOL) which is comprised of a single-item scale measuring global QOL as well as 5 subscales: physical symptoms; physical well-being; psychological; existential; support. Disease stage was self-reported. Our two QOL measures were the SF-12 and the single-item scale from the MQOL. We evaluated (1) the relationship of the existential well-being subscale to the SF-12 and single-item scale measures as compared to the other MQOL subscales, (2) the differences global and subscale QOL scores between early and advanced stages, and (3) the interaction between stage and existential well-being in predicting QOL.

Results: Existential well-being was a more powerful predictor for QOL than disease stage. Also, the MQOL existential and physical well-being subscales had significantly stronger correlation with both SF-12 and global single-item QOL scores than physical symptoms, psychological, and support subscales. Physical well-being was the subscale most strongly correlated with both QOL measures. There was no significant difference in scores on any MQOL subscale between early and advanced stages. There was also no difference between single-item scale QOL scores across stage groups, however SF-12 scores were significantly higher in early stage subjects.

Conclusions: Existential well-being plays a more significant role in determining QOL in people living with cancer than stage of disease. This sense of meaning and purpose may be constant throughout progression of disease and contributes more to a single-item global QOL rating than severity of physical symptoms. Further research should explore the impact of increased attention to existential well-being throughout the full spectrum of disease.



Year-Out Research

David Hamilton Smith Fellowship

Joanna Walker, CC3

Preceptors:

Norma B Lerner, MD, MPH Jill Cholette, MD

University of Rochester Medical Center

Department of Pediatrics: Hematology/Oncology, Critical Care

Risk Indicators for Central Venous Catheter-Related Thrombosis in Critically Ill Children

Introduction: Thromboembolic disease has been documented with increasing frequency in children and is currently one of the most common complications in hospitalized infants and children¹⁻³. Central venous catheters (CVC) are the most frequent cause of deep venous thrombosis (DVT) and pulmonary embolism in children⁴⁻⁷. There is little pediatric-specific information regarding the pathophysiology and risk prediction of CVC-related thrombosis^{2, 3, 5, 8, 9}.

Objectives: The primary aim of this study was to obtain pilot data regarding risk indicators for CVC-related thrombosis in children in the critical care setting. Markers of inflammation (wide-range C-reactive protein (wCRP) and soluble CD40 ligand (sCD40L)) and platelet activation and aggregation (urinary 11-dehydro thromboxane B2 (uTxB2), VerifyNow units, and sCD40L) were assessed for an association with thrombus development. Secondary objectives were to gain information regarding the potential roles of inflammation and platelet activation in the pathophysiology of venous thrombosis, and to establish the incidence of CVC-related thrombus in a single institution Pediatric Intensive Care Unit (PICU).

Methods: A prospective single-institution observational study was performed at the Golisano's Children's Hospital at Strong (GCHS) PICU October 2008 through July 2009. Subjects were children age newborn to 17.99 years old who were admitted to the PICU and estimated by the intensivist to require a CVC for at least 48 hours.

Study blood and urine samples were collected at three time points: 1) within 90 minutes of catheter insertion (blood) and 90 minutes to 5 hours following insertion (urine), 2) between days 3 and 5 following CVC insertion, and 3) prior to CVC removal or patient discharge. Subject demographics, pertinent clinical data, and CVC characteristics were documented. Patients were regularly assessed for signs and symptoms of VTE (pain, redness, swelling, discoloration, and ulceration). Doppler ultrasonography was performed following CVC removal or prior to patient discharge. One of two experienced radiologists formally interpreted the grey scale and Duplex ultrasonography and thrombi were categorized as superficial or deep, and occlusive or nonocclusive.

Results: Twenty-eight subjects were enrolled and 30 CVC's were studied.

Subject Characteristics: The mean subject age was 5.84 years (range 0.04 to 17.66 years). The most common primary diagnosis was infection (13 (46%)) followed by trauma (4 (14%)). Five subjects had a history of previous VTE (18%). Twenty-four of the 28 patients survived to discharge (86%).

CVC Characteristics: Sixteen of the 30 CVCs were central and 14 were peripherally inserted central catheters (PICCs). Line malfunction occurred in 46% of the studied CVCs and catheter-associated sepsis occurred in 2 (7%). The mean duration of catheter placement was 10.4 days (range of 1 to 25 days).

Thrombosis: Thirteen (65%) of 20 ultrasounds were abnormal studies. Ten (50%) demonstrated a DVT and three (15%) displayed superficial venous thrombosis. Three (30%) of the 10 DVT's were symptomatic and clinically detected, the remaining seven (70%) were asymptomatic. **Correlations and Trends:** There was a nearly significant positive correlation between the day 3-5 wrCRP level and the development of a DVT. (Spearman's: $r=0.536$, $p=0.059$). When subjects with DVT were compared to those without, the difference in day 3-5 median wrCRP was also nearly significant (Mann-Whitney: $z=1.857$, $p=0.063$; DVT group median CRP: 107.6 mg/L; No DVT group median CRP: 38.8 mg/L). The CRP level decreased significantly from CVC insertion to day 3-5 in the No DVT group (Wilcoxon Signed Rank: $z=2.028$, $p=0.043$) but no such trend existed in the DVT group ($z=0.314$, $p=0.753$). There were no trends toward statistically significant correlations between sCD40L, uTxB2, or VerifyNow units and DVT. Platelet number and platelet aggregation increased between CVC insertion and the day 3-5 measurement and platelet number increased between day 3-5 and CVC withdrawal/patient discharge in all subjects (Wilcoxon Signed Ranks: $z=3.285$, $p=0.001$; $z=2.166$, $p=0.03$; $z=1.988$, $p=0.047$, respectively). Separate group analysis revealed a significant increase in platelet number between CVC insertion and withdrawal/patient discharge in the No DVT group only (Wilcoxon Signed Rank: No DVT group $z=2.366$, $p=0.018$; DVT group $z=1.481$, $p=0.139$). Urinary TxB2 decreased between CVC insertion and withdrawal/patient discharge in all subjects (Wilcoxon Signed Rank: $z=2.093$, $p=0.036$).

Conclusions: Central Venous Catheter-related DVT in critically ill children is a common complication, occurring in 50% of cases in our institution. The majority of DVT's are clinically occult and require imaging to diagnose. Patients with prolonged inflammation as evidenced by an elevated CRP lasting 3-5 days following insertion of the CVC may be at increased risk of developing a DVT. Future studies with greater power will be necessary to examine and substantiate these correlations and trends.

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