



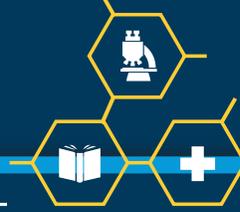
GW RESEARCH DAYS

— WEDNESDAY, APRIL 5, 2017

HEALTH & MEDICINE RESEARCH DAY

THE GEORGE WASHINGTON UNIVERSITY

WASHINGTON, DC



GW RESEARCH DAYS

2017

HEALTH & MEDICINE RESEARCH DAY

WEDNESDAY, APRIL 5, 2017

MARVIN CENTER

800 21ST STREET, NW, 3RD FLOOR

8:00-9:00 a.m. Posters Setup (*Grand and Continental Ballrooms*)

JACK MORTON AUDITORIUM

805 21ST STREET, NW

8:00-9:00 a.m. Registration and Breakfast

9:00-9:05 a.m. Welcome to Research Days 2017

Jeffrey S. Akman, MD
*Vice President for Health Affairs and Dean,
School of Medicine and Health Sciences*

9:05-9:10 a.m. Introduction of Keynote Address

Paul Brindley, PhD
*Professor of Microbiology, Immunology, and Tropical
Medicine, School of Medicine and Health Sciences
The George Washington University*

9:10-10:00 a.m. Keynote Address

Christopher Plowe, MD, MPH, FASTMH
*Frank M. Calia, MD Professor of Medicine
Founding Director, Institute for Global Health
Director, Division of Malaria Research
University of Maryland School of Medicine*

*"The Science and Politics of Malaria Elimination
in Myanmar"*

10:00-10:30 a.m. Coffee break

10:30-11:30 a.m. William Beaumont Research Award
Oral Presentations

Moderators: Michael Froehlich and Jacob Rubin

Lauren Jacobs
*"Germline ETV6 mutations confer susceptibility to acute
lymphoblastic leukemia and thrombocytopenia"*

Brendan Campbell
*"Less than one third of high-risk patients eligible for
hepatitis c virus screening received appropriate testing:
A community-based safety-net hospital experience"*

Sharjeel Chaudhry
*"Protecting the endothelium from thromboinflammatory
injury using parmodulins"*

MARVIN CENTER

800 21ST STREET, NW, 3RD FLOOR

12:30-3:00 p.m. Poster Presentations and Judging
(*Grand and Continental Ballrooms*)

3:00-4:00 p.m. Awards Ceremony and Oral Presentations
(*Includes 10-minute presentations by winners of oral
competition awards*) (MC 309)

MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH

950 NEW HAMPSHIRE AVENUE, NW, 1ST FLOOR AUDITORIUM

4:30-4:35 p.m. Welcome and Introduction of Keynote Address

Lynn R. Goldman, MD, MS, MPH
*Michael and Lori Milken Dean
Milken Institute School of Public Health
Professor of Environmental and Occupational Health*

4:35-5:15 p.m. Keynote Address

LaQuandra S. Nesbitt, MD, MPH
*Director, Department of Health
Government of the District of Columbia*

*"Transforming Health and Wellbeing in the District of
Columbia: Role of the Public and Private Sectors in
Achieving Health Equity"*

5:15-5:30 p.m. Poster Award Winners Announced

Melissa J. Perry, ScD, MHS
*Professor and Interim Associate Dean for Research
Milken Institute School of Public Health*

Reception to follow.



GW RESEARCH DAYS

APRIL 5, 2017

3:00-4:00 p.m.

AWARDS CEREMONY

SCHOOL OF MEDICINE AND HEALTH SCIENCES, DONALD H. GLEW PRIZE

Moderator: **Katherine Chretien, MD**
*Assistant Dean for Student Affairs,
School of Medicine and Health Sciences*

Peter Berger:
*"Cytokine production varies between
hidradenitis suppurativa, chronic wounds and
normal keratinocytes in an in-vitro wound
closure model"*

INSTITUTE FOR BIOMEDICAL SCIENCES

Moderator: **Linda Werling, PhD**
*Professor; Director of the Institute for
Biomedical Sciences; Associate Dean
for Graduate Education, School of
Medicine and Health Sciences*

Rachel Burga:
*"Lymphocyte-nanoparticle biohybrids as a
combined nanoimmunotherapy for cancer"*

DEPARTMENT OF BIOMEDICAL ENGINEERING

Moderator: **Zhenyu Li, PhD**
*Associate Professor of Biomedical
Engineering*

Aleksandra Klimas:
*"Automated High-Throughput All-Optical
Dynamic Cardiac Electrophysiology for
Drug Testing and Disease Modeling Using
hiPSC-CMs"*

SCHOOL OF NURSING

Moderator: **Angela M. McNelis, PhD, RN, CNE,
ANEF, FAAN**
*Professor; Associate Dean for
Scholarship, Innovation, and Clinical
Science; Interim Associate Dean for
Research, School of Nursing*

Kathleen Hewitt:
*"Disparities in Cardiac Rehabilitation Referral for
Patients with Myocardial Infarction in the United
States"*

RESIDENT ORAL PRESENTATION

Moderator: **Jeffrey Berger, MD**
*Associate Dean for Graduate Medical
Education, School of Medicine and
Health Sciences*

Shahram Majidi, MD, Neurology, PGY 4
*"Prevalence and Risk Factors for Early Seizure
in Patients with Traumatic Brain Injury: Analysis
from National Trauma Data Bank"*

GRADUATE MEDICAL EDUCATION RESEARCH COMPETITION WINNERS

Moderator: **Jeffrey Berger, MD**
*Associate Dean for Graduate Medical
Education, School of Medicine and
Health Sciences*

Case Report (Tie):
Samah Nassereddine, MD, Leukemia Fellow
*"A Rare Case of Lymphomatoid Granulomatosis
occurring with Ulcerative Colitis"*

Hind Rafei, MD, Internal Medicine, PGY 2
*"Disseminated Intravascular Coagulation
Like Reaction Following Rituximab Infusion:
A Case Report and Review of a Rare
Phenomenon"*

Clinical Science (Tie):

Yasmine Assadipour, MD, Surgery, PGY 6
*"SDHB mutation status and tumor size, but
not tumor grade, are important predictors of
clinical outcome in pheochromocytoma and
abdominal paraganglioma"*

Shahram Majidi, MD, Neurology, PGY 4
*"Prevalence and Risk Factors for Early Seizure
in Patients with Traumatic Brain Injury:
Analysis from National Trauma Data Bank"*

Basic Science:

Raul Sebastian, MD, Surgery, Research Year
*"Gene Therapy and Wound Healing in
the New Nanotechnology Era: 'Inherently
Therapeutic Polymeric Nanoparticles for
Tailored Gene Expression and Improved
Wound Healing'"*

Quality Improvement Project:

**Jeremy Holzmacher, MD, Surgery,
Research Year**
*"Blood product wastage reduction by
utilizing enhanced physician-to-physician
communication initiatives"*

2017 DORIS DEFORD SPECK AND GEORGE SPECK, MD ENDOWED PRIZE

Moderator: **Katherine Chretien, MD**
*Assistant Dean for Student Affairs,
School of Medicine and Health Sciences*

Jason Chien:
*"Intra- and Peripapillary Capillary Density After
Plaque Radiotherapy for Choroidal Melanoma:
Analysis of Eyes Without Radiation Papillopathy"*

POSTER AWARD WINNERS ANNOUNCED

School of Medicine and Health Sciences
Institute for Biomedical Sciences
Biomedical Engineering
School of Nursing



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BASIC BIOMEDICAL SCIENCES



INSTITUTE OF BIOMEDICAL SCIENCES

Electrophysiological Techniques in Extracellular Recordings of the Mouse Optic Nerve

Myelin, insulation produced by oligodendrocytes around axons, facilitates the transmission of action potentials in myelinated neurons. Loss of myelin, in diseases such as multiple sclerosis, results in slower conduction velocities and may cause deficiencies in axonal communication. Electrophysiological techniques have been used to measure the electrical activity of individual neurons and entire nerves. While recording from a single neuron may be useful in studying specific ion channels, it may neglect influences from surrounding neurons, such as inhibition or enhancement of signals. Recording from a whole nerve produces a more complete response to a stimulus, which may be more physiologically relevant in some studies. This study tests the use of suction electrodes and bipolar electrodes for extracellular recordings of mouse optic nerves to measure the summation of neural responses (compound action potentials). Nerves were dissected behind the retina and at the optic chiasm. After being transferred to a bath with artificial cerebrospinal fluid, the caudal end was placed in a recording suction electrode. Suction electrodes were modified from glass capillary tubes using heat to narrow the inner diameter, forming an hourglass shape. This unique shape allows for nerves to fit tightly in the electrode, eliminating excess noise in the recording. The rostral end was stimulated by either insertion into a suction electrode or through contact with a bipolar electrode. Using both types of electrodes, compound action potentials were recorded from wild type mice at increasing stimulus pulses. These methods can be used to reliably stimulate and record from optic nerves and to measure the latency, duration, and intensity of the response. These electrophysiological approaches will be used to characterize the differences in mouse optic nerve functionality between wild type and the MBP-iCP9 transgenic mouse models, where an inducible form of caspase 9 (iCP9) can specifically target apoptosis in oligodendrocytes and induce demyelination.

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BASIC BIOMEDICAL SCIENCES



INSTITUTE OF BIOMEDICAL SCIENCES

High pH Fractionation for Enhancing the Proteome Coverage in Tissues Dissected from the Early Frog (*Xenopus laevis*) Embryo

Discovery measurement of the proteome raises an opportunity to better understand how differential expression of the genome underlies the formation of various tissue types during early embryonic development. To enhance the detectable proteome, we and others have developed high-sensitivity mass spectrometry instruments and protocols for the removal of abundant proteins, such as pelleting of yolk proteins using density gradients in the frog (*Xenopus laevis*) embryo. Here, we test high pH fractionation to improve the identification and quantification of proteins in the early developing *X. laevis* embryo.

The main goal of this work was to enhance the identification and quantification of proteins in the early developing frog (*Xenopus laevis*) embryo. While *X. laevis* is a powerful model of developmental biology and health studies, the proteome of the early embryo is dominated by abundant yolk proteins (>90% of the proteome), which hinders the characterization of low-abundance proteins. Building on the success of high pH fractionation, we proposed that this approach would help improve protein identifications in *Xenopus* tissues by minimizing the complexity of the samples prior to liquid chromatography-Mass spectrometry analysis. To test this, we pooled tissues from $n = 10$ embryos and extracted proteins using a SDS based lysis buffer and precipitated the proteins overnight in cold acetone. The extracted proteins were then digested with trypsin for 5 h at 37 °C. The resulting peptides were split into two sections: one was processed further by high-pH fractionation and the other was measured directly, serving as the control. To further improve protein identification, we also revised mass spectrometer parameters such as normalized collision energy, ion trap time, and dynamic exclusion time for MS². This systematic approach helped increase the number of protein identifications from ~600 to ~900 protein groups in the control sample. The high pH fractionation led to identification of more than 1,400 protein groups, corresponding to ~35% increase in identifications compared to the control. The additional ~500 proteins identified by high pH fractionation corresponded to medium- to low-abundance proteins. At present, we are developing this approach to further improve protein identifications. We aim to use the method to quantify protein regulation as the embryo undergoes successive stages of early development to gain a deeper understanding of gene translation during vertebrate embryonic development.

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BASIC BIOMEDICAL SCIENCES



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Single Locus Resolution of Transposable Element Expression Using RNA-seq

Characterization of Human Endogenous Retrovirus (HERV) expression within the transcriptomic landscape using RNA-Seq is complicated by uncertainty in fragment assignment because of sequence similarity. We present Telescope, a computational software pipeline, which provides accurate estimation of transposable element expression resolved to specific genomic locations. Telescope directly addresses uncertainty in fragment assignment by reassigning ambiguously mapped fragments to the most probable source transcript as determined within a Bayesian statistical model. We demonstrate the utility of our approach through differential analysis of HERV expression in primary CD4+ T cells infected with HIV-1, and found that HML2_1q22, was significantly up-regulated. Telescope performs robust analysis of the retrotranscriptomic landscape in RNA-Seq experiments, revealing a differential complexity in the transposable element biology of complex systems not previously observed.

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BASIC BIOMEDICAL SCIENCES



INSTITUTE OF BIOMEDICAL SCIENCES

The Role of Harakiri, a Mitochondrial Apoptosis Mediator, in Maintaining Membrane Stability of Myositis Muscle

BACKGROUND

Currently, the cause of myositis is unknown, but disease onset has been associated with viral infections. Although attempts to identify viruses in myositis skeletal muscle have failed, several studies have shown that a viral signature is present. Therefore, we postulated that viruses affect the epigenome in individuals with a susceptible genetic background.

OBJECTIVE

To investigate this, we hypothesized that a virus alters DNA methylation in the promoter regions of genes, leading to their aberrant expression and disease phenotype in skeletal muscle.

METHODS

Gene expression and methylation profiling were performed on myositis (PM and DM) skeletal muscle biopsies and human myotubes infected with Coxsackie B (8 MOI for 120 h) virus. A comparison analysis was performed to identify common changes in methylation and gene expression from myositis muscle and infected myotubes when compared to controls. Validation studies to investigate potential mechanisms were performed *in vitro* using skeletal muscle cells.

RESULTS/DISCUSSION

Comparison between data sets identified genes involved in membrane stability (*TRIL*, *COL5A1*, *MFAP4*, *MBP*) and cell death (*HRK*). We find that harakiri (*HRK*) is up-regulated in myositis skeletal muscle cells and show that these cells repair poorly after injury when compared to controls. Interestingly, *HRK* is activated by innate immune pathways and localizes to mitochondria, which are recruited to the site of injury during membrane repair and are located around the periphery of muscle fibers in myositis patients. Here, we demonstrate that HRK-induced mitochondrial deficiency could contribute to membrane instability and weakness of the muscle.

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BASIC BIOMEDICAL SCIENCES



INSTITUTE OF BIOMEDICAL SCIENCES

Mutations in INPP5K Cause a Form of Congenital Muscular Dystrophy Syndrome Overlapping Marinesco-Sjögren Syndrome and the Dystroglycanopathies

A large proportion of patients affected by congenital muscular dystrophies (CMDs) associated with brain and eye phenotypes remain unexplained. Here, we show that mutations in inositol polyphosphate 5-phosphatase K (INPP5K) cause a novel syndrome where CMD is present with short stature, intellectual disability (ID) and cataracts. The clinical presentation resembles both a milder form of dystroglycanopathy and Marinesco-Sjögren Syndrome, a myopathy associated with ID and cataracts. INPP5K, which is also known as Skeletal Muscle and Kidney-enriched Inositol Phosphatase (SKIP), has been involved in phosphatidylinositol phosphate (PIP) metabolism and Akt signaling at the plasma membrane, and in protein processing in the endoplasmic reticulum. It is expressed highly in the muscle and has been implicated as an important factor in myocyte differentiation, but has also shown increased expression in the brain and eyes during fetal development.

Exome sequencing was performed on a group of patients with CMD and reduced dystroglycan glycosylation, and a subset were found to have mutations predicted to be pathogenic in INPP5K. We introduced patient mutations into recombinant INPP5K to assess phosphatase activity and found that mutations ablated or significantly reduced enzyme activity. Zebrafish were then used to investigate the role of INPP5K in muscle, brain, and eye development using morpholino oligonucleotide (MO) injections into fertilized oocytes. MOs were effective in knocking out zebrafish *inpp5k* and analysis of muscle, brain, and eye tissue showed a consistent phenotype with the patients' presentation. We have confirmed that mutations in INPP5K lead to a CMD syndrome with features of both dystroglycanopathy and Marinesco-Sjögren Syndrome. While the link to reduced dystroglycan glycosylation remains to be elucidated, INPP5K and PIP processing are critical for muscle, eye and brain development and could represent a novel target for therapy development.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

AM251 Enhances RGC Axon Growth in an Embryonic Retinal Explant Model

Glaucoma is a leading cause of irreversible blindness worldwide and is characterized by progressive destruction of neural connections between retinal ganglion cells (RGCs) and the brain. These neural connections normally fail to regenerate after injury, but recent evidence suggests that special experimental conditions in animal models of optic nerve injury can encourage regrowth of axons. There is probably significant mechanistic overlap between regenerative and developmental axon growth, and lipid messengers called endocannabinoids (eCBs) modulate several types of developmental axon growth by activation of the eCB receptor CB1R. However, the role of CB1R in developmental RGC growth is not fully understood.

In this study, retinal explants were obtained from embryonic day 15 mice and cultured on glass coverslips. Cultures were maintained for 16 hours in the presence or absence of CB1R antagonist AM251. Immunocytochemistry, laser confocal microscopy, and image analysis were used to quantify RGC axon growth. All experiments were performed in a masked fashion.

CB1R antagonism by AM251 significantly increased mouse embryonic RGC axon growth. The total number of axon tips was significantly greater in the AM251-treated group compared to vehicle (110 vs 70 respectively, $p=0.0151$). Moreover, median axon length increased to 330 μm vs. 240 μm for AM251 stimulation vs. vehicle alone, respectively ($p<0.00005$).

These results suggest that CB1R activity inhibits developmental axon growth and could be a target for axon regenerative therapies.

PRIMARY PRESENTER

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Metformin Impairs Mitochondrial Function in Mesenchymal Stromal Cells

BACKGROUND

Metformin is a common drug used to treat type 2 diabetes (T2D) but its exact mechanism of action remains unknown. It has been shown that metformin not only inhibits the mitochondrial respiratory chain complex-I but also inhibits mTORC1 in cancer cells. However, it is important to establish whether metformin also affects normal human cells, particularly multipotent cells. Here, we investigated the effect of metformin on mitochondrial respiration of mesenchymal stromal cells (MSCs).

METHODS

Human adipose tissue-derived MSCs were cultured for 3-14 days in different concentrations of metformin (0.025-5mM). Oxygen consumption rate (OCR) of MSCs exposed to metformin was evaluated by Seahorse XFP using a Cell Mitochondrial Stress Test. mRNA expression of mitochondrial specific genes (qPCR) was also evaluated. To verify reversibility of metformin effect on MSCs, cells that were previously exposed to metformin for 3 days were then cultured in metformin-free media for another 7 days, followed by OCR and qPCR assessment.

RESULTS

Basal mitochondrial respiration was reduced (40%) when MSCs were exposed to 0.25mM metformin for 3 days. However, higher concentrations of metformin (1-5mM) nearly nullified basal respiration concomitantly with reduction in maximal respiration. Interestingly, the OCR reduction was reversed once metformin was removed from the culture media. Upregulation of apoptotic genes such as caspase3 and p21 was observed followed by cell proliferation reduction (20-30%) when MSCs were exposed to lower and near physiological concentrations of metformin (0.025-0.25mM) for 7 and 14 days. Interestingly, basal and maximal respirations were not affected by the latter conditions. Mitochondria specific gene expression analysis revealed that PGC1A and TFAM were upregulated.

CONCLUSION

Our study confirms that metformin reversibly impairs mitochondrial respiration and proliferation of MSCs, particularly at higher doses. At lower doses and on prolonged exposure to metformin, MSCs are able to escape the phenomenon possibly by increasing expression of mitochondrial genes. These findings may impact therapeutic approaches in cancer and metabolic diseases (T2D).

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BASIC BIOMEDICAL SCIENCES



SCHOOL OF MEDICINE AND HEALTH SCIENCES
CHILDREN'S NATIONAL MEDICAL CENTER

Vitamin D and Glucocorticoids Interact to Reduce Ubiquitin C in Asthmatic Airway Epithelium

RATIONALE

There is increasing evidence that vitamin D insufficiency contributes to more severe asthma through decreased sensitivity to glucocorticoids. Indeed, low serum 25(OH) vitamin D levels are linked with the need for exogenous glucocorticoids and increased asthma severity. We previously showed a strong association between low 25(OH)D levels and asthma in urban youth.

OBJECTIVES

We propose a hypothetical synergism between 25(OH)D and glucocorticoid signaling pathways as a potential mechanism.

METHODS

Nasal epithelial cells were collected from youth between 6 and 20 years of age, inclusive, with physician-diagnosed asthma for 1 year or more, current asthma medication use, and current asthma symptoms. Cells were cultured for 90 minutes *ex vivo* with exposure to dexamethasone (DEX) and/or 1,25(OH)₂D. mRNA expression was compared among conditions and selected genes were validated.

MAIN RESULTS

Of 91 current participants, 57% were male and 88 (97%) had persistent asthma. The mean(SE) age=12.1(0.4) years, BMI percentile for age=70(3)%, and serum 25(OH)D=19.6(0.9) ng/mL. Sixteen participants were randomly selected for gene expression studies—there were no significant differences between this subgroup and the overall cohort. Whole genome analyses in 7 participants showed 34 transcripts that met present call filters and a DEX*1,25(OH)₂D interaction $P \leq 0.01$. Functional and network analyses showed 20 of these genes are regulators of transcription and form a regulatory network centralized to UBC (Ubiquitin C). Notably, UBC was down-regulated by DEX only in the presence of 1,25(OH)₂D in a dose-dependent manner. Selected network members known to enhance ubiquitination in the lung (i.e. ANAPC1, PAIP1, and S100A13) were validated in the 16 participants. All three were also repressed by DEX only with increasing doses of 1,25(OH)₂D.

CONCLUSION

Protein ubiquitination has been shown to decrease alveolar epithelial barrier function and increase inflammatory pathways in the lung. Our findings suggest that vitamin D and DEX together reduce ubiquitination which may improve barrier function and affect inflammation. The role of vitamin D in airway inflammatory diseases such as asthma remains unclear, although altered sensitivity to glucocorticoids may be a mechanism by which vitamin D supplementation could improve asthma.

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BASIC BIOMEDICAL SCIENCES



SCHOOL OF MEDICINE AND HEALTH SCIENCES

Mg-Supplementation Attenuated Lipogenic and Oxidative/Nitrosative Gene Expression Caused by Anti-HIV Drug Therapy in HIV-1-Transgenic Rats

OBJECTIVE/BACKGROUND

With the use of combination anti-retroviral therapy (cART) containing protease inhibitors (PIs), HIV-1 replication was shown to be dramatically reduced. However, PI-containing cART can cause significant lipid side effects and oxidative stress. We determine if Mg supplementation might attenuate the systemic oxidative/nitrosative stress and lipogenic effects caused by a clinically used cART in a HIV-1 transgenic rat (Tg) model.

METHODS

A PI-based cART (atazanavir-ritonavir plus Truvada) was given orally to control and HIV-1-Tg rats at doses similar to human equivalent for 18 weeks. A 6 fold higher than normal MgO in the diet was introduced to determine the effect of Mg supplementation. Relative Expressions of selected oxidative/nitrosative and lipogenic genes from livers were determined by real-time quantitative PCR and the expression levels of genes were quantified with values normalized by 18s mRNA.

RESULTS

cART treatment led to a 10-fold upregulation of the Sterol regulatory element-binding protein-1 (SREBP-1) gene in the Tg rats, which is a key transcription factor required for cholesterol biosynthesis. This upregulation was completely prevented by Mg supplementation. Nrf2, which is a master transcription factor that regulates the expression of antioxidant proteins, was down-regulated 50% in the HIV-Tg rats, and was further reduced to 25% in Tg+cART rats. Two selected downstream responsive genes, heme oxygenase-1 (HMOX1) and Glutathione S-transferase (GST) were examined. Both HMOX1 and GST, which are protective antioxidant genes were elevated in HIV-Tg alone but were suppressed dramatically by cART. Both HIV and cART-induced down-regulation of Nrf2 was attenuated, and changes in expressions of HMOX1 and GST were reversed by Mg-supplementation. Concomitantly, inducible NOS (iNOS) was upregulated 2-fold in the Tg+cART rats, which was normalized by Mg-supplementation. Correspondently, cART treatment led to increases in plasma 8-isoprostane (lipid peroxidation indicator) levels in both control and HIV-1-Tg rats; these elevations were lowered by Mg-supplementation. In addition, significantly higher level of plasma nitrotyrosine was found in the cART-Tg group; such elevation was suppressed in cART-Tg rats plus Mg-supplementation. Furthermore, both plasma triglyceride and cholesterol level were elevated in cART-Tg group, which again were lowered by Mg- supplementation.

CONCLUSION

The lipogenic and oxidative/nitrosative effects caused by cART in the HIV-1-TG rats were confirmed by the qPCR and biochemical data. The downstream regulation by Nrf2 confirmed that the antioxidant response in the HIV animals was severely compromised. However these abnormal metabolic and oxidative stress effects were substantially attenuated by Mg-supplementation.

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BASIC BIOMEDICAL SCIENCES



SCHOOL OF MEDICINE AND HEALTH SCIENCES

A Study in Retinal Pathology and Peripheral Vision Changes in Alzheimers Dementia

This study documents the effects of Alzheimers Disease (AD) on the peripheral retina. It is well-known that AD patients experience a dramatic degeneration of vision, unique to the effects of aging alone. Though primarily a neurodegenerative disease, AD has been correlated with a thinning retinal nerve ganglion, vascular changes, and other retinal pathologies. However, few studies have looked at the peripheral retina in AD patients. It is well-known that central and peripheral vision have very different functions to the vision. Central is associated with specific details and colors and is perceived by the cones of the retina, while peripheral, associated with the rod cells of the retina, is for dim-light, motion, and less-detailed processing.

Until now, very few ophthalmological studies have studied the peripheral retina. However, neurological studies have documented the profound loss in peripheral processing experienced by AD patients. For instance, a phenomenon commonly associated with AD is a loss of “spatial recognition.” This is the ability to use peripheral vision to recognize an environment without fixating on it. AD has also been associated with visual hallucinations. While the cause of these hallucinations isn’t well-understood (whether it is due to neural or retinal degeneration), a similar phenomenon is observed in Age-related Macular Degeneration (AMD). AMD similarly causes an accumulation of retinal drusen and pathology—except this is centered in the center of the retina, and this loss of vision has been associated with similar hallucinations even in the absence of neurodegeneration. It should be noted that AMD and AD can occur simultaneously and are both linked to similar cardiovascular risk factors.

This study utilizes a new form of fundus imaging, Ultra-Wide Field Imaging, whereby the entire retina can be imaged—to the very extent of retina used for visualization, up to 90 degrees of eccentricity. This study compared the retinas of AD patients with age-matched controls. The findings illustrate an accumulation of drusen and increased vascular tortuosity in the peripheral retina of AD patients. The conclusions suggest a less-invasive method to track the progression of AD. Furthermore, this UWFI technique could help illuminate the process behind the loss of vision, especially peripheral, experienced by AD patients.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

An Intronic Variant in DCHS2 is Associated with Bone Mineral Density in Children and Young Adults

PURPOSE OF STUDY

Fragility fractures lead to significant morbidity and mortality in seniors. Recently, Compressive Strength Index (CSI) has been validated as a predictor of hip fracture risk. Han et al. have identified 3 genes that may play a role in determining CSI in Caucasians and Asians: FADS1, FADS2 and DCHS2 containing SNPs (FADS1/rs174549; rs174583, FADS2/rs174577, DCHS2/rs7672337). This study sought to examine whether these polymorphisms also influence other measures of bone quality in children and young adults.

METHODS

Cohorts: The Assessing Inherited Markers of Metabolic Syndrome in the Young (AIMMY) cohort included Caucasian males: N=55 (avg 24 yrs) and females: N=54 (avg 22 yrs). Total body and lumbar bone mineral density (BMD) were analyzed. The Bone Health Cohort included African American children (age 5-9): 46 males and 41 females. Phenotypes were total body minus head BMD and lumbar BMD. *Genotyping:* Three SNPs were genotyped using the Illumina Multi-Ethnic Genotyping Array. Rs7672337 was genotyped utilizing a Taqman assay. Subjects and SNPs that fell below the quality thresholds were eliminated from the data set. The relationship between genotype and phenotype was tested using ANCOVA models where phenotype was the independent variable, genotype was the dependent variable, and age was a co-variant. For those ANCOVA models using the additive genetic model, where a statistically significant overall F-test was observed, post-hoc pair-wise comparisons between genotypes were performed. Post-hoc p-values were adjusted for multiple comparisons using the Sidak method.

RESULTS

In the AIMMY cohort, lumbar BMD was found to be significantly associated with rs7672337 (DCHS2) in Caucasian females ($p=0.047$). No other significant associations were seen within the AIMMY or Bone Health cohorts.

CONCLUSION

An association was seen when observing the variant rs7672337 near the DCHS2 gene and lumbar BMD in female young adults from the AIMMY cohort. With all other conducted analysis, no significant association was uncovered. This suggests DCHS2, FADS1 and FADS2 do not play a role in total BMD or lumbar BMD development. Furthermore, this could suggest that other factors within the two measures, CSI and ALM, play a more prominent role than opposed to BMD. While the BMD measurement used was primarily hip BMD, if association with hip BMD was strong, then an association with total BMD should have been observed. As this was not the case, this could suggest that DCHS2, FADS1 and FADS2 have a stronger association with femoral neck area and/or weight.

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Concussion Screening Evaluation: BESS vs Sway

INTRODUCTION

Rapid evaluation of concussion is important in the pre-hospital setting as an easy test. It is also useful in the ED, as too often little is done for concussed patients. The Balance Error Scoring System (BESS) is the current gold standard for evaluating balance, one of the best predictors of concussion. SWAY, a new gyroscope based iPhone application, is being proposed as a more sensitive and more objective test than BESS. This study will compare Sway to BESS to determine if there is equal efficacy.

METHOD

74 scholastic and collegiate athletes were administered baseline balance evaluations using Sway. Sway is scored out of 100 points and uses the iPhone's gyroscope to measure balance while the device is clutched to the tester's chest with both hands and eyes remain closed. In conjunction with their evaluations, we scored each athlete using BESS. Subjects are assessed one point for the following errors using BESS: Removing hands from the mobile device clutched to their chest; opening the eyes; stepping, stumbling, or falling; remaining out of the test position for five seconds; moving the hip into more than 30° of hip flexion or abduction; or lifting the forefoot or heel. No foam pad was used and subjects used their hands to clutch mobile device to chest instead of keeping hands on hips.

RESULTS

The average score of 4.1 on BESS correlates to an average score of 77.1 on Sway. There is moderate to strong correlation between Sway and BESS results that is statistically significant ($P < .05$). The Sway average score has a STDev of 14.2. The BESS average score has a STDev of 2.9. According to "Normative data for the balance error scoring system: Implications for brain injury evaluation" (G.L. Iverson, M.L. Kaarto, and M.S. Koehle), the 76-90th percentile of individuals ages 20-39 scored 4-6 on BESS.

CONCLUSION

Sway is equally, if not more, sensitive than BESS. While BESS is judged by humans and creates the possibility of human error to occur while evaluating subjects, Sway is completely automated so to minimize human error and give a completely objective score. Sway can replace BESS for rapid balance screening and still maintain clinical accuracy.

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Mitochondrial Signaling Facilitates Repair of Injured Muscle Fibers

BACKGROUND

Skeletal muscle contraction produces the force needed for animal motility, but the resulting mechanical strain can damage the plasma membrane of individual skeletal myofibers. While small increases in cytosolic calcium are essential for myofiber contraction, myofiber plasma membrane damage causes a large increase in calcium, which if not contained can cause myofiber death. Mitochondria are the source of energy required for skeletal muscle contraction; however, mitochondria are also increasingly being recognized for their role in cell health through maintaining calcium homeostasis and redox signaling. We recently identified mitochondria in skeletal muscle as an integral requirement for the repair of plasma membrane damage, but the mechanism by which mitochondria facilitate the repair of injured myofibers remains unclear.

METHODS

We monitored plasma membrane repair in muscle cells and myofibers following focal injury by real-time imaging. By genetically and pharmacologically altering calcium, ROS, and F-actin we investigated injury-triggered acute and localized changes in these entities and how they interact to repair injured muscle cells.

RESULTS

Blocking mitochondrial ATP production does not affect the ability of injured muscle cells to repair, demonstrating a non-bioenergetic role of mitochondria. Instead, mitochondria take up calcium entering muscle cells due to plasma membrane injury and inhibition or genetic deletion of the mitochondrial calcium uniporter (MCU) compromises the ability of muscle cells to repair. Mitochondrial calcium uptake transiently increases the production of mitochondrial ROS (mROS), and blocking mROS production compromises repair of injured muscle cells from focal injury and eccentric exercise-induced injury. Transient increase in mROS, due to calcium uptake or by use of pharmacological inhibitors, initiates signaling that promotes polymerization of F-actin at the site of injury. This local increase in F-actin is mediated by RhoA GTPase. Blocking mitochondrial function, calcium uptake, and mROS production all prevent actin polymerization. A chronic increase in ROS also prevents cell membrane repair identifying the novel signaling role of mitochondrial calcium and mROS in repairing injured muscle fibers.

CONCLUSION

In contrast to the role of chronic redox imbalance in muscle damage and dysfunction, our results identify that acute change in redox signaling by mitochondria is essential to repair muscle cell membrane injury.

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Identifying the Functional Consequences of Six1 Mutations in Ear Development

Mutations in *SIX1* and in its co-factor, *EYA1*, underlie Branchiootorenal Spectrum disorder (BOS), which is characterized by variable branchial arch, otic and kidney malformations. Several mutations of *SIX1* have been identified in BOS patients. Because the developmental effects of these mutations are not known, we synthesized four mutant versions of *Xenopus Six1* that contain the single amino acid changes (V17E, R110W, W122R, Y129C) identified in some BOS patients. Injection of mRNA encoding either the Y129C, V17E, or R110W mutations into blastomeres that give rise to neural crest and cranial placodes showed some differences compared to embryos injected with wild type *Six1* mRNA: the *Sox11* placode expression domain was broader. Instead the W122R mutant seems to have no effect on the neural crest domains. Compared to the phenotypic defects seen in the screened patients we postulate that the Y129C, V17E, and R110W *Six1* mutations cause inner ear defects because placode gene expression is affected. In contrast, W122R *Six1* mutations may affect the external ear because epidermal gene expression is affected.

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Overexpression of Wilms' Tumor Protein (WT1) in DIPGs Indicates a Possible Immunotherapeutic Target for DIPG

BACKGROUND

Diffuse Intrinsic Pontine Glioma (DIPG) is a deadly pediatric brain cancer that makes up 10-15% of all central nervous system (CNS) tumors in children. Surgery is not an option due to its anatomical location and infiltrative nature. It is amongst the most challenging tumors to treat. Combination of chemotherapy and focal radiation therapy is the primary therapy for DIPG, but the benefits of the radiation therapy is temporary. Immunotherapy is a technique that is gaining more interest in CNS tumors. Identification of tumor associated antigens is one of many requirements in developing an effective immunotherapy.

OBJECTIVE

To validate Wilms' tumor protein (WT1) as a potential tumor associated antigen in DIPGs using patient derived cell lines and patient formalin fixed paraffin embedded (FFPE) specimens.

METHODS/DESIGN

DIPG patient FFPE specimens were immunohistochemically stained for WT1 using mouse monoclonal anti-WT1 antibody. FFPE specimens and patient derived cell lines were also co-stained for K27M histone H3 protein mutation (p.Lys27Met) and WT1 using immunofluorescent (IF) staining methods. The fluorescence intensity was measured to compare WT1 level in the two histone mutation subgroups of DIPG (H3.3K27M and H3.1K27M). In addition, frozen tumor tissues and patient derived cell lines were used to validate WT1 protein levels in western blot.

RESULTS/DISCUSSION

Immunohistochemistry (IHC) staining of patient FFPE specimens showed strong WT1 immunoreactivity in tumor compared to adjacent normal tissue. In addition, our IHC staining showed weak to absent WT1 immunoreactivity in H3.1K27M subtype tumor specimens compared to strong to moderate in H3.3K27M subtype tumor specimens. IF staining of cell lines confirm this differential WT1 levels in the subtypes. Western blot of tumor tissues and cell lines were performed to further validate WT1 levels. These results suggest that WT1 is a potential DIPG tumor associated antigen which can be utilized for immunotherapy.

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Early Detection of Amylin Aggregation with a Miniature Optical-Fiber Based Sensor

Type II diabetes mellitus comprises 90-95% of all diabetes diagnoses in the United States and carries a high morbidity. One well-known finding in the pathophysiology of the disease is the loss of function of the β -cells of the pancreatic Islets of Langerhans that produce and secrete insulin and amylin, leading to impaired ability to regulate glucose metabolism. Recent research has revealed that in patients with diabetes, an excess of amylin monomers in the serum aggregates into toxic oligomers that accumulate on the exterior surface of the plasma membrane of the β -cells, and the presence of these amylin deposits is correlated with β -cell death via apoptosis. Diagnosis at an early stage in the disease process is essential for optimal management and reduction of the incidence of its serious complications which include cardiovascular and renal disease and limb loss. This project develops a method for detecting the early incidence of amylin aggregation by a surface-plasmon resonance biosensor developed here at GW. The sensor is fabricated by attaching antibodies differentially sensitive to amylin monomers and oligomers, by detecting shifts in the optical response of gold nanoparticles to which they are bound. The platform for the nanoparticles is the end of an optical fiber, so the biosensor can be made portable and capable of in-vivo detection of amylin aggregation. The critical bottlenecks in the workflow for sensor fabrication will be described, as will its successful implementation for protein sensing. Results to date demonstrate that the sensor can distinguish different types of antibodies and different morphologies of amylin by measuring the kinetics of binding between the analyte and the sensor. The ability to detect pathologic changes that occur before symptoms of diabetes are present carries great promise for improving outcomes by narrowing the window between disease onset and initiation of treatment. Further extensions of this work offer the potential to sense amyloid fibers related to degenerative neural disease in the early stages of plaque formation.

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Cooperative Interaction between the Renal Neuropeptide FF Receptors and the Angiotensin II Type 1 Receptor

Despite breakthroughs in medical genetics and molecular biology, the genetic basis for essential hypertension has proven to be difficult to decipher. Understanding the mechanisms that regulate blood pressure is a challenge that requires the characterization of novel regulators of renal sodium transport and blood pressure. The neuropeptide FF (NPFF) is a mammalian neuropeptide encoded by the *NPFF* gene and believed to be expressed in neurons. This study aims to demonstrate the presence of NPFF and its receptors, NPFF-R1 and NPFF-R2, in the renal parenchyma and determine their interactions with dopamine and angiotensin II receptors. We report that NPFF and its receptors are expressed in human renal proximal tubule cells (hRPTCs) and that they interact with the D_1 -like dopamine receptors (D_1R and D_5R) and the angiotensin II type 1a receptor (AT_1R). The NPFF receptors co-immunoprecipitated and colocalized with the D_1R and D_5R in hRPTCs and human kidney. NPFF treatment inhibited cAMP production, while the D_1R/D_5R agonist fenoldopam stimulated cAMP production in hRPTCs. Co-treatment of NPFF abrogated the effect of fenoldopam, indicating antagonism between these receptors. Fenoldopam treatment at the basolateral side of polarized hRPTCs grown in Transwells® increased the intracellular Na^+ concentration, indicating inhibition of sodium exit from the cell. This was prevented by co-treatment with NPFF, which did not change the intracellular Na^+ by itself. We further evaluated the interaction of NPFF and its receptors with the renin-angiotensin-aldosterone (RAS) system, which counteracts the physiological effects of dopamine. The NPFF receptors co-immunoprecipitated and colocalized with the AT_1R in hRPTCs and human kidney. Additionally, C57B1/6 mice under pentobarbital anesthesia were treated with NPFF (10 μ g/100 μ l per kidney, 1 hour) alone, angiotensin II (1 μ g/kg/min, I.V., 1 hour) alone, or NPFF and angiotensin II together (1 hour), and blood pressure and heart rate were monitored over time. Treatment with NPFF alone increased the blood pressure (106 vs. 125 mm Hg, $n=1$) and heart rate (339 vs. 391 beats/min) which normalized within 1 hour, while co-treatment with angiotensin II sustained the increase in blood pressure (125 mm Hg) and heart rate (462 beats/min). Angiotensin II infusion resulted in an increase in blood pressure (124 mm Hg) and heart rate (385 beats/min). Our preliminary findings indicate that the renal NPFF may be a negative regulator of D_1R/D_5R and also a positive modulator of AT_1R . Further uncovering the functional relevance of renal NPFF will allow a better understanding of the dynamic regulation of Na^+ transport and blood pressure homeostasis.

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Blood RNA Biomarkers of Coronary Artery Disease: A Potential Signature of Regulatory T Cell Imbalance

BACKGROUND

Cardiovascular disease is the major cause of death and morbidity in developed countries. Atherosclerosis contributes to about 650,000 myocardial infarctions (MI) per year in the U.S. alone. The current gold standard for diagnosing coronary artery disease (CAD) is coronary angiography with cardiac catheterization. Surprisingly, despite well-established clinical indications, about 40% of the 1 million diagnostic cardiac catheterizations return a result of 'no blockage'. The present studies identify an RNA signature associated with CAD in patients presenting with a clinical suspicion of CAD.

METHODS

Whole blood RNA was analyzed by single-molecule next-generation sequencing (NGS) of RNA (RNAseq) to identify transcripts associated with CAD (TRACs) in a discovery group of 45 and a validation group of 51 patients presenting for coronary catheterization. Whole blood RNA was depleted of ribosomal RNA (rRNA) and then sequenced on a SeqLL Single Molecule Sequencer. The resulting short reads were aligned to the human transcriptome and the number of reads per kilobase of exon per million (RPKM) was determined and compared between groups by a combined fold-change/p-value filter.

RESULTS

A group of transcripts that decreased ~1.7-fold were identified in patients with mild to severe CAD (>20% stenosis). Using only 7 TRACs, a classification model was designed with an accuracy of 80.2% (C=0.873), which was markedly better than a clinical risk prediction model (accuracy=54.2%, C=0.636). The TRACs appeared essentially independent of comorbid risk factors for CAD and reflected changes in T cell RNA markers. Transcripts such as FoxP3, ICOSLG, IKZF4/Eos, SMYD3, TRIM28, and TCF3/E2A suggest that TRACs are RNA markers of Treg-like cells, consistent with known reductions in Treg/Teff ratios in CAD. Further, the low expression level and small fold changes, combined with effects of the RNA stabilization method, may explain why these transcripts have not been detected in prior microarray-based studies.

CONCLUSIONS

These studies identify a novel mRNA signature of a Treg-like defect in CAD patients and provide the blueprint for a diagnostic test for CAD. In the future, this test could be expanded toward a diagnosis of CAD in asymptomatic patients, which could potentially prevent unexpected MI, provide physicians the opportunity for early intervention, and for monitoring the effectiveness of therapy.

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Deciphering the Molecular Mechanism for Integration of a Human Cytomegalovirus-Encoded Signal Anchored Protein Into the Outer Mitochondrial Membrane

Human cytomegalovirus (HCMV) congenital infection is the leading viral cause of birth defects in developed countries. An HCMV protein, viral mitochondria-localized inhibitor of apoptosis (vMIA), prevents apoptotic death of infected host cells. Following its synthesis at the endoplasmic reticulum (ER), vMIA traffics unconventionally through the mitochondria-associated membranes (MAM) to localize at the outer mitochondrial membrane (OMM), where it inserts as a signal anchored (SA) integral membrane protein. While the majority of nuclear encoded mitochondrial proteins utilize the highly conserved translocase of the OMM (TOM) for mitochondrial import, the mechanisms underlying insertion of SA OMM proteins is poorly understood. We are testing whether vMIA uses TOM to integrate into the OMM. To that end, we have developed approaches using fluorescence lifetime imaging microscopy (FLIM) and fluorescence resonance energy transfer (FRET) to examine if vMIA interacts with Tom20, one of the TOM receptors at the OMM. To test whether vMIA uses the pore function of Tom40, we inhibited mitochondrial import using dequalinium chloride (DECA), an FDA approved antimicrobial drug that blocks mitochondrial protein import at the translocase of the inner mitochondrial membrane (TIM) and thereby reduces Tom40 import of mitochondrial proteins. We show that vMIA traffics rapidly from the ER, through the MAM to the OMM, where it organizes in nanoscale clusters. Homo-FRET using lifetime measurements showed that vMIA can form homo-oligomers at the OMM. Furthermore, FRET studies using acceptor photobleaching and FLIM approaches identified that vMIA also interacts efficiently with the OMM receptor, Tom20. This result suggests that vMIA may utilize a Tom20-dependent pathway for its integration into the OMM. We have also determined a non-toxic dose of DECA, which inhibits mitochondrial matrix protein import in human cells. Under these conditions, we will find that DECA did not block vMIA insertion into the OMM. This result suggests that vMIA does not use the Tom40 pore function for OMM insertion. Understanding vMIA's mechanism of OMM insertion and identifying inhibitors to block it, could enhance apoptotic death of HCMV-infected cells and thereby their clearance.

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Antinuclear Antibodies and Hidradenitis Suppurativa

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic, debilitating inflammatory disease of apocrine sweat glands, characterized by recurrent abscessing inflammation. The pathogenesis of the condition is not well known although there may be an immunologic basis to the condition. Antinuclear antibodies result from immune system dysregulation, which can cause autoantibodies to cellular and nuclear antigens. Although it is a nonspecific test, it is known to be a highly sensitive test for diagnosis of connective tissue diseases including systemic lupus erythematosus. The purpose of this study is to explore antinuclear antibody positivity in HS.

METHODS

This research was conducted through the Wound Etiology and Healing Study (WE-HEAL Study), a biospecimen and data repository approved by The George Washington University IRB (041408). All subjects gave written informed consent for longitudinal collection of their data. Age, gender, race, disease duration, smoking status, BMI, Hurley stage, Hidradenitis Sartorius Score (HSS), and active nodule counts were analyzed according to ANA positivity.

RESULTS

In this subset of 64 HS patients, there were 10.9% who tested ANA+ at enrollment. There were no significant differences in age, gender, race, disease duration, smoking status, or baseline BMI between the ANA+ and ANA- groups.

HSS Score was higher in ANA negative patients (61.1 +/- 52.9 compared to 26.1 +/- 39.9, $p=0.066$). Baseline Hurley stage was significantly higher in the ANA negative group ($p=0.000491$) with 59.6% Hurley Stage III, compared to only 14.3% of patients Hurley Stage III in the ANA positive group. ANA negative patients had higher mean Active Nodule counts although this difference did not reach statistical significance (3.6 +/- 2.2 compared to 2.0 +/- 2.8, $p=0.1963$). Two patients changed from negative to positive ANA, and they received immunosuppression with TNF- α inhibitors, which are known to carry a risk of drug induced lupus.

CONCLUSION

ANA prevalence in the US population 12 years and older has been shown to be approximately 13.8%. HS patients who are ANA positive did not differ greatly from ANA negative patients in terms of their demographics in our study population. HS disease activity scores were higher in patients that are ANA negative. The immunologic mechanisms of HS have yet to be elucidated; however, we did not find a high prevalence of ANA positivity in this population at baseline. There were a small number of patients who developed a positive ANA in response to treatment with TNF- α inhibitors but this is a known side effect of this class of drugs.

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In Vivo Delivery of Third Generation Oligonucleotides Targeting DUX4 Using a New Mouse Model of FSHD

Facioscapulohumeral muscular dystrophy (FSHD) is an autosomal dominant disorder caused by aberrant expression of the double homeobox 4 (DUX4) gene. Aberrant expression of DUX4 has been shown to affect critical molecular pathways, which results in muscle pathologies and weakness in FSHD. Knock down of DUX4 using antisense oligonucleotides is a viable treatment for FSHD. In an in vitro study, we showed that several third generation antisense oligonucleotides (3GAs) targeting DUX4 reduced expression of DUX4 mRNA effectively. In addition, the treatments partially corrected defects in myogenesis in cell culture. The purpose of this study is to determine whether 3GA can be systemically delivered into skeletal muscles and reduce expression of DUX4 in vivo. A newly developed FSHD mouse model (FlexD mice) was used for the study. The FlexD mice were treated with fluorescein tagged 3GA (3GA-F) via intramuscular (IM) and subcutaneous (SC) injections, respectively. Mice treated intramuscularly received 20µg of 3GA-F into the tibialis anterior (TA) muscles (n=3). Mice treated subcutaneously received one injection of 30mg/kg 3GA-F (n=2). The TA muscles were harvested 24 hours afterwards and stained for hematoxylin and eosin to determine muscle pathology. In addition, the muscles were immunofluorescently stained for a sarcolemmal protein, dystrophin, to determine the localization of the 3GA-F. In addition to single injection with 3GA-F to determine localization of the 3GA-F, a separate group (n=3) of mice were treated with 30mg/kg of two different 3GAs, which targeted different regions of DUX4, via subcutaneous injections every other day for total 3 injections. Our results showed that 3GA entered muscles after both local and systematic delivery. One of the 3GAs slightly reduced DUX4 and a DUX4 regulated gene, Trim36, after 3 SC injections, however the change did not reach significant level. Delivery of antisense oligonucleotides to intact muscles for therapeutic purpose has been very challenging. Our findings showed that 3GA were able to enter muscles by local and systemic delivery, which is important for future therapeutic development for FSHD. Experiments to optimize the dosing regimen of 3GA to further enhance the knockdown of DUX4 and its downstream target genes are currently underway.

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Hectd1 Promotes Retinoic Acid Signaling in the Epicardium Required for Myocardial Proliferation During Heart Development

Congenital heart defects (CHDs) are the most common structural birth defects in the United States. During heart development of the murine heart, epicardium expresses signaling factors that increase proliferation and differentiation of the adjacent myocardium. Disruptions in this communication may lead to hypoplastic ventricle phenotypes. One of the main signaling factors involved is retinoic acid (RA). Deficient levels of retinoic acid are associated with hypoplastic and thin-walled ventricles. Previous work demonstrates that the novel E3 ubiquitin-protein ligase *Hectd1* promotes RA signaling. *Hectd1* is highly expressed in the epicardium and mutation of *Hectd1* results in defects in myocardial proliferation that resembles those seen in mice with defects in retinoic acid signaling. However, in addition to CHDs, *Hectd1* mutant embryos exhibit a number of developmental phenotypes including neural tube closure and placental defects, which may indirectly influence heart development. To determine if CHDs are due to a role of *Hectd1* in the heart, we utilized the Cre-lox system to specifically delete *Hectd1* in cardiac lineages. *Hectd1* was conditionally knocked out in mesoderm-derived cells, using Cre expressed under the control of *Mesp1* and *Nkx2.5* promoters. *Mesp1-Cre* is expressed throughout mesoderm-derived cell lines in the embryo and *Nkx2.5-Cre* is expressed in mesoderm-derived cardiac tissue. Our results show that *Hectd1* is required in the mesodermal heart lineage for myocardial development. Future experiments will determine if *Hectd1* in the epicardium using *Wt1-Cre*.

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Poly-ADP-Ribose Polymerase (PARP) Inhibition Enhances Ischemic/diabetic Wound Healing By Promoting Angiogenesis Through FOSL1

INTRODUCTION

Amputations resulting from poor perfusion associated with ischemic/diabetic wounds is a major health problem globally. To improve upon limb-salvage therapeutics, a better understanding of impaired angiogenesis in these challenging wounds is required. PARP is hyper-activated in both ischemic and diabetic conditions but its role and impact in impaired cutaneous healing remains unclear.

METHODS

Using a previously established protocol, mice were made diabetic and ischemic by streptozocin infection and femoral artery ligation, respectively. Excisional wounds were created on the ventral surface of the thighs, followed by treatment with either PJ34 (a PARP inhibitor) or a vehicle. Daily digital photographs were used to monitor healing expressed as % of original sizes. Wound tissues were collected for molecular analysis of endothelial cell markers. Flow cytometry was used to analyze peripheral blood mononuclear cells for endothelial progenitor cell (EPCs) markers. In vitro angiogenesis assays were performed with HUVECs cultured under hyperglycemic and hypoxic conditions, with and without PARP inhibition (either by PJ34 or PARP1 siRNA).

RESULTS

Improved wound healing resulting from PARP inhibition was observed as early as day 7 ($71 \pm 9\%$ vs. $43 \pm 6\%$ in control group, $p < 0.05$). Western blot analysis showed PARP inhibition increased VEGFR2 by two-fold and eNOS by three-fold compared to control ($p < 0.05$). PARP inhibition also promoted EPC mobilization into the peripheral blood (VEGFR2+/CD133+ cells increased from 0.074% to 0.62% and VEGFR2+/CD34+ cells increased from 0.10% to 1.27%). In vitro angiogenesis assays showed that PARP inhibition enhances migration, invasion, and tube formation. RT-qPCR of known angiogenesis factors (CXCR7, FOSL1, ITGA6 and others) revealed that PARP inhibition increases FOSL1 expression by five-fold.

CONCLUSIONS

PARP inhibition increases FOSL1 gene expression, promotes angiogenesis, and enhances ischemic-diabetic wound healing. Because FOSL1 controls endothelial cell assembly into capillary tubes, investigating the detailed interaction between PARP and FOSL1 will foster discovery of new therapeutic targets to improve ischemic/diabetic wound healing.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

GPR83 Function Contributes to Salt Resistance

The G protein-coupled receptor (GPCR) 83 (Gpr83) is an orphan receptor belonging to the rhodopsin-like family of GPCRs. Gpr83 was originally identified as a glucocorticoid-induced transcript in a murine T cell line and referred to as glucocorticoid-induced receptor. Gpr83 is expressed in brain hypothalamic nuclei relevant to energy metabolism control and has a role in the central regulation of energy metabolism. Gpr83 is also expressed in the kidney but its function is unknown. We found that Gpr83 is expressed in mouse renal proximal and distal convoluted tubules, as well as in human renal proximal tubule cells (hRPTCs). High salt diet increased Gpr83 transcription by 2-fold ($P < 0.05$; $n = 4/\text{group}$) in Swiss Jim Lambert (SJL/J) and Bagg Albino (BALB/c) salt-resistant mice, relative to C57 Black (C57Bl/6J) salt-sensitive mice. In C57Bl/6J mice on normal salt diet, the lack of one (Gpr83^{-/-}) or both Gpr83 (Gpr83^{-/-}) alleles resulted in an increase in systolic blood pressure (SBP, ~20 mm Hg ($P < 0.05$; $n = 4/\text{group}$, measured under anesthesia) compared with Gpr83^{+/+} littermates, suggesting that Gpr83 is needed to keep a normal BP. Renal-specific Gpr83 silencing by the renal subcapsular infusion of Gpr83 siRNA (3 $\mu\text{g}/\text{day}$; 7 days) increased SBP in C57Bl/6J mice on a normal salt diet, relative to mice treated with non-silencing siRNA (120 \pm 5 vs 98 \pm 6 mmHg; $P < 0.05$; $n = 4/\text{group}$). In hRPTCs, forskolin (10 μM , 30 min) increased Gpr83 mRNA (3.5 \pm 0.06 vs 1.0 \pm 0.12-fold; $P < 0.05$; $n = 4-5/\text{group}$), the effect of which was blocked by the protein kinase A (PKA) inhibitor H-89 (20 μM , 1 h). In hRPTCs, phorbol myristate acetate (200 ng/mL, 30 min) which activates protein kinase C (PKC) decreased Gpr83 mRNA (0.43 \pm 0.2 vs 1.0 \pm 0.04-fold, $P < 0.05$; $n = 4-5/\text{group}$), effect that was partially blocked by the PKC inhibitor GF109203x (1 μM , 1 h). Stimulation of hRPTCs with ZnCl₂ (100 μM , 1 h), an activator of Gpr83, increased AKT (2.5 \pm 0.5 vs 1.0 \pm 0.06-fold; $P < 0.05$; $n = 4-5/\text{group}$) and ERK1/2 (1.4 \pm 0.1 vs 1.0 \pm 0.08-fold; $P < 0.05$; $n = 4-5/\text{group}$) phosphorylation and decreased p-38 mitogen-activated protein kinase (MAPK) phosphorylation (0.1 \pm 0.05 vs 1.0 \pm 0.1-fold; $P < 0.05$; $n = 4-5/\text{group}$). Our results suggest that Gpr83 may protect against the development of salt sensitivity. PKA positively while PKC negatively regulates Gpr83 expression. Gpr83 function may be mediated by the phosphorylation of AKT/ERK1/2 and dephosphorylation of MAPK. Thus, several pathways are involved in the Gpr83-mediated regulation of salt-sensitive hypertension.

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Comparison of Two Techniques for Humeral Reconstruction in Unconstrained Shoulder Arthroplasty

There has been an increasing interest in achieving true anatomic replication of native anatomy in unconstrained shoulder arthroplasty. Reconstruction of the humerus is generally done in one of two ways: guided resection of the humeral head using intramedullary cutting guides and version bars and reconstruction with a fixed angle prosthesis or freehand resection of the native humeral head, based on perceived anatomic neck anatomy and reconstruction with a variable angle prosthesis. The purpose of this study is to determine which technique used for proximal humerus reconstruction in shoulder arthroplasty more reliably reproduces native anatomy. Ten sets of cadaveric upper limbs (20 shoulders) were scanned for a pre-resection CT scan to establish preoperative version, neck-shaft angle, center of rotation (COR), and head height. The cadavers were then divided into two groups so that both groups had an equal number of right limbs. Half of the cadavers underwent a freehand cut based on surgeon defined anatomic neck. The other half underwent humeral head resections using a fixed intramedullary guide. The free-hand cut group was reconstructed with a prosthesis that allows the head to be matched to the anatomic cut with 15° of variability in all planes (Depuy-Synthes Global AP). The group cut with the intramedullary guide was reconstructed using a fixed angle stem (Zimmer BF Shoulder). The limbs were then again scanned and the measurements from the reconstructed proximal humeri were compared to those from the native cadavers. The following measurements were taken: humeral head height, neck shaft angle, humeral version (based off the humeral epicondylar axis), and COR in the axial, craniocaudal (CC), and medial to lateral planes (TX). There were no statistically significant differences between the two groups' delta values with respect to head height ($p=.2794$), neck shaft angle ($p=.8311$), version (.1197), or center of rotation as measured in the axial ($p=.109$), craniocaudal ($p=.1754$), or medial to lateral planes ($p=.7343$). However, the fixed angle prosthesis tended to more accurately reproduce native anatomy with regard to humeral height, version, and neck shaft angle. The variable angle prosthesis tended to more accurately replicate COR in the axial, craniocaudal, and medial to lateral planes of reference with standard deviation values that reflected this trend when compared to the fixed angle prosthesis. The results of our study suggest that, with respect to the accuracy of proximal humerus reconstruction in TSA, variable and fixed angle prostheses are equally accurate in reconstructing native proximal humerus anatomy.

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Molecular Signatures of the Different Types of Hyperlipidemia According to the Fredrickson Classification

Hyperlipidemia, characterized by abnormally high levels of lipoproteins in the plasma, is one of the biggest epidemics facing our healthcare system today. The Center for Disease Control and Prevention (CDC) estimates that about one-third of American adults have some form of hyperlipidemia and that of those, only one-third are well-managed. With the growing obesity problem in America and the significant, detrimental health effects that hyperlipidemia can cause, developing new, more effective tools to help prevent, diagnose and treat hyperlipidemias is an urgent matter of public health.

Hyperlipidemias can be classified into three main categories: Primary (familial) caused by specific genetic abnormalities, secondary (acquired) abnormal plasma lipoprotein concentrations due to another underlying disorder, or idiopathic elevated lipoprotein. All three forms can almost double the risk of developing cardiovascular disease, the leading cause of death in the United States, and thus for decades scientists have sought to research, organize and understand how the chronic elevation of these lipoproteins in the blood circulation influence the human body. However, recently, researchers have begun to question the clinical usefulness of one of the most widely used hyperlipidemia classification models which first originated in 1967 and adopted by the World Health Organization, the Fredrickson familial hyperlipidemia classification. This classification is based on the pattern of lipoproteins in the plasma, which was resolved by physical analytic techniques, and includes five categories. Although Fredrickson's model was instrumental in the original understanding of familial hyperlipidemias, this classification is not based on molecular causes of hyperlipidemias and therefore it has limitations in its clinical use, especially in the era of precision medicine. Thus, the objective of this project was to conduct a comprehensive literature review of the published biomedical literature for molecular defects in patients with different types of familial hyperlipidemias. Using this knowledge, we sought to better understand how molecular mechanisms govern elevated lipoproteins and then to subsequently integrate this information into the previously established Fredrickson classification. Our hope is that with this project, along with further research in the future, we are one day able to produce a more useful clinical tool which will provide a better explanation for hyperlipidemias and lead to better patient treatments.

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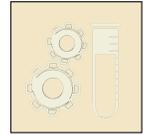
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SCHOOL OF ENGINEERING AND APPLIED SCIENCE

Hidden Bleed Ultrasound Phantom

Every year, GW hospital treats 300 gunshot wound victims and, per protocol, doctors and nurses will calculate a patient's ankle brachial index (ABI) to determine whether or not the injuries sustained by the lower extremities require surgery to repair any internal bleeding. If a patient scores a 0.9 or above on the ABI, they are further examined for damage to the vasculature of their legs. However, patients that score closely to a 0.9 are prematurely sent home from hospitals because their ABI score is within the normal range but post injury internal bleeding can be extremely slow and not affect the ABI value. This is dangerous since their internal bleedings injuries can worsen and have to seek treatment again. Our group proposes using ultrasound as a diagnostic tool to detect internal pseudoaneurysms if a patient scores close to a 0.9 on the ABI. To test the effectiveness of ultrasound in pseudoaneurysm detection, we are developing a tissue ultrasound phantom of the leg with a femoral artery to test ultrasound in this application. We are going to create and develop multiple leg tissue phantoms with femoral arteries, which consist of the same acoustic properties of real tissue and blood. Then, we will mimic different potential gunshot induced pseudoaneurysm scenarios on these phantoms to observe their effects. The phantom will be attached to a peristaltic pump to facilitate blood flow and a pressure sensor will collect data which will allow the maximum and minimum pressures within the artery, ABI and BPM to be calculated via a microcontroller. After ultrasound imaging is performed on the phantom, the image is analyzed using ImageJ and the pseudoaneurysm can be detected and measured. When the femoral artery is punctured, we expect to see the blood mimicking fluid slowly ooze from the puncture site and pool around the artery within the gel. The gel and blood mimicking fluid will contain a similar acoustic attenuation to real blood and soft tissue. This will prove that the gels are biomimetic and can be used in future research to study sonography and produce an algorithm that self detects trauma induced pseudoaneurysms while minimizing the user variability associated with ultrasound in clinical settings.

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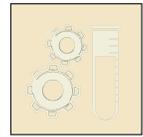
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Acoustic vaporization threshold of lipid coated perfluoropentane droplets

Phase shift droplets that can be vaporized in situ by acoustic stimulation offer a number of advantages over microbubbles as contrast agents due to their higher stability and smaller size distribution. They have potential applications in tumor imaging and drug delivery. The acoustic vaporization threshold (ADV) of droplets with perfluoropentane (PFP) core has been investigated extensively via optical and acoustical means. However, there are noticeable discrepancies among reported ADV thresholds between the two methods. In this study, we thoroughly discuss the criteria and the experimental methodology of determining the ADV threshold. In addition, we explain the possible reasons for the discrepancies between the optical and acoustical studies of the droplet vaporization. The ADV threshold was measured as a function of the excitation frequency by examining the scattered signal from PFP droplets (400-3000nm). The threshold increases with frequency—2 MPa at 2.25 MHz, 2.5 MPa at 5 MHz and 3 MPa at 10 MHz. The scattered response from droplets was also compared with the scattered response from a microbubble at the corresponding excitation pressure and frequency. We found the ADV threshold to increase with frequency. The ADV threshold values determined here are in agreement with past values obtained using an optical technique.

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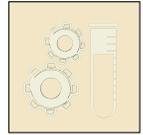
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Speech Analysis to Determine Emotional States of Children with Autism Spectrum Disorder

INTRODUCTION

While previous research has been conducted to find effective means of determining emotional states of speakers, relatively few efforts have been reported on determining emotional states of users with disorders that affect emotional expressions, such as Autism Spectrum Disorder (ASD). The goal of our research is to modify real time emotion prediction models to better suit children with ASD.

METHODS

In order to create a program that is able to predict the emotion being expressed in a live audio sample, a Support Vector Machine (SVM) had to first be made. An SVM was trained using audio features extracted from audio clips within the IEMOCAP dataset. In order to extract features, the audio clips were filtered using various methods, such as Fast Fourier Transforms, Linear Predictive Coding, Mel-Frequency Cepstral Coefficients. These extracted audio features were then used in combination with the annotated data from the dataset to create a mapping of which general combination of features and feature intensities correspond to which emotion elements and their intensities. The annotated data used took note of the expression of emotion elements of arousal, valence, and dominance along with their intensities of expression throughout the audio clip. Audio features of real time speech samples are then able to be extracted and compared to the mappings created by the SVM in order to predict which emotional elements are being expressed and to what extent.

RESULTS

When training the SVM, only a portion of the dataset was used so that when it came time to test the accuracies of the predictions, the other portion of the dataset could be used. The accuracies of prediction for each emotion element was then found. Arousal had the highest prediction accuracy with 60%, valence came in second with 51%, and dominance had the worst accuracy with 46%.

FUTURE WORK

Since the IEMOCAP dataset contains audio clips from mainly neuro-typical adults, this prediction model's accuracy has to be tested on data from neuro-typical children as well as from children with ASD in order to determine the relevance of its prediction model. This data will then be used to improve speech analysis methods and more accurately predict emotions being expressed by children with ASD.

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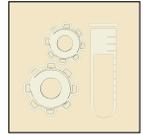
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Motion Learning For Emotional Interaction And Imitation Of Children With Autism Spectrum Disorder

Children with autism spectrum disorder (ASD) often display difficulty with social interaction. We aim to improve their emotional communication skills through the use of an assistive robotic framework, which will identify and dynamically respond to emotion-revealing body language detected through multimodal inputs.

Children with ASD may differ from neurotypical children in areas such as sensory interpretation, communication methods, and emotional response. As a result, children with autism may have difficulty interacting with their peers. Studies show that the incorporation of robots, music, and imitation techniques into therapy sessions all promote the child's level of interest in interacting with others.

We propose the use of an autonomous social robot to identify emotional movements, and to reciprocate them through imitation, in order to form empathy with the child and encourage engagement. This will be accomplished by using multi-dimensional motion learning of dynamic movement primitives.

A dynamic movement primitive (DMP) is a generalized task with specific position goals and end points joined in a sequence to create a scalable movement. Robots utilize DMPs to reproduce core movements in variable settings.

For standard DMP techniques, such as DMP with weighted least squares (WLS), the duration, position, and intensity of the activation weights are preset. Usually, they are evenly distributed across the duration of the movement. For DMP with GMR, the span and placement of the activation functions are modified as the motion is learned.

DMP with GMR is a better method for computer replication of human movements (motion learning) than traditional DMP methods due to its capability for producing more accurate simulations while using the same number of activation states. Our current work can successfully detect the user, generate a skeletal framework, and track, record, and replicate movements in a 1D trajectory. We can record and generate 3D representations of the user's movements, and are working towards 3D replication and testing next.

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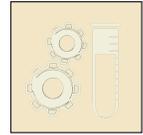
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SCHOOL OF ENGINEERING AND APPLIED SCIENCE

Vital Ring: a Wearable Wireless Multiple-Lead ECG Sensor Embedded in a Flexible Finger Ring

Every year over 380,000 Americans die from a heart attack, of which one third happens outside a hospital. A personalized cardiac monitoring device that can easily conduct regularly heart activity measurement will help identify this group of people. Moreover, the on-demand diagnosis ability in the case of this group of people feel heart irregular may help these people get emergency room timely and get the right measurement timely. Electrocardiogram (ECG) is one of the important tools that widely used in the clinical diagnostic of heart diseases and the hospital cardiac monitoring. By combining the flex PCB technology and PMDS material, a wearable flexible ECG device of a finger ring size is demonstrated, which can be worn and conduct ECG measurement anytime and anywhere. The ring format is significant small and nonintrusive, comparing to other available devices, which makes it easy and comfortable to wear for a long period. At the same time, the ring can provide multiple lead measurement, which can provide more information and is not commonly seen in other wearable ECG sensors.

The ring device can be easily use with smart phones. The Bluetooth low energy (BLE) microcontroller inside ring can communicate with any BLE enabled phone and send the ECG measurement via BLE protocol. The smartphone app can be used to view the ECG plots, analyze them or even send them to their physician. The ring can also be used without phone, then the data will be stored in the ring. The operation of ring is simple. By touching the ring to any part of body, the ECG signal between the wearing finger and the other touch spot is measured, and multiple leads of signal is measured by touch different part of body. By using the ring device daily, long term heart activity can be monitored and saved to keep track of heart health and to be used identify potential heart problems. By using the device when people feel irregular heart activity, early diagnosis can perform to alert people to go to emergency room and get early treatment. This ring is helpful to improve people's daily life and prevent them from extreme heart conditions.

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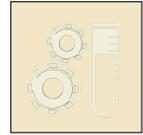
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Sodium-Calcium Exchanger Inhibition Results in Ventricular Fibrillation in Hearts with Pressure Overload Induced Hypertrophy

INTRODUCTION

5.1 million people in the United States have heart failure (HF). Improved treatment of heart failure is critically important because approximately half of patients diagnosed with HF die within 5 years. Cardiac myocyte calcium (Ca^{2+}) imbalance is a characteristic of HF and may cause diastolic dysfunction and focal arrhythmias. During contraction, ryanodine receptors release Ca^{2+} , which is primarily removed by the sarco/endoplasmic reticulum Ca^{2+} -ATPase (SERCA) and the sarcolemmal sodium calcium exchanger (NCX) to initiate relaxation. There is evidence that NCX activity is elevated in failing hearts to compensate for reduced SERCA activity. We tested the hypothesis that NCX inhibition in HF hearts would result in greater contractile dysfunction and arrhythmias than in sham hearts.

METHODS

Rats underwent either sham or trans-aortic constriction (TAC) surgery to induce pressure-overload HF. Rat hearts were excised and Langendorff perfused with a Krebs-Hensleit solution, pH=7.4, oxygenated with 95% O_2 /5% CO_2 . Left ventricular developed pressure (LVDP), heart rate, and coronary flow rate were acquired. After a stabilization period, increasing concentrations of the NCX inhibitor SEA0400 were added. In a subset of hearts, Western blots were performed using SERCA, NCX, and Cx43 antibodies.

RESULTS

During perfusion, baseline LVDP was reduced in TAC animals compared to the sham animals (75.5 ± 19.6 vs 136.2 ± 5.4 mmHg), while heart rate did not differ (222 ± 25 vs 199 ± 22 bpm). Immediately after the final addition of SEA0400, heart rate remained constant (231 ± 21 vs 215 ± 26 bpm). However, approximately one minute after the final concentration of SEA0400 was added, 3 out of the 4 TAC hearts experienced ventricular fibrillation (VF). Western blot analysis did not show a significant change in SERCA or NCX protein expression in the TAC model.

CONCLUSION

Most notably, NCX inhibition resulted in VF for 3 out of 4 TAC hearts, while no sham ($n=3$) hearts experienced VF. LVDP dropped to $84 \pm 4\%$ of baseline in TAC hearts, while sham hearts exhibited no change in LVDP. Surprisingly, this decrease in LVDP was not accompanied by an increase in diastolic pressure (7.6 ± 1.7 vs 6.5 ± 2.6 mmHg). Our results suggest that the sodium calcium exchanger is more important for maintaining contractile function in failing hearts than in healthy hearts. As inhibition of NCX results in decreased LVDP and induces VF in TAC hearts, it is likely that increased NCX activity compensates for decreased SERCA activity in hypertrophic/failing hearts.

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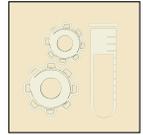
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Toward Real-time Lesion Detection for Cardiac Ablation from Auto-fluorescence Hyperspectral Images

Atrial fibrillation (AF) is a common cardiac arrhythmia caused by abnormal electrical activity originating in ectopic foci in the left atrium. AF can be treated by creating scar tissue to eliminate that activity. Recently, radiofrequency ablation (RFA) has been used to treat the tissues, and electrical conduction testing is used to determine the ablated region. Electro-anatomical mapping can improve RFA therapy success rates. That method must visualize the ablated region directly during the procedure. MRI and CT had been proposed for visualization, but those methods are expensive, space-consuming, and do not provide real-time monitoring. This study seeks to make practicable another visualization approach called auto-fluorescence hyperspectral imaging (aHSI). In that approach, ultraviolet light illuminates the tissues in the left atrium and then tissues emit auto-fluorescence light. We wish to detect the loss of fluorescence of nicotinamide adenine dinucleotide (indicating loss of cells' viability, and thus successful ablation) even in the presence of the auto-fluorescence of atrial collagen. This requires detailed separation of the fluorescence spectra arising from successfully-ablated lesions and from unablated tissue. We use a camera that acquires aHSI data in bands (every 10nm from 420nm to 720nm) with a tunable filter. Light is delivered to and recorded from the cardiac tissue by fiber-optic light guides contained in a catheter. The goal of providing real-time identification of ablated tissue using low signal-to-noise-ratio (SNR) signals requires that the minimum number of bands of wavelengths be acquired and used in classification. A clustering method (k-means) was applied to detect the lesions in the aHSI images. Results show that the detected lesion areas are correct and clearly visible. Further study was conducted to decrease the number of bands from 31 to 4 (using bandpass filters) without reducing the accuracy of lesion detection. This assists in making the approach fast and robust to noise—an important consideration because the total light power that the catheter can deliver is limited. The power therefore should be allocated to the most useful wavelength bands. Through an optimization procedure, we divide the 31 original bands into four contiguous groups. We add the bands in each group to create new, increased-SNR images that are used to detect lesion areas by k-means. We find that four bands are sufficient for accurate lesion detection. These studies provide promising methods to realize real-time intraoperative monitoring and identification of ablated and unablated tissues during the procedure.

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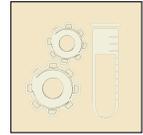
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SCHOOL OF ENGINEERING AND APPLIED SCIENCE

Developing an Adaptive Robotic Tutor to Teach Math Skills to Children

INTRODUCTION

Studies have shown that teaching methods can be facilitated with the use of robot-based technologies. Their effectiveness has been shown to approach, and often surpass, the effectiveness of human tutors. This can be attributed to their ability to achieve a higher level of engagement with children who respond better to technology-based teaching. This work discusses a novel approach for a math-teaching robotic platform with a simulation of the humanoid robot, named Robotis OP2.

IMPLEMENTATION

We developed a novel game-based math activity, targeting children between the ages of 4-7 years. This multi-level game presents questions ranging from number/shape identification to basic arithmetic to more difficult word problems as the child progresses from one level to the next. A deck of cards with all the possible answers to the questions is placed before the child. The child selects one and places it in front of the robot when he has an answer.

The robot uses image processing (shape detection) to read this card, evaluate it and respond to the child. Shape detection module identifies the type and number of shapes on the card. It is implemented in C++ using Visual Studio. It implements the following steps: 1) convert image to gray scale 2) count number of edges using OpenCV's findContours() function, 3) identify detected shapes as square, triangle or circle and 4) count the number of each shape.

For enhanced attentional focus and a more natural social interaction, we also used a face detection to ensure the robot only asks a question when the child is present in its field of view.

In addition, we also designed and implemented a novel Electrodermal Activity-based learning algorithm that allows the robot to estimate the child's internal state. This, in turn, enables it to adapt its teaching method, depending on whether the child is nervous or calm, to achieve an intelligent, individualized teaching process.

We have successfully implemented this interaction as a simulation. We have also proposed possible qualitative and quantitative measures that can be obtained to assess the child's progress. We have also designed questionnaires to record the child's feedback. This robot-based tutoring framework is developed using 3D graphic simulator, Webots, and screenshots and videos are captured to present our work.

Future work includes deployment of our application to the robot, and conducting a full-scale user study to evaluate the effectiveness of our robot as a math tutor for young children.

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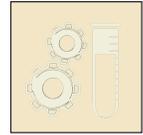
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SCHOOL OF ENGINEERING AND APPLIED SCIENCE

A Robotic Framework to Overcome Sensory Overload in Children with Autism Spectrum Disorder: A Pilot Study

INTRODUCTION

Experiences of sensory overloads are reported to be central to the autistic experience. A higher prevalence of such unusual sensory responses is seen in children on the autism spectrum, when compared to their typically developing and developmentally delayed counterparts. This work focuses on a novel framework designed to teach children with Autism Spectrum Disorders (ASD) how to react to a variety of sensory stimuli. We hypothesize that observing the robot's reactions to stimuli in socially acceptable ways will enable the children to mold their own behaviors accordingly.

THE FRAMEWORK

Two different robotic platforms are used: a mobile robot with a character display, Romo, for facial expressions, and a small humanoid robot, Mini, for emotional expression through gestures and movements. We first introduce the child to Romo's expressions through an Emotion Game, implemented as a computer game, whereby children react to each of Romo's emotions by selecting the emotion it makes them feel. The next set up consists of five sensory stations, one for each of the visual, auditory, olfactory, gustatory and tactile senses. The robotic agent navigates them one by one, and responds to the different stimuli presented to it. The stimuli are chosen to emulate scenarios, both negative and positive, encountered by children in their everyday lives, some of which may possibly be sources of sensory overload to these children. RGB-D sensors are used to record and quantify children's movements. All sessions are video-recorded.

PILOT STUDY

Using this framework, we conducted a small pilot study consisting of eight participants, three children with ASD (two played the emotion game only) and five neurotypical children. Each session lasted about 15 minutes. The purpose of this preliminary study was to identify a general response to our framework, and to verify if the children's responses meet our expectations. Our next step is to conduct a more long-term user study, involving a much larger number of participants, to improve the reliability of the obtained results.

RESULTS

Most participants clearly displayed high levels of engagement in the interaction and were able to accurately interpret the robot's behaviors to a large extent. One child with ASD, even though he did not focus entirely on the activity at hand, imitated the robot's behaviors voluntarily, and was enthusiastic about learning how to control the robots himself. RGB-D sensor data shows meaningful patterns of short-term effects, together with qualitative analysis of the video recordings.

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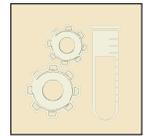
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SCHOOL OF ENGINEERING AND APPLIED SCIENCE

Breast Cancer Detection by an Infrared Imager: Evaluating the Thermal Resolution

Early detection of breast cancer is the key to higher survival rates for breast cancer patients. We are investigating infrared thermography as a noninvasive adjunct to mammography for breast cancer screening. Thermography detects elevated skin temperatures that arise from increased blood flow as a consequence of the angiogenesis that accompanies tumor growth. Previous work indicates that differences of as little as 0.1 K can be clinically important. This study assesses the suitability for thermography of the N2 Imager thermal infrared camera by measuring its thermal resolution and determining the effect of automatic gain control (AGC).

To measure the thermal resolution, a blackbody (BB) thermal radiator, was imaged with the N2 Imager at temperatures ranging from 32°C to 42°C, 60 images were recorded at each temperature. The line of best fit between temperature and the count value for each pixel was computed, and the mean line of best fit was found. The thermal resolution was calculated by dividing the mean standard deviation (across all pixels) by the mean slope and was found to be 47.5 mK/digital count, using a 95% ($\pm 2\sigma$) confidence interval derived from the mean line of best fit. To test AGC, a cup of water at 44°C was allowed to cool to room temperature; 60 images were taken every minute for 25 minutes. The experiment was repeated with AGC OFF and ON. When AGC is ON, the digital count is saturated at all temperatures, because AGC maintains a fixed gain by distributing the detected temperature range over the entire grayscale (14-bits). Therefore, the cool-down curve of the water cup was not observed with AGC ON, but clearly seen when AGC was OFF.

The results confirm that the N2 Imager is suitable for a preliminary clinical study that began in September 2016. Patients diagnosed with breast cancer are imaged with the camera for a total time of 15 minutes. This is done to observe the cool-down of the breast tissue. Therefore, for our purposes, AGC must be kept off; otherwise valuable data related to the cool-down of breast tissues would be lost. Current work includes acquiring images from breast cancer patients, as well as developing a software to analyze images and locate warm regions on the breast.

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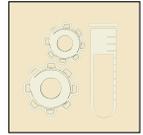
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Automated High-Throughput All-Optical Dynamic Cardiac Electrophysiology for Drug Testing and Disease Modeling Using hiPSC-CMs

Future modeling of cardiac diseases and patient-specific drug testing will rely on effective use of human stem cell-derived cardiomyocytes (hiPSC-CMs). These cells are often criticized for their immaturity and variability in phenotype, emphasizing the lack of adequate tools for massively-parallel screening and quantification of electrophysiological parameters. OptoDyCE, our automated high-throughput platform, combines optogenetics and fast optical imaging to perform functional characterization of both 2D and 3D hiPSC-CMs constructs. We validate the system's ability to predict cardiotoxicity *in vitro* by performing dose-testing of vanoxerine, a compound withdrawn from clinical trials when found to have pro-arrhythmic effects. We also demonstrate the applicability to disease modeling through functional characterization of a new hiPSC-CM model of a rare genetic disorder, Ogden syndrome. This all-optical approach provides a high-throughput means of cellular interrogation, including characterization of the relationship between membrane potential and intracellular calcium. Variation over space (effects on cell coupling and synchronization) together with temporal instabilities (alternans, early and delayed after-depolarizations, spontaneous calcium release, and after-contractions) can be quantified to assess irregularities in hiPSC-CMs not possible by other methods.

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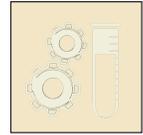
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SCHOOL OF ENGINEERING AND APPLIED SCIENCE

Ultrasound-enhanced Drug Delivery for Treatment of Onychomycosis

INTRODUCTION

Onychomycosis is a fungal nail disorder that can be extremely painful. In onychomycosis, the fungus lives on the nail bed. Due to the poor permeability of the nail, current antifungal drugs, which are applied to the top of the nail, are unable to reliably reach the nail bed, making them ineffective in treating the fungus. The aim of our study has been to determine the effectiveness of using ultrasound to increase the permeability of the nail with the goal of improving outcomes in the treatment of onychomycosis.

MATERIALS AND METHODS

Porcine nails were used for all experiments. Two sets of ultrasonic experiments were performed. In both experiments, planar ultrasound transducers were used to sonicate the nails using frequencies of 400 kHz, 600 kHz, 800 kHz, and 1 MHz, an intensity of 1 ± 0.1 W/cm² and a duration of 5 min in continuous mode. In the first experiment, the luminosity experiment, a piece of porcine nail was placed in a beaker beneath the ultrasound transducer. The beaker was then filled with a drug-mimicking hydrophilic blue dye. After treatment, a microscopic image of the nails' cross section was taken. This image was analyzed to compare the average brightness - and therefore permeation of dye. In the second experiment, the diffusion cell experiment, a Franz Diffusion Cell was used. The nail was placed above a receiving compartment filled with saline and the donor compartment was filled with the same blue dye. The nail was sonicated and the absorbance of the receiving compartment was measured to determine the permeation of dye through the nail. The final experiment was a safety modeling experiment performed using PZFlex software and a model of the human toe.

RESULTS AND DISCUSSION

In both the luminosity and diffusion cell experiments, the nails were found to have more permeation at higher frequencies. In the luminosity experiments (n=8 per group), the 600 kHz and 800 kHz frequencies were found to be statistically significant ($p < 0.05$). The diffusion cell results found statistical significance ($p < 0.05$) at 400 kHz, 600 kHz, 800 kHz and 1 MHz tests (n=6). In the temperature modeling experiment a safe temperature increase was found at all frequencies.

CONCLUSIONS

Our ongoing study efforts focus on testing the diffusion of an antifungal nail polish drug, ciclopirox, through the porcine nails. If proven successful our method may find a clinical application due to the non-invasive nature of proposed therapeutic ultrasound treatment.

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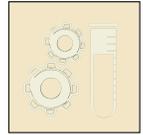
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SCHOOL OF ENGINEERING AND APPLIED SCIENCE

Wearable Sweat Alcohol Sensor

In 2010, despite education and awareness, 112 million individuals self-reported being impaired while driving their vehicle and 1.2 million individuals were arrested for driving under the influence of alcohol or narcotics. It was reported in 2012 that 10,322 deaths were related to alcohol-impaired driving crashes and the annual cost related to alcohol related incidents totals close to \$59 billion. Although commercially alcohol sensors are available, they typically measure breath, therefore lacking continuous monitoring capabilities and requiring user operations. To address this challenge, there is a growing interest in developing non-invasive wearable sensors, capable of monitoring blood alcohol content (BAC) continuously and in real-time. Such devices could potentially be a valuable tool for research and consumer protection.

Transdermal alcohol monitoring is one of the method to achieve this goal. It measures the transdermal alcohol content (TAC), alcohol vapors released form the skin, and estimates the exact BAC level based on the readings. This technology has been widely adopted in the criminal justice system, especially in alcohol abuse. However, existing monitors are expensive, bulky, and not accessible to typical consumers.

In this project, we designed and prototyped a wearable transdermal alcohol sensor based on modern low-power electronics and state-of-the-art ethanol fuel cell technologies. The footprint of the fabricated prototypes is 62 x 29 x 12mm, which can be fixed onto one's body like a transdermal patch. A small electrical signal proportional to the alcohol concentration is generated and recorded by the sensor system in real-time. The stored data can be transferred to a PC through a customized USB cable. A windows-based program is developed to retrieve, analyze, and display the data. Powered by a CR2032 coin battery, the sensors can last over 3 days. 10 healthy subjects are recruited to conduct alcohol consumption experiments while wearing the devices, to calibrate and characterize our sensor prototypes. The results are compared against the BrAC values measured by the commercial breathalyzer BACTRACK S80.

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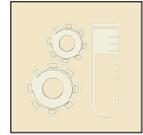
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Big Data Approach to Electron Microscopy Acquisition and Analysis of Neuronal Tissue: Utility in Analysis of Neuronal and Synaptic Alterations in a Mouse Model of 22q11 deletion Syndrome

A novel approach was applied using scanning electron microscopy and block-face imaging to areas of the nuclei of the hypoglossal nerve to compare the neuronal architecture and cellular alterations in the mouse model of DiGeorge Syndrome. Since the swallowing and feeding is frequently compromised in human patients carrying this disease our hypothesis is that XII neurons are affected by the deletion in a way that prevents them to perform their function. Therefore, the focus was on XII cranial nerve, because it contains the neurons innervating the tongue. To accomplish the objective, an approach for data acquisition and analysis is designed that allows sampling the entire area of the XII nucleus at 2nm pixel size. This approach allowed us to apply several strategies for data collection and analysis that are impossible with traditional electron microscopy methods.

Brainstem tissue was collected from wild type mice and LgDel mice (carrying similar 22q11 deletion as the patients with DiGeorge Syndrome) after perfusion with glutaraldehyde. The brainstems containing the XII nucleus were cut into 400 μm sections, fixed with osmium tetroxide, infiltrated with uranium acetate, dehydrated in ascending alcohols, and infiltrated in resin that was polymerized in wafers at 60°C. Thin sections of 100 μm were cut with a diamond knife and mounted on silicon wafers for imaging. Imaging was performed using the FEI Helios SEM (FEI), equipped with solid-state circular backscattering detector. Imaging was done using 2kV accelerating voltage and current between 100-400 pAmps. MAPs software was used to integrate at different layers the low magnification data (500x), moderate magnification data (5000x) and high magnification data (80,000x). The images at the highest magnification were taken at 2nm pixel size. Serial tile images from one side of the nucleus were taken and stitched together in one large RAW image, which was further transferred to Photoshop for data conversion. Sections of the large image were then selected and transferred to Arivis software as .tif data for segmentation and analysis. Manual annotations are made and stored using Arivis. The data is exported into a spreadsheet. The purpose of the research is to quantitatively explain cellular degeneration and understand the structural differences between Wild types cells and LgDel cells in hopes of one day treating the issues created by DiGeorge Syndrome.

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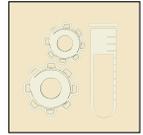
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SCHOOL OF ENGINEERING AND APPLIED SCIENCE

3D Morphological Analysis of Neurons in Hypoglossal Nucleus in Mouse Model of DiGeorge Syndrome

Pediatric dysphagia is a condition characterized by difficulties in feeding and swallowing in infants and children. The tongue is one of the structures involved in feeding and swallowing, and abnormalities in tongue control occur in patients suffering from dysphagia. Cranial nerve XII, hypoglossal nerve, is a nerve that originates from the hypoglossal nucleus in the brain stem and innervates the tongue; it is responsible for proper functionality of the tongue. DiGeorge Syndrome feeding and swallowing abnormalities occur in the early developmental stages of the disease. The goal of this research is to further identify morphological differences of neurons within the hypoglossal nucleus. These anatomical and physiological differences will be observed in wild type mice (WT) and in mice with a large deletion of genes (LgDel) that is equivalent to 22q11DS (the gene deletion causing DiGeorge Syndrome) in humans. These differences will be studied by evaluating parameters, such as volume and quantity of neurons in the hypoglossal nucleus. As well as, the dendritic lengths, sizes, and branching points will be analyzed as well the volume of individual neurons in the hypoglossal nucleus "" which have undergone electrophysiological measurements and parameters.

Utilizing confocal and fluorescence microscopy techniques with the ZEISS 710 confocal instrument, the student acquires 3D data sets that can be further analyzed. The images will then be observed to identify qualitative differences of the cells. Next, the images will be analyzed utilizing Imaris because Imaris contains options that allows users to import these image sets and reconstruct 3D structures from these data sets. The 3D reconstructions obtained will allow the student to obtain quantitative data that can be further analyzed. The data obtained strongly suggests some issues with the neural circuitry of the hypoglossal due to the smaller neuronal sizes, which may potentially be a factor in developmental dysphagia. Another striking discovery is that the standard deviation of the mean volumetric value of the neurons increases in LgDel animals (i.e., variability). Finally, we found that some of the hypoglossal neurons show alterations in their dendritic branching and some show misdirected axons. Both morphological parameters support the signal processing and integrative function of hypoglossal motor neurons, but we will need to analyze 40-60 more cells in order to validate the initial finding and to build reliable population data.

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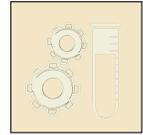
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Effects of ultrasound in presence of microbubbles for cartilage and bone tissue regeneration in 3D printed scaffolds

Gas-filled microbubbles encapsulated with lipids and other surfactants are highly responsive to ultrasound, which has led to their effective role as ultrasound contrast agents (UCA). In this study, for the first time, we used lipid-coated microbubbles (MB) and lipid and nano-hydroxyapatite (n-HA) coated MB prepared in-house to better harness the beneficial effects of ultrasound stimulation on proliferation and chondrogenic and osteogenic differentiation of human mesenchymal stem cells (MSCs) within novel 3D printed poly (ethylene glycol) diacrylate (PEG-DA) hydrogel scaffolds with and without embedded n-HA. A significant increase in cell number ($p < 0.001$) was observed with low intensity pulsed ultrasound (LIPUS) treatment in the presence of 0.5 % (v/v) MB and lipid and n-HA coated MB after 1, 3 and 5 days of culture in scaffolds with and without n-HA. MSC proliferation increased by 20% with LIPUS, 37% with LIPUS and MB, and 43% with LIPUS and lipid and n-HA coated MB for one day studies. MSC proliferation was also enhanced up to 40% after 5 days of culture in presence of MB and LIPUS while this value was only 18% when excited with LIPUS alone in scaffolds not embedded with n-HA. Our 3-week chondrogenic differentiation results demonstrated that combining LIPUS with MB significantly enhanced both Glycosaminoglycan (GAG) and type II collagen production. Therefore, integrating LIPUS and MB appears to be a promising strategy for enhanced MSC growth and chondrogenic and osteogenic differentiation for potential tissue engineering and regeneration therapies.

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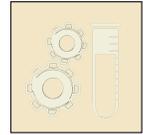
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SCHOOL OF ENGINEERING AND APPLIED SCIENCE

In Vitro Hydrodynamic Investigation of Polyvinyl Alcohol Scaffolds for Drug Delivery

In the field of tissue engineering, rapidly-prototyped polymer scaffolds are being researched for allografting and *in vivo*, ultra-fast drug release applications. Degradation of these scaffolds must match patient recovery time. General degradation of polymers occurs in two stages: polymeric matrix swelling and structural failure. Accordingly, the objective of this study is to monitor the degradation, diffusion, and transport of polyvinyl alcohol (PVA) scaffolds in an alkaline medium. The diffusion coefficient of diluted PVA was measured using a Polson cell apparatus and UV spectrophotometer. A Beer's Law calibration curve was found using known concentrations of dilute PVA and their absorption at 275 nm wavelength light. The base concentrations were then inserted into the bottom section of the Polson Cell while deionized (DI) water was inserted into the top as the solvent. The Polson Cell-sections were aligned for certain time durations and then offset. The absorption at 275 nm wavelength light of the solution from the top section was found. The diffused concentrations were determined using the absorbance values and the Beer's Law calibration curve. Using these diffused concentrations, the diffusion coefficient for a base concentration of 50 mg/mL was found to be $0.6096 \times 10^{-5} \text{ cm}^2/\text{s}$ ($\pm 4.3\text{e-}06$ at $\sim 25 \text{ }^\circ\text{C}$), analytically. The dynamic degradation was studied in a lab-scale, curved artery-based flow loop system with steady and unsteady flow conditions for PVA scaffold geometries of 20%, 40%, and 60% infill. The unsteady flow rate was modeled with a carotid artery-based pulsatile flow rate waveform. Two microelectromechanical systems-based (MEMS) were used to measure the pressure differential across the scaffold in the flow loop and the degradation of the PVA-scaffolds was monitored. All experiments were performed at room temperature ($\sim 25 \text{ }^\circ\text{C} \pm 1 \text{ }^\circ\text{C}$) with deionized (DI) water as the working fluid and pre-wetted scaffolds to ensure homogeneity. The results have tremendous potential to impact our understanding of drug-release and transport in clinically-relevant scenarios.

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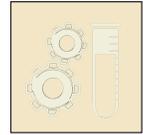
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SCHOOL OF ENGINEERING AND APPLIED SCIENCE

Low-Frequency, Low-Intensity Ultrasound as a Potential Treatment for Type 2 Diabetes

OBJECTIVE

The objective of this study was to explore the safety and efficacy of a potential new treatment method that utilizes a non-invasive application of ultrasound energy to induce exocytosis of insulin from pancreatic beta cells. Amperometric measurements offer confirmation of secretion as well as data that could lead to optimization in controlling the release via ultrasound application. Finite-element modeling studies provide information regarding the thermal and mechanical effects of therapeutic ultrasound in the human abdomen.

METHODS

Initial experiments focused on detecting exocytotic secretions from pancreatic beta cells in response to ultrasound stimulation using carbon fiber amperometry. Neurotransmitters, specifically dopamine and its precursor L-DOPA, were loaded into secretory vesicles in beta cells and co-released with insulin. Cells were stimulated at 800 kHz and an intensity of 0.5 W/cm² for 5 s, 10 s, and 15 s at various time intervals. Secretion of insulin was detected through the oxidation of these neurotransmitters using commercially available carbon fiber electrodes. A negative control group was included in which cells were not loaded with the dopamine and L-DOPA, however still exposed to ultrasound. Calcium dependence was evaluated by stimulating cells in the presence of an extracellular calcium chelator, EGTA. In parallel with these experiments, a finite-element modeling study to determine the safety of therapeutic levels of ultrasound to the human pancreas in vivo without adverse mechanical or thermal effects in the surrounding tissues.

RESULTS

Secretory amperometric readings were recorded after application of ultrasound at the parameters described above. With the application of consecutive ultrasound pulses, a prolonged response was recorded for a prolonged stimulation. In experiments where Ca²⁺ dependence was explored, a statistically significant lower response was observed ($p = 0.01$). In addition, the negative control group with unloaded cells did not produce an amperometric response. Ongoing work is focusing on finding the optimal acoustic windows for ultrasound applications in patients through simulations.

CONCLUSIONS

These results confirm that ultrasound stimulation induces secretory events in beta cells, and points towards a Ca²⁺ dependent process. Ongoing work is looking at the elucidation of mechanisms of ultrasound in the stimulation of insulin release and determining safety and effectiveness of this method in clinically relevant models including human pancreatic islets and in vivo diabetic rat model. Our proposed technology would directly target beta cell dysfunction, one of the underlying causes of insulin deficiency in type 2 Diabetes, potentially resulting in a new therapeutic approach for the treatment of type 2 Diabetes.

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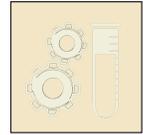
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Ultrasound Stimulation of Insulin Release from Pancreatic Beta Cells as a Potential Novel Treatment for Type 2 Diabetes

OBJECTIVE

We are proposing to use therapeutic ultrasound to correct for the inability of the pancreas to secrete insulin in patients with type 2 diabetes (T2D). Controlling T2D is often difficult as pharmacological management routinely requires complex therapy, and loses its effectiveness over time. Thus, there is a growing interest in finding alternative methods for the treatment of this disease. The objective of this study is to explore a novel, non-pharmacological approach that utilizes the application of ultrasound energy to augment insulin release from pancreatic beta cells.

METHODS

Our experiments focused determining the effectiveness and safety of ultrasound application in stimulation of insulin release from pancreatic beta cells. ELISA insulin release assay was used to determine and quantify the effects of ultrasound on insulin release in INS beta cells. Effects of ultrasound on cell viability were assessed by trypan blue dye exclusion and MTT cytotoxicity assays. Planar ultrasound transducers with center frequencies of 400 kHz, 600 kHz, 800 kHz and 1 MHz were used to expose cells for different durations at intensities ranging from 0.1 to 1 W/cm². Carbon fiber amperometry studies were used for studying the temporal dynamics of ultrasound-induced secretory release and coupled with real-time calcium (Ca²⁺) fluorescence imaging to highlight the role of Ca²⁺ in this process. Other studies included passive cavitation detection, thermal studies and finite-element modeling of the different experimental setups used in our studies.

RESULTS

Our results indicated that cell viability was not significantly affected during and for up to 30 minutes after treatment when cells were exposed to ultrasound frequencies of 800 kHz and 1 MHz, while keeping their metabolic activity at similar levels compared to the sham group. However, cell viability was highly reduced (by 80-90%) when the cells were exposed to ultrasound frequencies of 400 kHz and 600 kHz ($p < 0.001$). Cell exposure to ultrasound at frequency of 800 kHz resulted in release of approximately 25 ng/ml/10⁶ cells ($p < 0.005$) in comparison to no measurable release in cells of the sham group. Amperometry studies suggest that such release is at least partially regulated by Ca²⁺, an observation supported by increased intracellular Ca²⁺ during ultrasound exposure as observed with fluorescence imaging.

CONCLUSIONS

If shown successful our approach may lead to new methods in the treatment of diabetes and other secretory diseases. Our future studies will focus on application of optimized ultrasound parameters to more physiologically-relevant models such as human pancreatic islets and animal studies.

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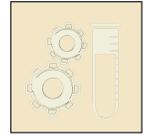
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SCHOOL OF ENGINEERING AND APPLIED SCIENCE

Inkjet Printed, Passive Sensing Networks with Biological Materials

Chemical sensors are needed for many applications, from toxic gas detection in hazardous work environments, such as a laboratory, to lab-on-a-chip devices. Current sensor designs require expensive fabrication processes, and designs are limited to one sensor per platform. Because current sensor designs are also electronic, onboard power supplies must be included, and thus limit the lifetime of the device. One solution to eliminate onboard power supplies would be to utilize colorimetric sensors, or sensors that can determine a concentration of a compound with the help of a color reagent. However, a simple method of manufacturing these types of sensors at a low cost and at a high volume is still not available.

To overcome these sensor limitations, inkjet printing can be utilized to create sensors at a low cost and high volume. Two biological solutions were made to be used as inks in an inkjet printer. The first, containing hydroxypropyl cellulose powder dissolved in deionized water, was shown to display effective color change using a Langmuir-Blodgett coating technique. The second, using M13 bacteriophage, displayed similar results using the same technique. The goal of this project is to recreate these results by fabricating sensors via inkjet printing, as the sensors could be made at a faster rate and a larger scale.

In order to print these sensors, each solution must have properties that fall within a certain range. Specifically, the surface tension of each solution must be within 28 - 42 dynes/cm, and the viscosity must be between 2 - 30mPa•s. Inks characterized outside of these ranges, while still printable, encounter poorer performance. The inks were characterized using a DeNouy Interfacial Tensiometer and a TA Instruments Discovery Hybrid Rheometer. After characterization, the inks were then printed using a Dimatix Materials Printer DMP-2831 onto gold-coated substrates. Cellulose sensors exhibited good printing, forming an even film across the substrate. The M13 bacteriophage sensors, on the other hand, showed poor film formation, displaying a beading effect most likely due to the high surface tension of the solution, or the low surface energy of the substrate. When tested in a homemade gas chamber, however, both sensor types exhibited color change. The M13 bacteriophage sensor, however, should be able to show a more discernable color change given a better film made from printing. The color change results were verified via a Matlab program showing the change in RGB intensity over time.

This research so far has proven that a biological material can be printed with reasonable accuracy using the DMP-2831, which is promising for the future of sensor devices. Further research will look into additives to decrease ink surface tension, or to change physical properties of the substrate in order to eliminate the beading effect shown on the M13 bacteriophage sensors. After obtaining a device displaying good printing, statistical tests can be performed to show the accuracy of the sensor, the optimal concentration of each volatile organic compound, and the minimum amount of volatile organic compound that can be detected by the sensing device.

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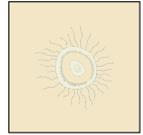
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miR-200b May Serve as Therapeutic Target for Triple Negative Breast Cancer

Breast cancer progression involves stepwise transition from atypical ductal hyperplasia (ADH), to ductal carcinoma in situ (DCIS) and then to invasive ductal carcinoma (IDC). Among the IDCs, triple-negative breast cancer (TNBC) is an aggressive subtype with poor prognosis, and accounts for a large number of metastatic cases and deaths. The dysregulation of microRNAs (miRNAs) in breast cancer has been widely reported. The stability of miRNAs in Formalin-Fixed, Paraffin-Embedded (FFPE) tissues and body fluids makes miRNAs as attractive diagnostic and therapeutic markers in breast cancer. The miR-200 family consisting of 5 members (miR-200a, -200b, -200c, -141, -429), has been shown to play crucial roles in cancer initiation and metastasis, and potentially be useful for the diagnosis and treatment of cancer. And miR-200 family has been shown to affect each step of the tumor metastatic cascade. Stable expression of miR-200b greatly reduced metastatic potential of TNBC cells, such as MDA-MB-231. However, the exact role of miR-200b in TNBCs is yet to be revealed. Our objective is to elucidate the potential diagnostic and therapeutic role of miR-200b in TNBC. In the present work, breast cancer cell lines were obtained from ATCC and cultured as instructed. With GW IRB approval, the breast cancer tissue blocks were obtained along with their pathological report, and subject to microdissection. The peripheral blood samples from patients were collected. Total RNA was isolated using Trizol reagent (Life Technologies) following the manufacturer's instructions. Real-time qRT-PCR analysis was performed using Taqman MiRNA Reverse Transcript Kit (Applied Biosystem). The results were analyzed by the Student's t-test. We found that lower expression of miR-200b in TNBC cells lines such as MDA-MB-231, Hs578T and MDA-MB-468, compared to non-TNBC cells lines, MCF-7, T47D and the immortalized epithelial cells line MCF-10A. In clinical sample analysis, we found that lower expression of miR-200b in 8 of 10 (80%) TNBCs while in 9 of 20 (45%) non-TNBC tissues. However, we did not detect any significant changes of miR-200b expression among ADH, DCIS and IDC in both tissue and blood samples. These results suggest that loss of miR-200b expression plays a crucial role in TNBC aggressiveness, and targeting miR-200b may be a novel approach in treating TNBC.

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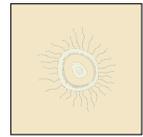
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SCHOOL OF MEDICINE AND HEALTH SCIENCES

A Retrospective Review of Cancer Findings Upon Excision of High Risk Lesions Found on Core Needle Biopsy in a Single Academic Breast Center with a Robust High Risk Screening Program

BACKGROUND/SIGNIFICANCE

A variety of high risk lesions are frequently diagnosed upon core biopsy of screen detected breast imaging abnormalities. However, the actual incidence of upstaging to cancer upon excision is not well established. In the current era of cost containment it has been suggested that excision of Flat Epithelial Atypia (FEA), Lobular Carcinoma In Situ (LCIS), Atypical Lobular Hyperplasia (ALH) and papillomas may not be necessary although there seems to be a remaining consensus that Atypical Ductal Hyperplasia (ADH) deserves an excision. Determining the cancer incidence from excisions of high risk lesions would help determine treatment guidelines. Surgical intervention may continue to be indicated after the diagnosis of a high risk lesion and risk reduction medical therapy may be considered in more cases.

MATERIALS AND METHODS

Using a retrospective review of electronic medical records and outside pathology reports from 2012-2016 at Pacific Breast Care Center, a UCIrvine Health Medical Practice, we established the incidence of findings of a cancer on excision of high risk lesions including the high risk lesions above, radial scars, and complex sclerosing lesions found in image guided core breast biopsies. We compared this to a cohort of excisions of benign lesions without high risk characteristics, also diagnosed with image guided core needle biopsy.

RESULTS

The electronic medical records of patients who had an image guided core needle biopsy with benign results during the years 2012 through 2016 were analyzed.

The preliminary review of patient electronic medical records showed an incidence of finding cancers in 24% of high risk lesions upon excision. The incidence without including the papilloma group showed a 31% incidence of finding cancers upon excision. The incidence of finding cancer in the benign group, without high risk lesions, was 1.4 %. Statistical analysis of the high risk biopsy group (n=96) and the not high risk biopsy group (n=69) demonstrated the alpha to be 0.05, and the power of the study to be 95% in detecting a difference between the high risk biopsy group's incidence of cancer (24%) and the not high risk groups (1.4%).

DISCUSSION

Based on the 24% rate of cancer on excision of high risk lesions found on core biopsy, excision should continue to be recommended to detect coexisting early cancers and therefore allow early treatment. Because the incidence of cancer is much lower in the papilloma group, 7%, papilloma excision should be considered on a case by case basis. One of the limitations of this study is the age differences in the high risk biopsy group and the not high risk biopsy group, 55 years versus 40.3 years. The possibility that the patient population in this clinic is a high risk group may be another limitation of the study, as this study has not yet examined the risk of the patients in each cohort.

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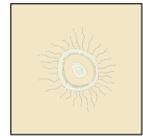
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INSTITUTE OF BIOMEDICAL SCIENCES

Lymphocyte-Nanoparticle Biohybrids as a Combined Nanoimmunotherapy for Cancer

T cell therapies have shown promise against leukemias, but little efficacy against solid tumors. Success is limited by an immunosuppressive tumor environment, which precludes effector cell accumulation at the tumor site or renders effector cells dysfunctional preventing tumor clearance. As such, strategies to improve effector cell function at the tumor site have the potential to enhance responses. We have observed that multifunctional nanoparticles can confer additional properties to existing cell-based immunotherapies including ablative heating, magnetic responsiveness, and localized drug delivery. We thus sought to evaluate whether immune cell-nanoparticle biohybrids (ImmunoNPs) could combine the potent cytotoxic capabilities of antigen-specific T cells and ablative therapy from nanoparticles to enhance immune responses within the suppressive tumor microenvironment.

We synthesized a robust biohybrid capable of antigen-dependent cytotoxicity, followed by localized ablative therapy to efficiently eliminate residual disease by conjugating T-cells with Prussian blue nanoparticles (which absorb light in the near infrared range). We demonstrated T stable cell-nanoparticle conjugation over at least 3 days (51-65.8% by flow cytometry). T-cells within the biohybrid retained their proliferative ability (66.4% for T-cells vs. 66.5% for biohybrid by CFSE dissolution) and effector phenotype (mean 62.7% CD8+ T-cells vs. 55.2% CD8+ biohybrid, n=7), with no significant increases in markers of exhaustion (PD1, TIM3, LAG3). Furthermore, we demonstrated improved cytotoxicity against tumor antigen-expressing target cells following treatment with ImmunoNPs: each component individually was able to decrease target cell viability from 92.7% (target cells alone) to 46.3% (T-cells alone) or 43.8% (NPs with laser), however maximal eradication occurred with the tandem biohybrid (target cell viability of 28%). Additionally, we found that ablative therapy with non-cellularized Prussian blue nanoparticles was capable of increasing tumor lymphocyte infiltration 3-fold (p<0.05) compared to untreated tumors in vivo, suggesting that photothermal ablation can augment endogenous immune responses.

We believe this work represents a novel modality that combines the strengths of cell-based immunotherapy with nanomedicine in order to achieve maximal therapeutic responses to challenging malignancies and infectious diseases.

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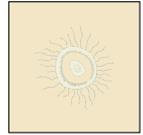
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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Usefulness of Breast-Specific Gamma Imaging (BSGI) in the Detection of Breast Cancer

BACKGROUND

Breast Specific Gamma Imaging (BSGI) is increasingly being used as a diagnostic tool for the detection of breast cancer, using technetium 99m sestamibi to identify physiological differences between cancerous and normal breast tissue. Our study retrospectively evaluates pathologic correlates to positive BSGI findings in the detection of breast cancer.

METHODS

A retrospective review was performed of patients with positive BSGI examinations (200 total) during a 1-year period. Using biopsy/surgical pathology or 2 years mammography/ultrasound/MRI follow-up as correlation, we determined the positive predictive values of BSGI findings when categorized by: (i) character of suspicious region [mass, non-mass, asymmetric diffuse], (ii) character surrounding breast parenchymal tissue [homogeneous, heterogeneous], (iii) breast density [dense, non-dense], and (iv) likelihood of cancer based on degree of observable radiotracer uptake update [1 - low likelihood, 2 - moderate likelihood, 3 - high likelihood].

RESULTS

There were 200 patients with 276 positive BSGI lesions, of which 130 were true positives; true positive rate (TPR) = 47.1%. There were 154 mass-like lesions, 108 non-mass-like, and 14 asymmetric diffuse; TPR's = 54.5%, 38.0%, and 35.7%, respectively. There were 149 findings with homogeneous parenchymal uptake and 127 with heterogeneous uptake; TPR's = 53.7% and 39.4%, respectively. There were 71 findings from non-dense breasts, of which 39 were positive for cancer (TPR = 54.9%), and 189 findings from dense breasts, of which 82 were positive (TPR = 43.4%). There were 104 lesions with a likelihood of cancer score 1, of which 24 were true positives (TPR = 23.1%); 65 lesions with likelihood of cancer score 2, of which 17 were true positives (TPR = 26.2%); and 107 lesions with likelihood of cancer score 3, of which 88 were true positives (TPR = 82.2%).

CONCLUSION

Understanding the positive predictive value of BSGI when categorized according to character of lesion, parenchyma, breast density, and degree of radiotracer uptake may improve early diagnosis of breast cancer. Variability in mass-like or non-mass-like character of positive BSGI findings are not useful determinants for probability of malignancy, while the degree of observable radiotracer uptake is. Therefore, subtle, small-area foci of radiotracer uptake should not be managed with less urgency than more obvious, large-area foci. Additionally, it is more difficult to detect cancerous lesions in women with heterogeneous parenchymal enhancement compared to homogeneous parenchymal enhancement. Lastly, detection of breast cancer with BSGI is not significantly affected by breast density, which makes it a promising modality for breast cancer screening.

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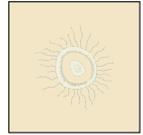
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Rnaseh2c is a Candidate Metastasis Susceptibility Gene in Breast Cancer

Metastatic breast cancer is a devastating disease with a 5-year survival rate of only 26%. This is due to a lack of effective therapies against established metastases and an inability to identify high risk patients who would benefit from specific adjuvant therapies to prevent metastatic progression. We have shown in mouse models that spontaneously arising tumors metastasize with different severity based on the mouse genetic background. Using systems genetics approaches we have identified genes correlated with metastasis and survival in both mice and humans. Rnaseh2c was identified as a novel candidate metastasis susceptibility gene. This gene encodes a scaffolding subunit of the Ribonuclease H2 enzyme which cleaves DNA at sites of misincorporated ribonucleotides to facilitate their removal. Experimentally modulating Rnaseh2c expression in a murine mammary cancer cell line resulted in significant changes in pulmonary metastasis, confirming this gene as a metastasis modifier. Mutations in Rnaseh2c are known to cause Aicardi-Goutieres Syndrome, a neurological autoinflammatory disorder that overlaps clinically with congenital viral infections and the autoimmune disease Systemic Lupus Erythematosus. Given this, we hypothesized that altered expression of Rnaseh2c in breast cancer cells affects metastasis by engaging the immune system. To investigate immune system involvement, we analyzed metastasis in immunocompromised mice. T cell deficiency ablated the effect of reduced Rnaseh2c expression on metastasis, revealing for the first time an Rnaseh2c-immune response axis in metastasis. Gene ontology pathway analysis following mRNA-sequencing of Rnaseh2c knockdown tumors revealed that 20% of the genes with altered expression are involved in immune system-related pathways, including T cell signaling and antigen presentation. Furthermore, genes with significant changes included Type I interferons, T cell markers, and immune regulators. These results confirm that Rnaseh2c is a novel metastasis modifier gene and validate our hypothesis that the immune system is mediating the effect of Rnaseh2c on metastasis. This mechanism highlights a potential new target for combination with immune modulatory therapies to combat this devastating disease and adds to a panel of genes we identified that together could determine patients with high risk for metastasis.

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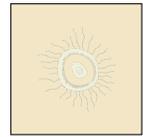
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The Rarest of Rare: Unlikely Presentation of Dermatofibrosarcoma Protuberans

A 31-year-old female presented to the emergency department following witnessed syncope. At the time of admission, she reported that she had a “small mass” on the left thigh that was previously excised in 2006 only to return two years later. Over the last three to four weeks, she noted rapid expansion, with associated discomfort, bleeding, and even functional impairment due to its size. On exam, the patient was febrile to 101F, sinus tachycardia to the 120s, and hypotensive 90/55 mmHg. Initial labs were noteworthy for leukocytosis of 15k as well as low hemoglobin and hematocrit of 7.2 g/dL and 24 respectively. The physical exam highlighted a 13cm x 16cm x 7cm, necrotic, ulcerating mass on the left hip. MRI imaging revealed a 13 cm x 13 cm heterogeneously enhancing mass along the left hip and thigh, indicating rapid progression from the 7.5 cm x 6 cm mass seen on a 2015 MRI. Management for acute blood loss included crystalloid and colloid products and initiation of broad spectrum antibiotic for a superimposed soft tissue infection. Histopathology highlighted a storiform pattern of monotonous, slender highly atypical, spindle shaped cells with focal regions of fibrosarcomatous change that demonstrated a fascicular, herringbone pattern of growth, consistent with Dermatofibrosarcoma protuberans. The patient underwent wide resection and flap reconstruction without adjunctive radio or chemotherapy per her preference.

Dermatofibrosarcoma protuberans is a rare soft tissue tumor that arises from the dermis and accounts for approximately 2 percent of all soft tissue sarcomas and less than 0.1 percent of all malignancies. The infiltrative soft tissue tumor is locally aggressive and has an increased probability to recur or metastasize if not resected with disease free margins. While rare to be evaluated and diagnosed in the outpatient setting, it is even more uncommon to have syncope as the presenting complaint for a soft tissue tumor. At the time of presentation, the size, associated functional impairment and resulting hemodynamic instability required immediate medical intervention and subsequent surgical treatment, highlighting this case as an extreme example of this tumor’s aggressive nature.

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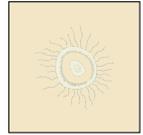
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Timosaponin A-III Induced Senescence Regulates Oncogenic Phenotype in Breast Cancer Cells by Down Regulating Polycomb Group Proteins

The polycomb group (PcG) proteins, BMI1 and EZH2, are important regulators of senescence, aging, and cancer; and are often overexpressed in several human malignancies including breast cancer. Aberrant expression of these proteins is associated with metastasis and poor prognosis in cancer patients. At present, very little is known about the therapy reagents that can efficiently inhibit the expression of polycomb group proteins such as BMI1 and EZH2. Here, we report that Timosaponin A-III (TAlII), a steroidal saponin obtained from the rhizomes of an herb, *Anemarrhena asphodeloides*, regulates the expression of polycomb group proteins in breast cancer cells. Treatment of breast cancer cells with Timosaponin A-III caused inhibition of BMI1 and EZH2 expression that was accompanied by downregulation of their respective PRC activity - histone H2A lysine 119 ubiquitinylation (H2AUb) and histone 3 lysine 27 trimethylation (H3K27me3). We also show that Timosaponin A-III reduces the oncogenic phenotype as seen by invasion and migration assays and induces cellular senescence as seen by SA-B-galactosidase assay in MCF7 and MDA-MB-231 cells. Real time PCR (qRT-PCR) analyses of mock and Timosaponin A-III treated breast cancer cells show transcriptional upregulation of microRNA expression—specifically the miR-200c/141 cluster that is known to be upregulated during senescence. Thus, our data suggest that Timosaponin A-III can be successfully used to inhibit the growth of tumors where PcG proteins BMI1 and/or EZH2 are overexpressed.

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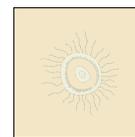
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Systematic Screening of Histone Deacetylase Inhibitors: Enhancing Immunological Function Against Cancer

Cancer is the result of a compromised immune system lacking the ability to recognize and eliminate transformed cells. These transformed cells induce an upregulation of negative regulatory tumor cells, which suppress T-cell activation and proliferation while inducing tumor tolerance.

Immunotherapy is a novel therapeutic modality that strengthens the immune system against cancer cells, which in turn avoid immunological tolerance of cancer cells and the impedance of transformed cells survival. Histone deacetylase inhibitors (HDACinh) are specific drug compounds that are largely used as anti-cancer drugs. HDACinh have demonstrated control of apoptosis, cell survival, along with immune functionalities. HDAC inhibition also modulates the expression of tumor associated antigens (TAA) and immunosuppressive proteins.

Our group has reported that the genetic and pharmacological abrogation of HDACs results in both, a decline in proliferation of tumor cells and important changes in immune regulatory pathways. For this reason, our group is currently focusing on the standardization of methodologies to identify changes in immunological markers without affecting other cellular mechanisms involved in cell survival: such as cell viability, necrosis, and apoptosis, which could interfere with the evaluation of the immune function.

In vitro cultured murine SM1 cells were subjected to eight concentrations from clinical grade compounds—Tubastatin A, Nexturastat A, MS275 and LBH589—to be analyzed within HDAC-Glo and ApoTox-Glo assays. The HDAC-Glo assay provided relative HDAC activity data, while the ApoTox-Glo assay specified the trends of Digitonin (viability control), Ionomycin (cytotoxicity control) and Mitomycin (apoptosis control). Upon inspection, the ApoTox-Glo recommended manufacturer controls compared to a pan-HDAC inhibitor LBH589 were deemed unreliable; LBH589 proved to be a universal control for the quantitative multiplexing protocol outlined. These results were then validated by Western blot protein analysis.

Traditional approaches involve the time consuming and costly execution of individual assays. However, multiplex assays allow for quantifiable evaluation of anti-tumor HDACinh affects within cellular pathways by minimizing execution time and maximizing comprehensive statistical analysis of signal outputs from a spectrophotometer. Furthermore, an assay in tandem with our systematic high-throughput platform can accurately evaluate therapeutic doses and innovate treatments for melanoma clinical trials, along with other varieties of cancerous cell lines.

The established reproducible and reliable protocol developed from this study will be important for identifying the dose range necessary to achieve immunological effects with minimal toxicity, thus improving the quality of life for treated subjects.

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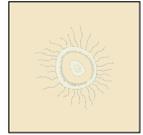
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Technique Optimization for Surgical Implantation of an Osmotic Pump for Delivery of Therapeutics via Convection Enhanced Delivery into Diffuse Intrinsic Pontine Glioma Tumors in Preclinical Mouse Models

INTRODUCTION

Diffuse intrinsic pontine gliomas (DIPG) are fatal, high-grade tumors arising in children. These tumors arise within the pons of the brainstem. DIPG constitutes more than 70% of all brainstem neoplasms and 10% of all childhood tumors. The median survival rate of children with DIPG is 9 months and it is a leading cause of pediatric brain cancer mortality. Due to the relative impermeability of the blood brain barrier (BBB), it is difficult to effectively deliver chemotherapy agents into the tumor. Convection-enhanced delivery (CED) is a method for direct delivery of agents into tumor via a continuous hydrostatic pressure gradient, thereby bypassing the BBB. By attaching an osmotic pump filled with chemotherapeutic agents, CED can achieve effective long-term continuous administration. Our objective is to optimize the technique for placement of the CED cannula carrying an osmotic pump into the pons of preclinical mouse models of DIPG.

METHODS

An osmotic pump with a capacity to infuse 100ul over 4 weeks was used. Two cohorts of mice were selected. A cannula was stereotactically implanted in both cohorts and connected to a subcutaneously placed osmotic pump loaded with Evans blue dye (EBD) or DII. The first cohort assessed the feasibility of cannula implantation into the pons of non-tumor bearing mice. The second cohort was stereotactically transplanted with murine DIPG cells and allowed to develop pontine tumors before cannula implantation. EBD and DII distribution were studied in vivo and at necropsy to assess targeted anatomical site and distribution. Post implantation survival was also assessed.

RESULTS

We established a methodology for surgical implantation of a cannula in the mouse pons, and assessed the distribution rate in healthy as well as tumor bearing murine models of DIPG. We first show that osmotic pump installation into pons itself is not associated with any observed side effects and does not affect the overall survival of the mouse. We further track the exact placement of cannula and delivery of the dye into the pontine tumor by comparing the tumor location in haematoxylin and eosin stained sections with DII and EBD signal at the infusion site.

CONCLUSION

We conclude that surgical implantation of a cannula in the mouse brainstem is feasible and provides an opportunity for drug testing by direct delivery to tumor. The next step is to study the delivery of therapeutics by this technique to determine tumor growth and survival in DIPG xenografts.

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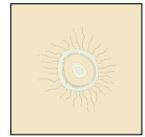
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SCHOOL OF MEDICINE AND HEALTH SCIENCES

HDAC10 Regulates Cancer Cell Motility and Vascular Activity through Repression of SPARC

Histone deacetylases (HDACs) classically function as transcriptional repressors, which inhibit transcription by modulating chromatin structure through histone deacetylation. While genetic and pharmacological research have demonstrated that many HDACs play important roles in controlling malignant behaviors of cancer cells, much less is known about the functions of *HDAC10*. To determine the downstream target for *HDAC10*, comparative RNA sequencing was used to analyze the gene expression profile of *HDAC10*-depleted cells. The data indicated that *HDAC10* could regulate *SPARC* (secreted protein acidic and cysteine rich) expression. It has been shown that in a panel of human melanoma cell lines, knocking-down *HDAC10* or exposing cells to an *HDAC10* inhibitor, highly upregulated *SPARC* levels. *SPARC* is a secreted glycoprotein that has been associated with an invasive tumor cell phenotype and a poor outcome in human melanomas. Cell migration and invasion assays indicated that the knockdown of *HDAC10* enhanced melanoma cells mobility and invasiveness. Also, vascular permeability assays demonstrated that the depletion of *HDAC10* contributed to the reduction of endothelial monolayer integrity and induction of lung vascular permeability. A short-term lung colonization assay was performed to monitor cancer cell extravasation in vivo. Knocking-down *HDAC10* significantly promoted melanoma cells' extravasation. Because *SPARC* is a critical tumor-secreted permeability factor during melanoma metastatic dissemination to the lungs, *HDAC10* depletion might disrupt the integrity of vascular endothelial cell layers, facilitating melanoma cells extravasation in the lungs by upregulating *SPARC* expression. Defining the roles of *HDAC10* in cancer development will provide new insights in therapeutic strategies of cancer treatment.

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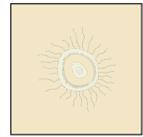
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A Patient with 5-FU Encephalopathy and End Stage Renal Disease

CASE PRESENTATION

A 49-year-old man with HIV (on HAART therapy), end-stage renal disease, and anal cancer presented with altered mental status, having just begun chemotherapy with mitomycin and a continuous infusion of 5-fluorouracil. Exam was significant for lethargy, difficulty concentrating, and confusion as well as occasional lip-smacking. Routine laboratory analysis was normal, other than elevated BUN and creatinine. Workup for toxic, metabolic, and infectious causes of acute encephalopathy was normal, including a normal ammonia level. Computed tomography of the head revealed no acute process. The patient's continuous 5-FU infusion was stopped, and he underwent hemodialysis without improvement in mental status.

Electroencephalogram showed diffuse encephalopathy without epileptiform activity. Diffusion-weighted images on MRI with identified an area of restricted diffusion in the splenium of the corpus callosum. Cerebrospinal fluid analysis was normal along with negative gram stain, culture, India Ink, Cryptococcal antigen, and VDRL. Four days after his 5-FU infusion was withheld, his mental status began to improve.

DISCUSSION

This case exhibits a rare complication of a common chemotherapeutic agent, 5-FU. The mechanism for the neurotoxic effect of 5-FU is unknown, although cases in the literature have postulated myelin swelling, vacuolization, and destruction. Direct toxicity to CNS progenitor cells and oligodendrocytes have been suggested as well. This correlates with the MRI findings typically seen in 5-FU encephalopathy, which in our case showed an area of restricted diffusion in the corpus callosum.

An interesting point is the involvement of ammonia, a catabolic byproduct of 5-FU, in the pathogenesis of encephalopathy. Ammonia level was normal in our patient, but hyperammonemia is a common finding in many cases in the literature. Development of encephalopathy in our patient suggests that ammonia may not play a singular role in the neurotoxic effect of the drug. This rather suggests direct neurotoxic effects from 5-FU or a buildup of metabolites, such as fluoroacetate, playing a more significant role. Presence of end-stage renal disease and use of a continuous infusion of 5-FU may have contributed to toxicity as well.

CONCLUSIONS

The mechanism of 5-FU encephalopathy leading to reversible white matter damage is not entirely clear. Therefore, diffusion-weighted MRI is an important tool in the workup for a patient on 5-FU presenting with acute encephalopathy. While there is still more to learn about the neurotoxic effects of 5-FU, available evidence suggests that prompt diagnosis and withdrawal of the drug is associated with reversible and favorable clinical outcomes.

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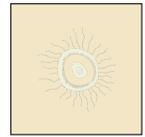
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Developing A Third Party HPV-Specific T Cell Bank For Use As An Immunotherapeutic Strategy for Immune Compromised Patients with HPV-associated Diseases

Immune-compromised patients, including those with primary immune deficiencies and recipients of stem cell transplants, are at risk for persistent Human Papillomavirus (HPV) infections and HPV-associated malignancies. Chronic HPV infection is characterized by a weak CD4+ T cell response and can lead to the development of HPV-associated malignancies. Recent vaccine studies suggest that cytotoxic T-cell responses against HPV antigens correlate with virus control. Adoptive transfer of third HPV-specific T cells may be efficacious for immune deficient patients with HPV-associated diseases.

HPV-derived E6 and E7 are attractive targets for T-cells as they are immunogenic and play critical roles in malignant transformation. The early oncoproteins HPV16 E6 and E7 are ideal immunotherapeutic targets because they are only expressed in infected cells and malignant tumors, and promote malignant transformation through the inactivation of the tumor suppressor proteins p53 and pRb. A synthetic long peptide (SLP) vaccine against HPV16-E6 and -E7 has induced regressions of vulvar intraepithelial neoplasia but is less effective against established cancers, suggesting that the endogenous immune system fails to eradicate bulky HPV-associated cancers even after effective immunotherapies. Recent efforts by Ramos et al. have demonstrated success in expanding HPV16-E6 and -E7 specific cytotoxic T lymphocytes (CTLs) from patients with HPV-associated cervical and oropharyngeal cancers. We hypothesized that strategies for ex vivo priming and expansion of antigen-inexperienced and anergic T-cells would enable generation of HPV-specific T-cells irrespective of donor source; these cells can then serve as components of an off the shelf third party bank of therapeutic T cells.

We evaluated the feasibility of generating HPV-specific T-cells from peripheral blood of HPV-primed (n=2) and non-primed healthy donors (n=12) using GMP-compliant methodologies. Antigen presenting cells pulsed with HPV antigens were used to stimulate T cells in combination with different cytokines.

Preliminary results show we generated T-cells targeting HPV antigens from 8/14 donors. T cells expanded with a 142 median fold expansion after 23-25 days. The resultant product specifically recognized E6 or E7 proteins by IFN- γ ELISpot (mean 109.7 SFC/1-2x10⁵ cells (range 12.5-334) against HPV compared to mean 6.1 SFC/1-2x10⁵ cells, (range 0-23.5) for irrelevant antigen) and evaluated lines were comprised of 26 \pm 0.02% CD8+ and 59 \pm 0.08% CD4+ T cells. Current efforts are focused on developing a third-party T-cell bank and demonstrating functional activity against HPV-expressing targets.

In summary, expansion of HPV-specific T-cells is feasible from vaccinated and unvaccinated healthy donors, and may be used as an "off the shelf" immunotherapy for HPV-associated diseases post-HSCT.

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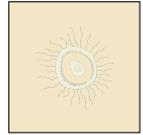
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Alternative Splicing of *FGFR3* as a Mechanism for Prostate Cancer Health Disparities

BACKGROUND

Prostate cancer (PCa) is the most diagnosed cancer in men and the second leading cause of male-cancer related deaths in the U.S. Dramatic ethnic disparities have been observed in PCa patients, as African American (AA) men are 60% more likely to be diagnosed with PCa and have a 2.4 fold higher mortality rate compared to European American (EA) men. Increasing evidence suggests that, after accounting for epidemiological factors, a remaining component of this disparity is due to intrinsic genetic and biological factors. Interestingly, recent exon array data from our lab suggest that differential expression of splicing factors (SFs) and differential alternative splicing may be occurring in AA PCa. We hypothesize that differential alternative splicing involving exon 14 of the *FGFR3* gene is generating a shorter, more oncogenic variant in AA PCa, which is absent or weakly expressed in EA PCa. Differential splicing of *FGFR3* and increased expression of SFs in AA patients may be mechanisms contributing to AA PCa health disparities.

RESULTS

Exon array data suggested *FGFR3* as a candidate for differential alternative splicing. Exon profiling and RT-PCR validated enriched expression of a short variant of *FGFR3* due to skipping of exon 14 in AA patient samples and cell lines. Cloning confirmed the presence of the *FGFR3-L* variant (containing exon 14) and the *FGFR3-S* variant (without exon 14) from an EA and AA PCa cell line, respectively. Enrichment of *FGFR3-S* resulted in increased cell proliferation in an AA cell line. RNA-seq data analysis suggests decreased survival of PCa patients with high *FGFR3-S/L* expression ratios. Additionally, our exon array data predicted increased expression of seven SFs in AA patients. RT-PCR and IHC analysis validated increased expression in AA specimens. Knockdown of these SFs resulted in decreased invasion and *FGFR3* splice switching in an AA cell line.

CONCLUSIONS

We have identified an oncogene of interest, *FGFR3*, which undergoes exon skipping that is specific to AA PCa. In cell lines, this shorter isoform of *FGFR3* leads to an increased oncogenic phenotype based on proliferation assays. We have shown that AA PCa patient specimens have increased expression of specific SFs compared to EA specimens and knockdown of SFs reduces AA PCa cell invasion and causes splice switching of *FGFR3*. Thus, differential expression of SFs and exon skipping in *FGFR3* may be one mechanism contributing to the increased aggressiveness of PCa in AA patients.

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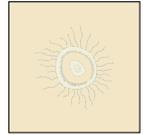
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Liquid Biopsy for Detection and Monitoring of Driver Mutations in Diffuse Intrinsic Pontine Gliomas (DIPGs)

Children diagnosed with diffuse intrinsic pontine glioma (DIPG) have a dismal prognosis, with a median survival time of about nine months post-diagnosis. One of the major factors contributing to poor prognosis is limited understanding of biology, thus the lack of effective therapy. We have recently identified that DIPGs are driven by partner mutations in growth factor and cell cycle regulatory genes, in addition to histone 3 K27M mutation. Currently, biopsies are obtained at diagnosis to help inform therapy. Despite biopsy-informed clinical trials, monitoring tumor response to treatment remains a challenge. MR imaging, -the standard for assessing tumor size and growth- is often not sensitive for detecting early tumor regression/progression in children with CNS cancers. Additionally, MRI is not a valid method for assessing tumor response to treatment in time sensitive clinical trials. We hypothesize that establishment of liquid biopsy-based platforms will allow for detection of circulating tumor DNA (ctDNA) that will reflect tumor regression or progression following therapy. We have used biofluids (CSF, plasma) from patients and their xenograft models, for detection and quantification of ctDNA. Using our sensitive and robust digital droplet PCR (ddPCR) system, we have identified the presence of most major mutations associated with DIPG in ctDNA. These include *H3F3A* K27M, *HIST1H3B* K27M, *ACVR1* G328V/R206H, and *PPM1D* E525X. We have also successfully conducted multiplexed detection of histone 3 K27M and its partner mutations in CSF samples obtained from DIPG patients. Furthermore, we have collected 50 biofluid samples from DIPG patients enrolled in a Phase 1 clinical trial to assess changes in ctDNA with correlation to disease progression. We have detected the presence of histone 3 K27M mutation in these biofluid samples, and our ongoing efforts include associating plasma ctDNA-mutation allelic frequencies to clinical outcome of DIPG patients enrolled in the Phase I clinical trial.

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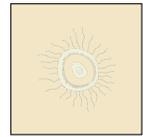
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Phase II Study: Induction Chemotherapy & Transoral Surgery as Definitive Treatment (Tx) for Locally Advanced Oropharyngeal Squamous Cell Carcinoma (OPSCC): A Novel Approach

BACKGROUND

The standard of care for OPSCC includes chemoradiation (CRT) or surgery with adjuvant radiation (RT). However, RT is associated with significant life long morbidity. We assessed the efficacy of a two-drug induction regimen, followed by transoral robotic assisted surgery (TORS) & neck dissection for locally advanced OPSCC.

METHODS

This is an IRB approved single-arm phase II study for untreated stage III or IVA OPSCC patients (pts) with an ECOG < 2 and GFR > 50 cc. Induction chemotherapy consisted of cisplatin 75 mg/m² and taxotere 75 mg/m² every 21 days for 3 cycles. Tumor shrinkage was examined after each cycle. If the primary tumor was ≥ 80% smaller, pts underwent TORS and neck dissection(s). At post-op visits, flexible laryngoscopy, blood work, and imaging with PET/CT and/or MRI were done. Short and long term toxicity, progression-free survival (PFS) and overall survival (OS), and quality of life (QOL) were evaluated.

RESULTS

Nineteen pts were treated and 14 are available for analysis. Thirteen were male, 12 were Caucasian, and 13 were HPV+. Median age at diagnosis was 57. Tumors involved the tonsil (11 pts) and base of tongue (3 pts). Three pts were stage III, and 11 were stage IVA. Tumor size was reduced on average by 58%, 84% and 92% after the 1st, 2nd and 3rd induction cycles respectively. Pathologic complete remission of primary disease occurred in 11 pts and in 7 pts with cervical lymph node disease. Four pts were given dose-reduced chemo and one pt was changed to carboplatin per protocol because of renal dysfunction. Pre vs post tx QOL scores did not change. At a mean follow-up (f/u) of 13 months (range 2.5 to 19.7), 13 pts are alive and well. Three pts recurred, and were treated with salvage CRT. One pt died of metastatic disease.

CONCLUSIONS

- 1) Cisplatin + Taxotere is an effective induction tx for OPSCC
- 2) Induction tx followed by transoral & neck resections without RT is a promising tx model for OPSCC. It appears effective while avoiding adverse effects of RT. Longer f/u is required to assess its true efficacy.

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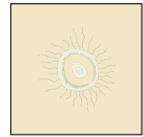
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Coagulopathy with Chimerism; the Risks of Rituximab

Rituximab is a chimeric monoclonal antibody directed against CD20 antigen primarily found on the surface of B cells. It is generally a well-tolerated medication used in a variety of hematologic and autoimmune conditions. The most common side effects are infusion reactions due to cytokine release ("cytokine release syndrome") and cytopenias, including thrombocytopenia. Coagulation abnormalities and fibrinolysis are quite rare and are reported only twice in the literature.

A 39-year-old man without significant medical history presented to the emergency room with severe, diffuse body pain. Presenting vital signs were significant for tachycardia, and physical exam was remarkable only for generalized rib tenderness and the absence of palpable splenomegaly. Admission laboratory results included white cell count 99,950/mm³ (segmented neutrophils 17%, blasts 55%), hemoglobin 14.7 g/dl and platelet count 58,000/mm³. Flow cytometry and bone marrow biopsy were consistent with the diagnosis of Precursor B cell Acute Lymphoblastic Leukemia. The patient was induced on hyper-CVAD, with Rituximab prescribed on days 1 and 11 of chemotherapy. He was initiated on fluids and routine tumor lysis prophylaxis.

On day 1 of chemotherapy, approximately one hundred fifty minutes after Rituximab infusion, the patient evolved fever of 102.4 °F with rigors, nausea, vomiting, pronounced sinus tachycardia (approximate rate of 150), tachypnea and profound hypotension to 82/51, consistent with a severe cytokine release syndrome. He was hemodynamically stabilized, and Rituximab infusion was held. Five hours later, significant coagulation abnormalities and relative cytopenias evolved in the setting of clinically significant mucocutaneous bleeding, and in the absence of schistocytes on peripheral blood smear. INR rose to 1.9 from 1.1, D-dimer rose to >20,000 from 4,770, and fibrinogen dropped to 422 mg/dl from 612 mg/dl, with further drop to 71mg/dl after 96 hours. Platelet and white blood cell counts dropped dramatically (14,000 to 2,000, and 63,910/mm³ to 10,420/mm³ (blasts 60%), respectively), while hemoglobin dropped to 13 g/dl from 11.8 g/dl. LDH level rose prominently. Uric acid level remained relatively unchanged, and liver tests rose marginally. In this setting, the patient was transfused with 1 pool of cryoprecipitate and with platelets. Fibrinogen levels increased to 138 mg/dl, with subsequent stability. The patient recovered without further hemodynamic instability or clinically significant bleeding.

This case illustrates the potential for clinically significant disseminated intravascular coagulation in the setting of severe cytokine release with Rituximab. This condition is critical to recognize quickly to ensure supportive transfusion and hemodynamic stability.

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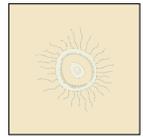
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Repurposing of Ligand-Gated Anionic Channel Therapeutics to Inhibit Tumor Cell Function

Oncogenic behavior has been shown to be directly influenced by the activity of voltage- and ligand-gated ion channels of the oncogenic cell. We have previously demonstrated that upregulated expression of voltage-gated sodium channel (VGSC) SCN5A in SW620 and SW480 human colon cancer cells is associated with activity-dependent enhanced invasive ability, which can be suppressed by siRNA-mediated knockdown or pharmacological inactivation (e.g. lidocaine, ropivacaine). As it remains unknown whether dysregulated VGSC expression in oncogenic cells enhances proliferative/metastatic potential by stimulating oncogenic signaling pathways, suppressing inhibitory pathways, or a combination of both, the focus of this study was to determine the status of signal transduction pathways following ion channel activation and/or inhibition. We hypothesized that upregulated VGSC expression enhances proliferative ability by stimulating oncogenic pathways and suppressing inhibitory pathways. By pharmacological activation of the over-expressed VGSCs in SW620 and SW480 human colon cancer cell lines, we concluded that VGSC activation resulted in both stimulative oncogenic signaling and suppressed inhibitory signaling, which were more consistently observed in the SW620 cell line vs SW480 cell line and more noticeable at 48h post-treatment vs 24h post-treatment.

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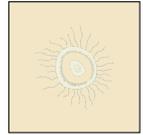
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Targeting TGF- β Pathway E3 Ligases in Inflammation Associated Cancers of the Liver

Multiple E3 ubiquitin ligases that regulate the TGF- β , have been known to be instrumental in the regulation of inflammatory cascades, apoptosis and cancer. However, to our knowledge, there remains a gap in the integration between genomics and underlying mechanisms of some of these E3 ligases, in the context of TGF- β signaling, and cancers with underlying inflammation. We first analyzed the transcriptome of 488 hepatocellular cancers (HCCs) and screened for mutations in The Cancer Genome Atlas (TCGA), and observed two different signatures (activated and inactivated) for 18 TGF- β pathway genes. While increased levels of TGF- β -related transcripts were associated with activation of hepatic fibrosis/immune/tumor microenvironment pathways, decreased levels of TGF- β members were associated with loss of TGF- β tumor suppressor function. HCCs characterized by the “inactivated” TGF- signature were associated with a significantly poorer survival, compared to HCCs with the “activated” TGF- signature ($p=0.0027$). We next analyzed 29 TGF- β -related E3 ligases, and observed raised expression of the following: KEAP1 (6.4% of HCCs), Smurf1 (8.2%), Smurf2 (9.1%), and Skp2 (9.1%), UCHL5 (16.5%), WWP1 (10%), WWP2 (11.8%), and PRAJA1 (12.7%). Interestingly, expression patterns corresponded with a few TGF- β signaling members regulated by some of these E3 ligases, namely Smad3 (altered in 54%) and β 2SP (27%). We identified that PRAJA1 targets Smad3 and β 2SP ubiquitination and degradation. We further observe raised levels of PRAJA (25%) and KEAP1 (70%) in 176 human liver cancers, by immunohistochemical labeling, compared to normal controls. Depletion of PRAJA and KEAP1 with either shRNAs or E3 ligase inhibitors, RTA402/405 substantially inhibited growth and induced apoptosis, through PRAJA/Smad3/ β 2SP and KEAP1/Nrf signaling, in HCC cell lines and xenografts. E3 ligases such as KEAP1 and PRAJA1 could be present as potential therapeutic targets for liver cancer in the context of TGF- β -signaling, an important approach given that few effective targeted therapeutics are available for this poor prognosis cancer.

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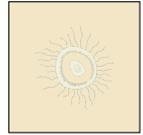
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Detection of HPV Related Oropharyngeal Cancer Using the COBAS HPV Oral Rinse Test

BACKGROUND

The majority of patients diagnosed with Oropharyngeal squamous cell cancer (OPSCC) are due to HPV infection. At present there are no reliable screening tests to detect patients with OPSCC.

OBJECTIVE

To assess the COBAS HPV oral rinse test as an early detection method for HPV-related OPSCC.

METHODS

After IRB approval, oral rinse specimens were collected on 187 patients treated at the head and neck service at MSKCC (45 patients with OPSCC, 61 with OCSCC and 81 patients with benign or malignant thyroid nodules). The COBAS HPV PCR test was used to detect 14 high risk HPV types (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) in these samples. In the OPSCC and OCSCC patients, tumor samples were classified as either HPV positive or negative using p16 immunohistochemistry and HPV in situ hybridization. The sensitivity, specificity, positive predictive value and negative predictive value of the COBAS HPV test was determined in the whole cancer cohort and also in the oropharynx cohort separately.

RESULTS

91.1% of the oropharynx cancer patients had HPV positive tumors compared to 3.3% of oral cavity cancer. Of the 81 normal patients, 79(97.5%) had no HPV in their saliva giving a specificity of the COBAS test of 98%. For the combined cancer cohort, the sensitivity, specificity, positive predictive value and negative predictive value of the COBAS HPV test were 79%, 90%, 85% and 86% respectively.

CONCLUSION

The COBAS HPV oral rinse test may be a potentially useful screening test for the early detection of HPV oropharyngeal cancer.

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BRAF V600E May Correlate with Immune Infiltrate in Microsatellite-Stable Colon Cancer

While BRAF is among the most well-established oncogenes in human cancers, more recently it has garnered attention for its role in suppressing antitumor immunity, especially in melanoma. Because tumor-infiltrating lymphocyte (TIL) density is strongly prognostic in colorectal cancer (CRC), we decided to investigate the connection between TIL density and the BRAF-activating V600E mutation in CRC.

We used ESTIMATE to quantify immune infiltrate in samples from the TCGA colon adenocarcinoma (COAD) dataset ($n = 216$). This is an algorithm that uses the gene-expression signature of 141 immune-related genes to infer the presence of immune cells in the tumor infiltrate. COAD samples with BRAF V600E mutations have more immune infiltrate than wild-type samples ($p < 0.05$).

The MSI-H subtype of CRC is characterized by epigenetic silencing of DNA mismatch-repair genes and higher mutational load, neoantigen expression and TIL density. Since it has been previously established that BRAF mutation is highly correlated with MSI-H phenotype³, we performed ANOVA to assess if BRAF mutation predicts ESTIMATE score independently of MSI-H phenotype. While the BRAF term was not significant in this multivariate linear model, we included an interaction term that was significant ($p < 0.005$), suggesting that both variables contribute to ESTIMATE score. To determine the effect of the interaction, we grouped samples into MSI-H and MSS groups and compared the wild-type and BRAF V600E subgroups within them. In the MSS group only, immune scores were significantly higher in the BRAF-V600E subgroup ($p = 0.05$).

Next, we sought to reproduce our results in an independent cohort of 619 CRC samples from the BROAD institute that have immune scores based on immunostaining. We grouped samples into TIL-positive and TIL-negative groups and compared the numbers of BRAF-V600E and BRAF-WT samples within each group. We observed a significant correlation between BRAF mutation and TIL+ immune score within the MSS group ($p = 0.01352$, odds ratio 5.76). Notably, the MSS group is the same group from the TCGA cohort in which we observed a significant correlation between BRAF mutation and ESTIMATE score.

The analysis we present here reveals a significant correlation between the BRAF V600E mutation and increased immune infiltrate in MSS tumors across two independent CRC datasets. Because V600E is an activating mutation, this finding suggests an immunity-stimulating role for BRAF in CRC, in contrast to BRAF's role in melanoma, which appears largely immunosuppressive.

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Intracranial Targeting of Glioblastoma Multiforme with Cold Atmospheric Plasma

Glioblastoma multiforme (GBM) is a highly malignant aggressive neoplasm of the primary central nervous system characterized by rapid growth, extensive angiogenesis, and resistance to current therapies. As the most common malignant primary brain tumor, GBM accounts for 45% of all brain tumors with over 20,000 new diagnoses per year in the U.S. Due to the highly aggressive nature of GBM, the median survival is limited to 16-19 months, with less than 30% of patients alive at two years after diagnosis. In this context, GBM treatment strategies remain largely palliative despite the advancement of multi-modal therapies. Thus, it is necessary to develop novel tools that can target proliferating tumor cells and enhance existing therapies. Conventional lasers in medical devices are based on the thermal interaction with tissues, which lead to necrosis and permanent tissue damage. In contrast, cold atmospheric plasma (CAP) has recently emerged as a novel therapeutic approach for targeting of cancerous tissue. Indeed, recent findings suggest that CAP jet interactions with tissue may allow for cell death without necrosis. However, studies to date have been limited primarily to subcutaneous implantation of tumors. While beneficial, this approach does not replicate the complex environment of the brain (i.e. GBM). Here, we developed a novel approach to target CAP to intracranial GBM tumors. Female athymic Foxn1^{nu} nude mice underwent implantation of U87 glioblastoma cells (10⁵ cells) into the brain frontal lobe, and were simultaneously instrumented with a custom endoscopic cannula. Tumors were allowed to develop for 7 days and mice were then treated intracranially with CAP (15 seconds total) using a novel plasma source. This new device, termed μ CAP, consists of a Pyrex syringe through which CAP, employing helium gas, is supplied via the implanted endoscopic cannula. Using *in vivo* bioluminescence imaging, the tumor volume in control animals increased nearly 1000% over the course of a week, whereas CAP treated tumor volumes remained at baseline levels. Histological evaluations confirmed CAP-mediated inhibition of GBM growth. These findings provide the first evidence for the potential of CAP to inhibit intracranial GBM tumor growth.

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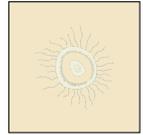
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Identification of genes involved in the repair of double strand breaks in fission yeast

Genomic instability is a hallmark of tumorigenesis and can arise from events including mutations, collapsed replication forks and DNA double strand breaks (DSB). Of these, the DSB is considered the most deleterious, where one DSB has the capability to induce cellular death. As a result, cells have two major pathways to repair such damage: homologous recombination (HR) and non-homologous end joining (NHEJ). This study will use a novel approach in order to characterize genes involved in such pathways.

The construction of a genome-wide deletion library in *S. pombe* provides for an excellent method in the characterization of gene biology. The unique feature of such library used in this study is the presence of barcode tags, or 20 nucleotide-long sequences. This allows for mutants to be sequenced in parallel. In this study, the use of this powerful tool is employed for probing novel genes involved in the DNA damage response and DNA repair pathways. To achieve this, the Bioneer V2 haploid-deletion library was utilized and 3,924 deletion strains were screened in response to the radiomimetic bleocin. 287 gene deletions displayed hypersensitivity to the drug and of these 52 mutants were selected for further study based on originality and gene ontology (GO) criteria. Results from sensitivity tests in response to bleocin and the DNA damaging agent, MMS showed that six genes—*iws1*, *elp6*, *mgr2*, *mpn1* and *cnp3*—had consistent hypersensitivity and were therefore further pursued.

Characterization of these genes occurred through the use of a non-essential minichromosome Ch16-RMYAH that allows for an HO-endonuclease induced break site resulting in a DSB. The DSB assay of *iws1*, *elp6*, *mgr2* and *mpn1* all revealed that these novel genes have a functional role in DNA repair. *iws1* was subjected to further tests, where it was seen to decrease H3K36 trimethylation, an important process in transcription and genome maintenance. The deletion of *iws1* was also determined to be synthetic lethal with a *wee1.50* mutant. In this work, four genes have been identified as novel DNA repair factors in *S. pombe* and *iws1* may have a role in HR.

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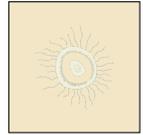
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miR-196b is a Potential Biomarker for Human Esophageal Cancer

Esophageal cancer is the sixth most common cause of cancer related death. Although multiple genetic and epigenetic alterations have been detected in esophageal cancer, molecular markers for early diagnosis and prediction of prognosis or treatment responses are quite limited. microRNA (miRNA) is a class of small-regulatory non-coding RNA, acting as either a tumor suppressor or oncogene by regulating gene expression through pairing with complementary seed of the targeted messenger RNAs (mRNA). A number of miRNA expression profiling studies have been conducted in esophageal cancer. By cross-referencing esophageal cancer data with miRNA expression profiling, we identify a group of dysregulated miRNAs in esophageal cancer, including upregulated miR-196b and miR-135a, and downregulated miR-141, miR-200a-5p, miR-200b-3p, miR-27b, miR-210. We first assessed the expression of miRNAs in esophageal cancer cell lines and primary esophageal cancer tissues by real-time reverse transcriptase-polymerase chain reaction (qRT-PCR). Significantly overexpression of miR-196b was observed in human esophageal cell lines KYSE-70 and KYSE-180 compared with normal esophageal squamous cell line HET-1A. Furthermore, the overexpressed miR-196b was detected in 12 out of 14 (86%) cancer tissues compared with matched normal tissues. TargetScan and miRanda bioinformatics tools were used to identify target genes of miR-196b. A list of targets was obtained, including ephrin type-A receptor 7 (EPHA7), one of members of the ephrin receptor (EPH) subfamily of the protein-tyrosine kinase family. We found a significant inverse correlation between miR-196b and EPHA7 expression in both cell lines and tissues. Luciferase assays revealed that miR-196b directly targets the 3'-UTR of EPHA7 gene. Forced expression of miR-196b resulted in significant downregulation of EPHA7 and promoted the proliferation and invasion in KYSE-70 and KYSE-180 cells. It has been reported that low EphA7 expression correlated with lymph node metastasis and poor prognosis for esophageal cancer. These indicate that EPHA7 may function as a tumor suppressor with immediate therapeutic potential. Our data suggest that miR-196b acts as an oncomiR by downregulating EPHA7 in esophageal cancer. Inhibition of miR-196b may improve anti-tumor efficiency by restoring the expression of EPHA7. Therefore, miR-196b might serves as a therapeutic target for esophageal cancer.

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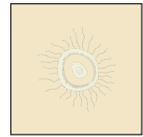
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Aggressive Signet Ring Cell Gastric Adenocarcinoma in a young man

INTRODUCTION

Gastric cancer is the fifth most commonly diagnosed cancer and the third leading cause of cancer related death worldwide. There are two types of gastric carcinoma: intestinal, characterized by cohesive tumor cells arranged in glandular formation, and diffuse, which is poorly cohesive with crescent-shaped eccentric nuclei. The diffuse type of gastric carcinoma, including signet cell carcinoma, is common in patients less than 50 years of age and is associated with advanced disease and poor prognosis. Diffuse type of carcinoma mostly found in patients without classic risk factors for gastric carcinoma such as untreated H. Pylori, or smoking history.

Signet cell carcinoma has a high rate of bone marrow metastasis, and can present with severe cytopenias. Once bone marrow metastasis is diagnosed, average life expectancy is 11 to 121 days. Though the global incidence of gastric carcinoma has declined since 1970, incidence of diffuse-type carcinoma has increased by ten-fold.

CASE PRESENTATION

A 26-year-old previously healthy man presented with 3 days of pre-syncope, back pain and weakness, along with recurrent epistaxis, fever and chills. On exam he was tachycardic and febrile and appeared pale with dry mucous membranes.

Serum studies showed a hemoglobin of 4.0 g/dL and a platelet count of 96×10^3 cells/microliter (compared to 13.9 and 163,000, respectively, twenty days prior). INR was 1.48 and alkaline phosphatase 305 IU/L.

Peripheral smear showed myelophthisic disease with teardrop cells, schistocytes, polychromasia, and nucleated red blood cells. CT demonstrated mediastinal, bilateral hilar, abdominal and retroperitoneal lymphadenopathy. MRI of thoracolumbar spine showed no pathological fracture but increased heterogeneous bone marrow signals.

Bone marrow /lymph node biopsies showed atypical hyperchromatic cells with a signet ring like appearance, positive for CK20 positive, negative for CK7 and TTF-1, suggesting a gastrointestinal primary cancer. Upper endoscopy showed an infiltrating mass in the greater curvature of the stomach and biopsy confirmed gastric signet ring cell adenocarcinoma. The patient received 4 months of palliative chemotherapy with Oxaliplatin, Mitomycin, Doxorubicin, Capecitabine but unfortunately died.

DISCUSSION/CONCLUSION

This case highlights the importance of keeping a broad differential diagnosis in a patient with pancytopenia. Our patient was a healthy young man and therefore initial suspicion for malignancy was low. He was eventually diagnosed with signet ring cell gastric carcinoma with bone marrow infiltration. Because of the rising incidence of signet ring cell carcinoma and its atypical presentation, physicians must be more vigilant about diagnosing this malignancy to maximize early diagnosis.

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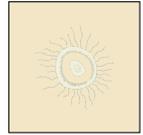
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Evaluating Expansion Protocols for Generating Cord Blood Derived Natural Killer Cell Therapies

Certain malignancies of the brain in children are still associated with high mortalities and poor prognosis. There are also indications that incidence may be steadily increasing. Current therapies are limited, and also expose the child's developing body to toxicity. There is thus a clear need for a novel therapy, and we propose to use immunotherapy based on natural killer cells as an alternative.

Natural killer cells are among the most critical cellular components of the innate immune response. As members of the innate compartment, they do not need to have encountered their target before they can kill them. Their ability to differentiate diseased cells from healthy cells, their ability to kill cells without need for MHC matching, and their ability to secrete cytokines that can recruit other immune cells make them attractive cell substrates for adoptive immunotherapy for difficult to treat cancers like pediatric brain tumors.

One major focus in the immune therapy field is developing off the shelf treatments. Cells that are banked will allow immediately accessible therapies, as opposed to those requiring manufacture upon patient identification. In this sense, natural killer cells derived from umbilical cord blood as a cell source may be advantageous. There are currently numerous established cord blood banks globally, which can serve as a source of these cells.

Therefore, we chose to develop cord blood derived NK cell therapies. To provide the most optimal cell product, we looked into comparing different methods of expanding these cells *ex vivo*. We also compared their expansion with cells derived from peripheral blood as a reference. We characterized phenotype and function of expanded cells by measuring cell proliferation by trypan blue exclusion, and expression of markers by flow cytometry.

Our preliminary results show that optimal expansion was seen in cells grown in in the presence of low dose IL2. We show purity of NK cells cultured with IL2+IL15 and IL2+IL15+IL7 using flow cytometry. We are currently looking at other cytokine combinations, culture media, and feeder cell ratios.

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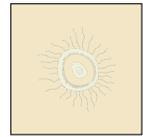
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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Pre-Incisional SPY Angiography Use in Nipple and Skin Sparing Mastectomy Surgery: An Institutional Review

INTRODUCTION

SPY angiography has been widely used to evaluate tissue perfusion in skin and tissue flaps during breast reconstruction. While limited studies have investigated SPY imaging in mastectomy surgery, only one has evaluated the use of SPY to identify the dominant blood supply to the mastectomy flaps and nipple areolar complex (NAC) prior to incision.

OBJECTIVE

To study the intraoperative use of pre-incisional SPY angiography and the ability to identify mastectomy flap and nipple-areolar complex perfusion prior to nipple and skin sparing mastectomies.

METHODS

A retrospective chart review of patients who underwent nipple-sparing mastectomy (NSM) and skin-sparing mastectomy (SSM) with intraoperative pre-incisional SPY angiography was performed from August 2016 to October 2016. Study variables included age, reason for surgery, change in incision location, post-operative ischemia, hyperbaric oxygen therapy (HBO), and excision of necrotic tissue. For the purposes of this review, cases were labeled prophylactic when neither breast was cancerous. A case was delineated as therapeutic if mastectomy was only performed on the breast containing cancer or if the patient underwent bilateral mastectomies when one or both breasts were cancerous.

RESULTS

This study included 27 mastectomies in 14 patients with average age of 44.3 ± 11.4 years. Ten cases were defined as prophylactic (71.4%) and 4 cases were defined therapeutic (28.6%). Most cases enabled breast surgeons to identify major perforators during surgery. The location of the planned incision was changed after SPY imaging in one mastectomy (3.7%) due to the location of vasculature. Of the 27 mastectomies, three (11.1%) experienced mastectomy flap or nipple-areolar complex necrosis. One underwent HBO, and all three required subsequent excision of necrotic skin.

CONCLUSIONS

This study describes the possible utility of SPY angiography to identify the dominant perforators supplying the mastectomy flap and nipple areolar complex (NAC). The major limitation is the small number of patients. We recommend larger studies to determine if there is any benefit of having breast surgeons perform SPY angiography prior to performing skin and nipple sparing mastectomies.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

A Comprehensive TCGA Based Analysis of the TGF- β Pathway in 33 Human Cancers

The dichotomy of the TGF- β pathway in inflammation, tumor suppression or metastases remains elusive. We analyzed TGF- β pathway in a PanCancer setting across 33 TCGA (The Cancer Genome Atlas) tumor types to address this question. We comprehensively catalogued 140 TGF- β pathway-related genes that are involved in cancer. We grouped core pathway genes (39/140 genes) into 8 different categories, including “TGF- β adaptors and targets” and “BMP ligands”. Our preliminary results reveal that the TGF- β pathway is frequently genomically altered in several tumor types, with 42% of the samples altered, in 18 out of the 33 tumor types. Genome wide mutation and CNV analysis suggests that most of those aberrations are due to mutations rather than CNVs. The tumor types with the largest percentage of samples with aberrations in at least one of the 39 TGF- β pathway genes are SKCM (68%), BLCA (67%), UCEC (65%), ESCA (65%), STAD (64%), and COAD (62%). *CREBBP* (5%), *SMAD4* (4%), *BMP1* (4%), and *EP300* (4%) are the most frequently altered genes overall. Our preliminary studies reveal frequent alterations in core pathway genes, including *SMAD3* and *SPTBN1* (β 2SP) in 41% of samples. Additional findings from this preliminary analysis include: (1) Association of inactivated TGF- β pathway at the transcriptomic level with suppression of the DNA damage response pathway and poor outcome. (2) Association of activated TGF- β pathway with increased expression of hepatic fibrosis/immune/tumor microenvironment-associated genes. (3) Involvement of several potentially targetable genes and DNA repair pathway genes in the disrupted TGF- β pathway. This multidimensional analysis demonstrated gene alterations for the pathway occur more predominantly in liver and gastrointestinal and some gynecological cancers, than in renal and brain cancers that showed relatively fewer aberrations.

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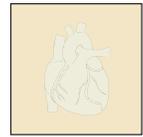
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Statin Use and the Risk of Cardiovascular Implantable Electronic Device Infection: A Cohort Study in a Veteran Population

INTRODUCTION

Cardiovascular Implantable Electronic Devices (CIED) infection is a serious complication that occurs in 1.6 % of patients after implantation and increases the rates of morbidity and mortality. The rate of CIED infection has increased since 2004, despite the use of perioperative antibiotics. This finding may be due, in part, to the escalation in the prevalence of MRSA, which cannot be eradicated with first or second generation cephalosporins. Statins have been found to possess pleiotropic properties which include anti-platelet, anti-inflammatory, immunomodulatory, and antioxidant. Furthermore, Thangamani et al. revealed in a recent laboratory study that statins exhibit an antimicrobial effect against Gram-positive bacteria. However, it is unclear if statins are effective in lowering the risk of CIED infection. Therefore, this study was conducted to evaluate the effectiveness of statins in reducing the risk of CIED infection.

METHODS

A retrospective cohort study was performed to assess the effectiveness of statins in reducing the risk of CIED infection. We analyzed data from VA Informatics and Computing Infrastructure (VINCI) database which includes all patients who underwent CIED placement at any Veterans Hospital in the United States between 2008 and 2015. A chi-square test and T-test were initially used to examine and compare the binary and continuous variables of demographic and health characteristics of subjects who had used statins and subjects who did not use statins before CIED placement. We then constructed a logistic regression model to estimate the adjusted relative risk of CIED infection among patients who were on a statin in comparison to patients who did not after adjusting for other confounding factors.

RESULTS

This study included 18970 CIED procedures, 98% of these procedures were performed in men with a mean age of 71 +/- 11 years. The rate of DM, HF, advanced CKD, CIED infection, positive MRSA status, and statin use were 23%, 15.7%, 3.3%, 1.14%, 12.6%, and 56%, respectively. The logistic regression analysis showed that statins significantly reduced the risk of CIED infection by 66% (OR 0.34 , p-value <0.0001), after controlling for all other effects.

CONCLUSIONS

Our study showed that in patients on statins who have received CIED, there was a 66% reduction in device infection, possibly related to an antimicrobial effect on gram-positive organisms, which are the most common cause of CIED infection. This information is clinically useful in reducing the risk of CIED infection. Further prospective clinical trials are needed to confirm our findings.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Secondary Prevention at the Aswan Heart Centre

Cardiovascular disease remains the leading cause of death globally, taking the lives of almost 18 million patients around the world each year. The overwhelming majority of cardiovascular deaths take place in low- to mid-income countries, suggesting that most cardiovascular deaths are preventable. In this study, current literature on secondary prevention of coronary artery disease was analyzed. Specific emphasis was given to preventative measures and successes in low income countries. Based on a literature review, a patient questionnaire to better understand patient adherence to preventative measures was created. This questionnaire focuses on patients receiving dual antiplatelet therapy post acute myocardial infarct treated by primary percutaneous coronary intervention. Additionally, this questionnaire has been adapted to fit the needs of the Magdi Yacoub Foundation Aswan Heart Centre, a cardiovascular hospital in Aswan, Egypt.

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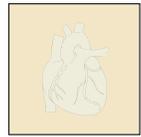
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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Transcatheter Aortic Valve Replacement Improves Right Ventricular Hemodynamics in High Surgical Risk Patients with Aortic Stenosis

INTRODUCTION

Aortic stenosis (AS) affects between 3-23% of elderly adults and is a major cause of morbidity and mortality. While surgical aortic valve replacement had been associated with prohibitive risk for many of these patients, transcatheter aortic valve replacement (TAVR) represents an emerging alternative approach. The hemodynamic efficacy of TAVR has been demonstrated in clinical trials; however, less is known in real-world practice. Specifically, AS worsens right ventricular function and pulmonary hypertension that may be associated with adverse outcomes. The goal of this study was to assess whether TAVR results in improvement of RV hemodynamics as measured by echocardiography.

METHODS

We reviewed 62 patients referred for TAVR to an urban academic medical center from 2014-2016. Transthoracic echocardiography (TTE) was performed before and after TAVR according to American Society of Echocardiography guidelines. Pre-TAVR and post-TAVR TTE were reviewed at blinded separate sessions. RV function was assessed by tricuspid annular plane systolic excursion (TAPSE), fractional area change (FAC), and tissue Doppler-derived tricuspid lateral annular systolic velocity (S'). RV size was quantified as the basal diameter in the apical four-chamber view. Pulmonary artery pressure was derived using tricuspid regurgitation velocity + right atrial pressure, with pulmonary artery hypertension defined as > 40 mm Hg. Left heart hemodynamics were also assessed using standard measures.

RESULTS

The study included 29 patients with fully retrievable TTE imaging available for review. Mean age was 79 ± 9.2 years (range 63-94), 70% were men, and all were at high surgical risk (STS Score 7.1 ± 5.3 , 33% hostile chest). Of the 29, 9 (31%) had mild to moderate chronic lung disease. RV size and FAC were similar pre and post TAVR. Significantly, TAVR resulted in improvement in pulmonary pressure in 14 patients (48% $p=0.03$), and RV function by TAPSE in 9 patients ($p=0.03$) and S' in 9 patients ($p=0.02$). 27/29 (93%) of patients demonstrated no or trace aortic insufficiency after TAVR. Regarding the left heart, TAVR also significantly improved left ventricular ejection Fraction in 21 patients (72%; $p=0.004$), aortic valve peak velocity in all 29 patients ($p<0.001$) and aortic valve mean gradient in all 29 patients ($p<0.001$).

CONCLUSION

In this real-world cohort, TAVR resulted in improvement in pulmonary hypertension and RV function. As pulmonary hypertension has been associated with worse outcomes, our data suggests that further studies are needed to determine whether these improvements observed are predictive of better long-term outcomes.

**This abstract was also accepted as a poster presentation to the 2017 American College of Physician Internal Medicine Meeting.

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SCHOOL OF NURSING

Disparities in Cardiac Rehabilitation Referral for Patients with Myocardial Infarction in the United States

BACKGROUND

Each year an estimated 635,000 Americans experience a myocardial infarction (MI) and a treatment that has been shown to decrease mortality is cardiac rehabilitation. Proposed federal legislation, S.488, supports nurse practitioners and clinical nurse specialists to meet "direct supervision" requirements for cardiac rehabilitation programs. If passed, nurse leaders will need to work closely with hospitals to ensure all eligible MI patients are referred.

OBJECTIVE

To identify demographic and clinical characteristics of MI patients associated with lower cardiac rehabilitation referral rates in a national U.S. cohort.

METHODS

This was a retrospective cohort analysis using 2011-2015 data from the American College of Cardiology's ACTION Registry-GWTGs. The cohort included 507,793 MI patients from 851 U.S. hospitals. Patients were stratified by referral versus non-referral and patient demographics and clinical characteristics were compared using χ^2 tests ($p < .05$).

RESULTS

A total of 78% ($n=395,948$) of patients were referral for cardiac rehabilitation. Patients aged ≥ 80 years (70.9%, $n=44,918$, $p \leq .001$) had the lowest rate of age groups. Women (75.2%, $n=123,191$) had significantly lower referral rates compared to men (79.3%, $n=272,757$) ($\chi^2 = 1110.168$, $p \leq .001$). Hispanic patients (65.5%, $n=19,149$) had the lowest referral rate of all race/ethnicity groups. Referral rates were significantly lower for patients without PCI (64.4%, $n=99,364$) or CABG (76.7%, $n=354,945$) during admission compared to those with PCI and CABG (83.9%, $n=296,584$, $p \leq .001$ and 76.7%, $n=354,945$, $p \leq .001$ respectively).

CONCLUSIONS

Patients who were aged ≥ 80 years, Female, Hispanic, or did not receive a PCI or CABG had lower referral rates. These results support a gap in referral for cardiac rehabilitation remains and there's a need for quality improvement.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

A Large Retrospective Analysis Reveals an Association Between Coronary Heart Disease and History of Depression and Anxiety

BACKGROUND

Coronary heart disease (CHD) and myocardial infarction (MI) continue to be leading causes of death in the United States. Effects of depression and anxiety on CHD and MI risk remain controversial. A number of studies have shown mixed results. Even fewer studies have examined the specific association of anxiety with MI. Limitations to existing studies include non-prospective designs, small sample sizes, and review of non-current data. Furthermore, effects of medication use for depression and anxiety on CHD and MI risk have not been fully elucidated. Our study examines the association between CHD/MI and all three of these important factors: anxiety, depression, and psychiatric medications, in a cross-sectional analysis of a large database of subjects in the United States. The large sample size and comprehensive adjustment for risk factors for CHD/MI are major strengths of this study.

METHODS

We analyzed data from the 2015 Behavioral Risk Factor Surveillance System (BRFSS) containing 441,456 subjects. A chi-square test was used to examine the binary variables of demographic and health characteristics of subjects with CHD/MI and subjects without CHD/MI. These characteristics include gender, age, hypertension (HTN), diabetes mellitus (DM), hyperlipidemia (HLD), chronic kidney disease (CKD), anxiety, depression, and medications for emotional problems. We then used logistic regression models to estimate the adjusted odds ratio of CHD/MI for these characteristics.

RESULTS

Univariate analysis revealed that being older than 60 years and having HTN, DM, HLD, and CKD significantly increases the odds of CHD/MI by 4.77, 5.03, 3.91, 3.48, and 4.47, respectively. Furthermore, depression and taking medications for emotional problems increases the odds of CHD/MI by approximately 70% with a p-value less than 0.0001. In contrast, anxiety significantly reduces the odds of CHD/MI by 38% with a p-value less than 0.0001. We then constructed two logistic regression models which showed that depression increases the odds of CHD/MI by 2.48, and anxiety reduces the odds of CHD/MI by 58%, after comprehensive adjustment for CHD/MI risk factors. Finally, medications for emotional problems are not associated with CHD/MI, after adjustment for other risk factors as well as depression or anxiety.

CONCLUSIONS

A national database was used to determine the associations between CHD/MI, depression, anxiety, and use of medication for emotional problems. Our analysis suggests that depression increases the odds ratio of CHD/MI while anxiety reduces the odds ratio of CHD/MI with medication having no effect. This information is clinically useful in assessing risk of CHD/MI in patients with concomitant mental health disease.

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Effects of 3D Printing on Viability and Proliferation Rates of Primary Cardiac Fibroblasts

In the fields of cell biology and tissue engineering, 3D printing has quickly become a popular and effective method for controlling cell growth and generating a complex biomimetic environment. However, there are still significant concerns that bioprinters decrease cell viability due to heat and mechanical stresses on cells when printed. Many in the field have shown that precise cell placement, complex arrangement, and incorporation of a variety of cell types can be achieved in 3D printed constructs. Yet, there is still a need for effective ways to accurately measure cell viability and behavior in real time. To address these issues, we compared the viability of primary cardiac fibroblasts and their survival in multiple passages before and after an extrusion-based 3D printing process, using methods new to this field. The goal was to set a standard of accurate and highly responsive assessment of cell behavior in 3D printed constructs, both short and long term. Analysis of cell viability was conducted with microscopy, immunocytochemistry, and bioluminescence imaging with Luciferin and Cytoscan™ LDH assays. To evaluate the effect of the 3D printing process on cell proliferation and viability, 3D printed live cell constructs were compared to cells cultured in monolayers over three sequential passages. 3D constructs were designed in SolidWorks as a thin 15mm diameter disk intended to fit on a 25mm coverslip. A single construct holds approximately 100K cells after printing. A BioBot 3D bioprinter was used to print cell laden BioGel, a cell printing material that is photocured using visible blue light. Future directions of this work include assessment of 3D printed constructs with different and multiple cell types, multi-layered tissue constructs, and different biocompatible materials.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Effect of Sexual Orientation on the Rate of Heart Attack

BACKGROUND

Lesbian, gay and bisexual (LGB) individuals often face discrimination that can negatively impact their health. Much of the previous literature has identified several relationships between sexual orientation and mental health, sexually transmitted diseases and substance abuse. However, as cardiovascular disease is the leading cause of death in LGB adults, very limited research has been conducted in this area. Previous studies have shown the increased prevalence of hypertension and heart disease in gay men compared to heterosexual men. Another study has shown that LGB adolescents had higher rates of smoking and alcohol abuse, predisposing them to cardiovascular disease. Our study aims to examine the association between heart attack and the various sexual orientations in a cross-sectional analysis of a large database of subjects in the United States.

METHODS

A cross-sectional analysis was performed in the database of 2015 Behavioral Risk Factor Surveillance System, which contains 441,456 subjects with an age of 18 years or older, to study the association between reported sexual orientation and heart attack. Initially, a chi-square test was used to examine and compare the binary variables of demographic and health characteristics between subjects with different sexual orientation. We then used logistic regression models to estimate the adjusted odds ratio of heart attack for subjects with different sexual orientation in comparison to straight subjects.

RESULTS

Univariate analysis revealed that compared to straight individuals, LGB subjects are younger, more likely to smoke cigarettes, and with similar weight distribution and rates of depression. LGB subjects are less likely to have diabetes, hypertension, and anxiety. We constructed three logistic regression models. The first model showed that LGB subjects have lower odds ratios for heart attack without adjustment for other risk factors [OR=0.699, P-value <0.001] and [OR=0.827, p-value <0.001]. The second model also showed that LGB subjects have lower odds ratios for heart attack after adjustment for DM, HTN, HLD, and CKD [OR=0.806, p-value = 0.002] and [OR=0.86, p-value=0.008]. The final model did not show any difference between LGB and straight subjects after only adjusting for age.

CONCLUSIONS

There is no difference in the rate of heart attack between LGB and straight subjects after adjustment for age. Nonetheless, this study revealed that LGB subjects have a higher rate of smoking and depression, which are known to increase the risk of CHD. Therefore, intervention programs should be developed to reduce tobacco use and to address depression among these groups.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Nonrheumatic Myopericarditis Post Acute Streptococcal Pharyngitis: An Uncommon Cause of Sore Throat with ST Segment Elevation

Nonrheumatic myopericarditis is an uncommon complication of acute pharyngitis caused by Group A Streptococcal infection (GAS). While the natural history of carditis complicating acute rheumatic fever is well established, the incidence, pathophysiology and clinical course of nonrheumatic myopericarditis are ill defined. Advances in rapid bedside testing for both myocardial injury and GAS pharyngitis have allowed for increasing recognition of this uncommon complication in patients presenting with a sore throat with associated chest discomfort. We describe a case of a 34-year-old man with GAS pharyngitis complicated by acute myopericarditis who presented with chest pain, ST segment elevation on electrocardiogram, and elevated cardiac biomarkers.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Characteristics and Outcomes of Patients with Heart Failure with Reduced Versus Preserved Ejection Fraction Among Patient Enrolled in Community Health Program

BACKGROUND

Readmission rates are high in the United States for both heart failure (HF) with preserved (HFpef) as well as reduced (HFref) ejection fraction. As the phenotype of patients and other co-morbid and socio-economic conditions may be different in both groups, we sought to compare the characteristics of patients in an urban, under-served population among with both types of HF. We also compared the effect of a novel community health worker (CHW) program on reducing 30-day readmissions among both groups.

METHOD

All patients with heart failure who participated in the CHW program between September 2014 and November 2015 were included in the study. Patients who were homeless, resided at a long-term care facility, or were not followed at the outpatient practice were excluded. CHW visited eligible patients at home multiple times over the 30 days following hospital discharge. Patient baseline characteristics, number of previous admissions and ER visits, as well as 30-days readmission and ER visits were collected. Continuous variables were compared using t-test, while categorical variables were compared using Chi-square and Fisher exact test as appropriate.

RESULT

A total of 87 patients were included in this study, of which 76% (n=66) were in HFref group. There were no differences in mean age, gender and race distribution between patients with HFref and HFpef. Patients with HFref were less likely to present with a history of chronic kidney disease (19.7% vs 55.0%, $p < .001$) CHW program resulted in a significant reduction in the mean number of hospitalizations per patients at 30 days (mean (SD): 1.65(2.0) at baseline vs 0.18(0.5) at 30 days, $p < .001$). Similar findings were observed in both HFref (mean (SD): 1.79 (2.1) vs 0.13 (0.4), $p < .001$) as well as HFpef (mean (SD): 1.17(1.4) vs 0.3(0.6), $p = 0.024$) groups respectively.

CONCLUSION

Patients with both HFref as well as HFpef were similar in their cor-morbidities and risk of readmission. Both groups benefited from CHW program with significant reductions in the 30 days readmission and improvement in quality life.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Chagas Heart Disease: A Comparison of Clinical and Intraoperative Pacing Parameters

BACKGROUND

Chagas heart disease is associated with the development of arrhythmias, heart failure with reduced ejection fraction (HFrEF), stroke and sudden death. We aimed to compare the clinical characteristics and intraoperative measurements of patients with and without Chagas disease who underwent cardiac device implantation in Honduras.

METHODS AND RESULTS

A total of 217 consecutive Honduran patients from a single center with indications for pacemaker implantation were included from September 2010 to September 2016. There were 47 patients with serologic positive Chagas disease [Male, 26(54.2%)] and 170 without Chagas disease [Male, 84 (49.4%)], (NS). Mean age was not different between two groups (61.4 ± 10.8 vs. 64.2 ± 17.7 , NS). The following variables were more frequent in the Chagas compared to non-Chagas group respectively: non-ischemic cardiomyopathy (NICM) [24(50%) vs. 24(14.3%), $P < 0.00001$], left ventricular ejection fraction $\leq 55\%$ [(46.7%) vs. (26.3%), $P < 0.009$], right bundle branch block (RBBB) [19(39.6%) vs. 39 (23.2%), $p < 0.02$]. The frequency of the left bundle branch block, sinus node disease, and pacemaker type (dual chamber, atrial only, or ventricular only) were not statistically different between two groups (data not shown). Among pacemaker parameters at the time of device implantation, the Chagas compared to non-Chagas group showed significantly lower R wave amplitude (7.94 ± 4.33 vs. 10.14 ± 5.28 mV, $P < 0.01$). There was no difference between two groups for the rest of ventricular pacing parameters: right ventricular (RV) pacing threshold (0.79 ± 0.33 vs. 0.82 ± 0.72 Volts) NS, RV pulse width (0.49 ± 0.02 vs. 0.48 ± 0.03 milliseconds) NS, RV lead impedance (873.4 ± 270.1 vs. 851.3 ± 282.9 Ohms), NS, and RV current (1.23 ± 0.71 vs. 1.16 ± 0.93), NS. Similarly, there was no difference between groups for atrial device measurements.

CONCLUSIONS

Our study shows higher frequency of left ventricular dysfunction, and RBBB in the Chagas disease compared to non-Chagas group. Among pacemaker parameters, a significantly lower R wave amplitude was noted in Chagas patients. The chronic myocarditis seen in Chagas cardiomyopathy affects the ventricular signal amplitude noted during implant.

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CHILDREN'S NATIONAL MEDICAL CENTER

Mono(2-ethylhexyl)phthalate Exposure Alters the Electrical Restitution Curve in Isolated Hearts

Medical devices are frequently manufactured with polyvinyl chloride (PVC) plastic, in combination with phthalate plasticizers to impart flexibility to otherwise rigid PVC. Since phthalate plasticizers are not covalently bound, these chemicals migrate out of the plastic device and into lipophilic solutions, including blood, parenteral nutrition, and pharmacological agents. As an example, Di(2-ethylhexyl) phthalate (DEHP) can make up to 80% by weight of flexible medical devices, including: blood storage bags, medical tubing, and cardiopulmonary bypass and ECMO circuitry. Phthalate leaching from these devices presents a significant intravenous route of exposure to patient populations. Our previously published in vitro studies have indicated that phthalate plasticizer exposure inhibits electrical conduction in isolated cardiac cells.

OBJECTIVE

To investigate the impact of phthalate plasticizer exposure on electrical restitution in isolated whole hearts.

METHODS

All animal protocols were approved by the Children's National Institutional Animal Care and Use Committee. Adult rat hearts were excised, the aorta cannulated, and transferred to a Langendorff-perfusion system. Hearts were perfused with oxygenated Krebs-Heinslett buffer, and electrodes were placed on the epicardial surface. Mechanical contraction was inhibited with 5 μ M Blebbistatin, and hearts were loaded with 200 nM RH237 to optically map action potentials. Hearts were subjected to a ventricular pacing protocol, and action potentials were recorded using an Andor iXon camera (> 500 fps). Electrical signals were collected using Iox2 software (EMKA technologies) and analyzed using custom MatLab scripts.

RESULTS

Exposure to clinically relevant concentrations of mono(2-ethylhexyl) phthalate (MEHP), the main metabolite of di(2-ethylhexyl) phthalate plasticizer, resulted in a steeper monophasic electrical restitution curve (slope = 1.8) compared with biphasic control (slope = 2.1, plateau slope = 0.1). MEHP-exposed hearts were also more susceptible to alternans at shorter cycle lengths, compared with control.

CONCLUSION

The effect of phthalate plasticizers on cardiac electrical activity has important clinical implications. Alterations in action potential duration restitution and the presence of electrical alternans are arrhythmogenic factors. Additional studies are necessary to resolve the impact of plastic chemical contaminant exposure in patients, and the impact on cardiac function.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Recognition and Management of Cardiac Arrhythmias: A Teaching Module for Physician Assistant Students

BACKGROUND

Electrocardiogram (ECG) diagnosis of arrhythmias is a core skill for medical trainees. The ideal method of instruction is not yet known. Prior studies have shown that trainees fare poorly on arrhythmia recognition and often rate their training as inadequate. We assessed the efficacy of a multimodality didactic and case-based teaching module on arrhythmia diagnosis and management amongst physician assistant (PA) students.

METHODS

A case-based, self-study module outlining evidence-based criteria for the diagnosis and management of cardiac arrhythmias was developed. Over 300 cases at the George Washington University Hospital were reviewed for inclusion to select 26 ECGs and telemetry events that best illustrated common supraventricular and ventricular arrhythmias, atrioventricular conduction abnormalities, and arrhythmias related to common medical conditions. All arrhythmias had been confirmed by electrophysiology studies. Additional examples were compiled into a databank used to administer pre- and post-tests to 48 PA students as a prospective validation trial. After the pre-test, students received a module-based lecture and self-study module for two weeks of independent study prior to the post-test. The primary endpoint was improvement in correct diagnosis. The secondary endpoint was improvement in correct next-step management. A sample size of 42 students was needed to achieve a 90% power and type 1 error rate of 5%. The paired t-test was used to compare pre- and post-test scores.

RESULTS

Correct diagnosis was made for $60 \pm 1.9\%$ of arrhythmias at baseline, which improved to $68 \pm 1.4\%$ on post-test ($p=0.01$). Correct management was identified for $46 \pm 1.5\%$ of arrhythmias at baseline and improved to $53 \pm 1.3\%$ on post-test ($p=0.008$).

CONCLUSION

Our results demonstrate poor baseline competency in diagnosis and management of common cardiac arrhythmias that significantly improved using our teaching module. A case and evidence-based multi-modality teaching module that incorporates didactics and independent-study improves ECG skills amongst trainees.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

A Cross-Sectional Study Reveals an Association Between Electronic Cigarette Use and Myocardial Infarction

BACKGROUND

E-cigarettes (E-cigarettes) have grown in popularity as an alternative to traditional cigarettes especially among consumers who want to reduce the risk of morbidity and mortality associated with smoking. Nonetheless, a recent study showed both E-cigarettes and traditional cigarettes cause an increase in oxidative stress and endothelial dysfunction, however this effect is less pronounced with E-cigarettes. Currently, there is a limited study that shows the impact of E-cigarette in the cardiovascular system. Therefore, data from the 2014 National Health Interview Survey (NHIS) was used to evaluate the effect of E-cigarettes on the cardiovascular system, specifically the effect on myocardial infarction (MI).

METHODS

Analysis of the 2014 National Health Interview Survey (NHIS) database was performed to examine the effect of E-cigarettes on MI. Initially, subjects were assigned to one of two groups: those with a history of MI and those without a history of MI. The t-test and chi-square test were subsequently applied to compare the different demographics and health characteristics between these two groups. A logistic regression model was then used to measure the association between E-cigarettes and history of MI. Data was adjusted for multiple risk factors for MI including age, gender, race, body mass index, income, the status of smoking cigarettes, and history of hypertension, diabetes, and hypercholesterolemia.

RESULTS

A total of 35,156 subjects were included in the final logistic model. This model showed that increasing age (OR, 1.04; $p < 0.001$), history of hypertension (OR, 2.72; $p < 0.001$), high cholesterol (OR, 2.19; $p < 0.001$), and diabetes (OR, 1.68; $p < 0.001$) are associated with increased odds of myocardial infarction. With respect to smoking, increased frequency of smoking was associated with increasingly higher odds of MI when compared to patients who had never smoked: every day smokers (OR, 2.75 $p < 0.001$), some day smokers (OR, 2.39; $p < 0.001$), and former smokers (OR 1.80; $p < 0.001$.) In contrast, females (OR, 0.49; $p < 0.001$), Hispanics (OR, 0.62; $p < 0.001$), and people with higher incomes (OR, 0.93 [95% CI, 0.90-0.96]; $p < 0.001$) have lower odds of heart attack. With respect to Electronic cigarette use and MI, analysis revealed an odds ratio of 1.42 with $p = 0.017$.

CONCLUSIONS

Our findings indicate that Electronic cigarette use, when adjusted for other risk factors, is associated with a 42 % increased odds of myocardial infarction. This increase in odds is consistent regardless of traditional cigarette smoking history. More studies are needed to further assess this risk.

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Intravenous Immunoglobulin in Combination with Intravenous Methylprednisolone in the Treatment of Calcinosis Associated with Juvenile Dermatomyositis (JDM).

BACKGROUND

Calcinosis is one of the hallmark complications of juvenile dermatomyositis (JDM), and is associated with long-term damage, functional disability, and poor quality of life. There is no known effective treatment of calcinosis and current treatment protocols have been limited to anecdotal retrospective studies. Two published case reports showed improvement of calcinosis in JDM patients treated with Intravenous Immunoglobulin (IVIG). We assessed the response of IVIG in combination with Intravenous Methylprednisolone (IV MPD) in five JDM pts with calcinosis.

METHODS

Retrospective medical record review of over 200 JDM patients was performed. 53 (26.5%) of JDM patients developed calcinosis, 4 of whom were on background immunosuppressive therapies, that received IVIG and IV MPD treatment for calcinosis. The number of anatomic areas, limitation of joint range, type of calcinosis, consistency, extent, signs of inflammation, and progression were used to assess response to treatment.

RESULTS

The median age at baseline was 14.8 years [13.7-17.7], 4 pts were male, and 3 were Caucasian, 2 Hispanic. Median disease duration at baseline was 5.5 years [2.9-10.0]. The median duration of IVIG treatment from baseline to clinical improvement in calcinosis was 9.0 months [5.0-13.0], with a dose ranging between 1g/kg- 2g/kg per month. Pts also received IV MPD ranging from 100 mg to 1,000 mg at the time of the IVIG infusion; 4 pts also received oral prednisone and MTX, 1 pt infliximab and 1 pt rituximab, among other therapies. The median Childhood Assessment Questionnaire score (CHAQ) was 1.6 [0.17-2.6] pre-treatment and 0.0 [0.0-1.1] at follow-up after treatment. Median Childhood Myositis Assessment Scale score (CMAS) was 48.5 [20.8-50.8] pre- and 51.0 [38.0-51.5] post-treatment, median Manual Muscle Testing (MMT) was 138.0 [127.0-145.0] pre- and 150.0 [128.0-150.0] post-treatment. Median number of anatomic areas involved with calcinosis was 6.0 [1.5-7.5] pre- and 6.0 [1.0-8.0] post-treatment, the median number of restricted joints was 5.0 [1.5-8.0] pre- and 0.0 [0.0-6.5] post-treatment.

CONCLUSION

Major clinical benefit was seen after the initiation of IVIG and IV MPD in this small case series of JDM patients with refractory calcinosis. Larger, controlled studies are needed to determine the effectiveness of immunosuppressive and immunomodulatory therapies for treatment of calcinosis associated with JDM.

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Early Outcomes after Carotid Endarterectomy compared to Carotid Artery Stenting for Carotid Stenosis in the National Surgical Quality Improvement Program Database

BACKGROUND

Carotid Endarterectomy (CEA) and Carotid Artery Stenting (CAS) are both viable treatment options for carotid artery stenosis. Factors including surgical risk, age, and symptomatic status are often used to help guide management decisions.

METHODS

We conducted a retrospective observational study using the National Surgical Quality Improvement Program (NSQIP) database to compare 30-day post-procedure outcomes including mortality, stroke, and myocardial infarction in patient with carotid stenosis undergoing CEA (n=54,640) versus CAS (n=488) from 2005 to 2012. Procedure type was identified by CPT codes.

FINDINGS

Patients undergoing CEA were more likely to be older and have symptomatic stenosis, and less likely to be white, have CHF, and have COPD. There was no significant difference between CEA and CAS in 30-day mortality (0.9% vs. 1.2%, p=0.33), stroke (1.6% vs. 1.6 p=0.93), myocardial infarction (0.9% vs. 1.6%, p=0.08), or combined outcome (3.0% vs. 4.9%, p=0.09). The interaction between symptomatic status and procedure type was not significant (p=0.29), indicating the association of symptomatic status with 30-day mortality was similar in cases receiving CEA and CAS.

CONCLUSION

Early outcomes after CEA and CAS for carotid artery stenosis appear to be similar in a 'real-world' sample and comparable to clinical trials. Patients undergoing CAS were more likely to be younger and surgically higher risk based on baseline characteristics likely reflecting clinical practice case selection.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Use of Patient to Physician Electronic Communication Differs among IBD patients based on Patient Age

INTRODUCTION

Inflammatory Bowel Diseases (IBD) are chronic diseases that span a lifetime. The complexity of IBD care necessitates close provider to patient interactions. Traditionally, patient care has been facilitated through traditional office visits and phone conversations. New technology has introduced innovative ways for patients to access healthcare providers. We hypothesize that a younger patient demographic is more likely to utilize newer technology to communicate with their providers. In this study, we seek to analyze the difference in modes of communication that IBD patients use to communicate with physicians dependent on patient age.

METHODS

The study was conducted at an urban, academic medical center. We performed a retrospective review of the IBD patients who visited the clinic during a 6-month time period. Patient data were compiled in a database maintaining subject confidentiality. The total number of patient encounters, including number of office visits, ER visits, email communications, and phone communications were collected. Statistical analysis was conducted using Fisher's Exact Test with significance set at $p < 0.05$. The study was approved by the university Institutional Review Board.

RESULTS

A total of 275 IBD patients presented to clinic during the 6-month time period. The mean age of the patient population was 42.9, with a range of 18 to 84. There were 831 total patient encounters, including office visits, ER visits, phone communications, and email communications. There were 429 total office visits and 402 non-office encounters. Patients ≤ 40 years of age (207 office visits vs 153 non-office encounters, 57.5%, $p=0.003$). There were 242 total email communications. Patients ≤ 40 years of age (81 emails, 33.5%, $p=0.0003$). Patients > 40 years old were more likely to communicate by phone than by email (61 calls vs 53 calls, $p=0.01$). There was no significant difference in the number of ER visits vs the number of office visits in both groups ($p=0.88$).

DISCUSSION

Access to healthcare providers is an important issue, particularly for those with chronic illnesses requiring complex management. While outpatient visits remain the most important setting for disease management, modern technology has played an increasingly important role in patient-physician communication. Our data indicates that younger IBD patients prefer email over other communication modalities, while older patients prefer the traditional office visit. These findings reflect the need to evaluate the role of the traditional office visit in a world that increasingly values faster methods of communication.

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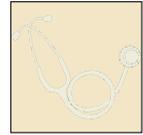
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Development of a Screening Tool for COPD in Patients with Preserved Pulmonary Function

BACKGROUND

There is a significant proportion of patients with smoking related lung disease who are not included within the definition of COPD by GOLD criteria. GOLD guidelines use spirometry to define obstruction as FEV1/FVC < 70%. Recently, there have been studies showing that patients with and without airflow obstruction have similar respiratory consequences. Here we aimed to develop a screening tool for the presence of smoking-related lung disease in patients with no airflow limitation.

METHODS

A review of pulmonary function tests (PFTs) performed at our institution from 2012 to 2016 identified patients with normal ventilatory flows and lung volumes, but decreased DLCO. Of these patients, we selected for analysis those who had a CT scan performed within two years of the PFTs. We took the radiologist's interpretation of the CT scans as evidence of presence or absence of emphysema and these groups were subsequently compared.

RESULTS

Of 6,492 PFTs performed during the study period XX(%) met study criteria. These PFTs were performed in 320 patients. 178 (56%) of these patients had a CT scan with 33 (19%) diagnosed with emphysema and the remaining had other radiological findings. A two-tailed T-test was performed to compare the two groups. A logistic regression model based on significant variables (t-test; $p < .05$) revealed that age, BMI, smoking history, male gender, and DLCO as independent predictive variables. A receiver operating curve identified with a 84% sensitivity and 78% specificity patients with normal spirometry and reduced DLCO who may have radiographic evidence of emphysema on chest CT imaging.

CONCLUSION

This study proposes a model to identify patients with normal spirometry and low DLCO who have a high probability of emphysema on CT imaging. This model may identify patients with smoking related lung disease who otherwise would have been undetected by GOLD criteria. Prospective validation of this tool is needed.

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Nasogastric Decompression is Associated with Increased Hospital Length of Stay but No Reduction in Need for Surgery in ED Patients with Acute Small Bowel Obstruction

BACKGROUND

Small bowel obstruction (SBO) is one of the most common causes of surgical admissions, occurring nearly 300,000 times per year and costing the US healthcare system an estimated \$1.3 billion dollars annually. Standard early management of acute SBO includes Nasogastric (NG) decompression of the GI tract proximal to the obstruction. This procedure is uncomfortable for patients and there is controversy regarding its clinical benefit. The primary objective of this study was to determine if NG decompression was associated with a reduction in surgical management of small bowel obstruction.

METHODS

We performed a retrospective chart review of 181 patients admitted to an urban academic teaching hospital from the Emergency Department (ED) with a diagnosis of small bowel obstruction and CT confirmation over a two-year period from September 2013-September 2015. All subjects received an abdominal CT scan read by attending radiologist as either "definite" or "likely" SBO. Using established methods of chart review, a team of abstractors collected data regarding demographic characteristics, past medical history, clinical signs, ED course and hospital course. To accomplish the primary objective, we compared patients who received NG decompression with those that did not, to primary endpoints of surgical intervention, bowel resection during surgery, and hospital length of stay (LOS).

RESULTS

Among subject population, 93 (51%) of patients received NG decompression and 88 (49%) did not. There was no significant difference in baseline characteristics between the two groups. In patients who received NG decompression, there was no association with a reduction in surgery ($p=0.20$) or bowel resection ($p=0.41$.) A significantly increased distribution of median hospital length of stay for those receiving NG decompression versus those who did not receive NG decompression was observed of 5 days versus 3 days ($p<0.0001$).

CONCLUSION

NG decompression is not associated with a reduction in surgery or a reduction in need for bowel resection but is associated with an increase in hospital length of stay. Future prospective randomized studies are needed to confirm these associations.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

A Review of Pain Control in Pediatric Cardiac Bypass Surgery

BACKGROUND

Children undergoing cardiac surgery with cardiopulmonary bypass receive high dose opioids for analgesia and to reduce the neurohormonal stress response. While opioids have excellent pharmacodynamics profiles adverse effects include: respiratory depression, bradycardia, nausea, vomiting, and tolerance. Additionally, opioids with short half-lives like fentanyl require several boluses to be administered during surgery causing fluctuating levels analgesia. Several strategies to advance pain control incorporate regional and neuraxial anesthetic techniques, however anticoagulation preclude its routine use. Alternatively using opioids with longer half-lives for analgesia may improve pain control and reduce adverse effects.

OBJECTIVE

The objective of this study is to quantify postoperative opioid requirements in pediatric patients following cardiac bypass surgery.

METHODS

Electronic medical records were retrospectively reviewed for 64 pediatric patients following cardiac bypass surgery at Children's National Health System from June of 2014 through February of 2016. Intraoperative and postoperative opioid class and dose was recorded for outpatients with designation ASA class 2-4. The data was compiled and analyzed to obtain a mean and standard deviation for future study.

RESULTS

64 cardiac surgery patients (mean age 4.3 ± 1.7 , mean weight 17.1 ± 7.5 kg) receiving between 10-30mcg/kg of fentanyl, the mean total dose of morphine in the first 24-hour postoperative period was 0.363mg/kg, with a standard deviation of 0.239.

CONCLUSIONS

The data from this internal case review of pain control in pediatric cardiac bypass surgery will be used delineate the appropriate sample size for studying postoperative pain control. This is applicable to our study that compares intraoperatively administered fentanyl to methadone on postoperative opioid requirement. This internal case review of 64 cardiac surgery patients (mean age 4.3 ± 1.7 , mean weight 17.1 ± 7.5 kg) receiving between 10-30 mcg/kg of fentanyl showed a mean total dose of morphine in the first 24-hour postoperative period was 0.363 mg/kg, with a standard deviation of 0.239. Assuming no difference between the two treatment strategies in the population, a total sample size of 76 in each group will provide 80% power to detect a difference of 0.109 in means, using a two-sample t-test at the 0.05 significance level. The high amount of postoperative morphine required, as determined by this study, reveals the need to find alternative pain control strategies such as opioids with longer half-lives and regional techniques. Exploring the effectiveness of methadone, a long acting opioid, to reduce postoperative adverse effects is an area of future study.

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An Unusual Presentation of Giant Cell Arteritis Causing Delay in Diagnosis

Giant Cell Arteritis (GCA) is a large artery vasculitis, affecting the aorta and its branches, that typically presents with jaw claudication, headache, fever, and monocular vision changes. Rarely, patients may present with bilateral acute vision loss and thus GCA is often overlooked as the primary etiology leading to diagnostic delays and significant morbidity to patients. Here we present a case of GCA that initially presented with bilateral acute vision changes.

A 71-year-old woman with past medical history significant for hypertension, asthma, and COPD presented to an outside hospital with a low grade fever, headache, back pain, and transient bilateral vision changes. She was admitted to the outside hospital and initiated on empiric antibiotics for presumed Pyelonephritis in the setting of urinalysis positive for leukocyte esterase and CBC with a leukocytosis of 20k.

Our patient developed persistent bilateral vision loss on the third day of admission prompting a workup for acute thromboembolic stroke. Initial imaging with a non-contrast CT head and non-contrast MRI brain did not show any ischemic or hemorrhagic changes. The patient's vision continued to deteriorate resulting in complete loss of visual acuity and her persistent vision loss prompted transfer to our tertiary academic hospital for further evaluation.

On admission to our hospital, the patient's physical exam revealed temporal muscle tenderness, jaw tenderness, and complete visual field deficits, labs were significant for WBC 20K, ESR 110, and CRP 359, and imaging studies including MRI face/neck/orbit with and without contrast showed "nonspecific non-mass like enhancement of the retro-orbital fat, muscles of mastication" indicating an underlying inflammatory process. Infectious workup did not yield an etiology for her continued low grade fever including Chest X-Ray, CBC, Urinalysis, Blood Cultures, etc. Ophthalmology and Neurology were also consulted. Given the elevated inflammatory markers, persistent visual deficits, as well as clinic picture, our patient was initiated on high dose steroids upon transfer to our hospital. Bilateral temporal artery biopsies were performed revealing "lymphohistiocytic inflammation involving adventitia and branching vessels consistent with temporal arteritis." Unfortunately, despite the initiation of high dose steroids, there was no improvement in our patient's visual acuity and she was later discharged to a rehab facility for further occupational therapy in the setting of her new visual deficits.

This case illustrates a rare presentation of GCA that caused a diagnostic delay resulting in significant morbidity for our patient. Although bilateral vision loss is a rare presentation of GCA, this particular constellation of symptoms should have prompted earlier consideration of GCA and thus earlier initiation of steroids. Magnetic resonance imaging/angiography (MRI/MRA) could potentially be considered as part of the diagnostic workup as preliminary studies have shown abnormal contrast enhancement in patients with abnormal contrast enhancement. Considering GCA early in the diagnostic process in a patient presenting with bilateral vision loss is vital and MRI/MRA may be part of the diagnostic workup for GCA in the near future.

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A Case Control Study to Evaluate the Prevalence of Nonalcoholic Fatty Liver Disease (NAFLD) Among Patients with Moderate to Severe Psoriasis

BACKGROUND

International case-control studies have demonstrated that psoriasis is associated with an increased prevalence of nonalcoholic fatty liver disease (NAFLD).

OBJECTIVE

To establish the association of psoriasis and the presence of NAFLD in psoriasis patients attending a tertiary dermatology clinic center in the United States.

METHODS

A 6-year case-control study was conducted at the George Washington Medial Faculty Associates dermatology clinic from December 2009 to April 2016. Adult psoriasis patients were matched by age, sex, and body mass index (BMI) with healthy controls. NAFLD was diagnosed by ultrasonography after exclusion of secondary causes of liver disease. Conditional logistic regression was used to assess the association between NAFLD and psoriasis. Adjusted least-square means were computed to assess associations between baseline covariates (including BMI and metabolic syndrome components) and NAFLD among psoriasis patients.

RESULTS

In total, 101 psoriasis patients (mean age 44.2 ± 13.6) and 51 controls (mean age 44.7 ± 14.5) were enrolled. NAFLD was more prevalent in psoriasis patients compared to controls (21.2% vs. 7.8%, $P < 0.04$). However, psoriasis was not associated with NAFLD when patients were matched by age, sex, and BMI (OR 2.63; 95% CI, 0.51 - 13.6; $P = 0.25$). Compared to psoriasis patients without NAFLD, those with NAFLD were more likely to be obese (BMI 34.9 vs 27.2, 95% CI 32.4 - 37.5 vs 25.9 - 28.5, $P < 0.01$). NAFLD in psoriasis patients was also associated with significantly higher measurements of glucose, AST, ALT, triglycerides, VLDL, and BMI.

LIMITATIONS

This was a cross-sectional study.

CONCLUSION

Our findings suggest an increased presence of metabolic syndrome components in psoriasis patients with NAFLD. Physicians should consider diagnostic imaging for NAFLD in psoriasis patients who have or are at risk of developing metabolic syndrome.

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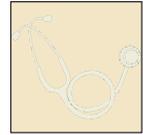
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Low Serum Trypsin Levels Predict Deep Pancreatic Cannulation Failure during ERCP in Patients with Chronic Pancreatitis

BACKGROUND

Deep pancreatic cannulation failure (DPCF) during ERCP in patients with chronic pancreatitis (CP) can occur in the presence of duct obstruction due to strictures and/or stones. There are currently no simple preprocedure clinical or laboratory tests that can predict DPCF during ERCP. Since low serum trypsin levels have been correlated with advanced chronic pancreatitis and exocrine insufficiency, we hypothesized that it might be a useful preprocedure test for predicting DPCF.

AIM

To assess whether low serum trypsin levels predict DPCF failure of deep pancreatic duct cannulation during ERCP in patients with chronic pancreatitis, after adjusting for obstructing strictures and/or stones.

METHOD

All adult (>18 year of age) patients with definite CP who were referred to a multidisciplinary pancreatitis clinic between 2010-2015 and underwent a serum trypsin level measurement prior to ERCP for the management of abdominal pain were evaluated. Serum trypsin levels are obtained in all CP patients as part of their evaluation for exocrine insufficiency. Exclusion criteria included chronic kidney disease, prior pancreatic resection, and/or type 1 diabetes mellitus as these conditions can affect serum trypsin levels independent of CP. Definite CP was defined as abdominal pain and/or acute recurrent pancreatitis in the presence of calcification(s) on CT scan and endoscopic ultrasound EUS and/or moderate to severe ductal changes based on the MANNHEIM criteria. Low serum trypsin was defined as values <19 ng/mL or <10 ng/mL based on laboratory assay. Failure of deep cannulation during ERCP was defined as the inability to advance any accessory (sphincterotome guidewire, cannula, and/or guidewire sphincterotome) upstream of an obstructing stricture and/or stone which would be necessary for the completion of therapeutic maneuvers (stone extraction, stricture dilation, stone extraction and stent placement). Heavy smoking and alcohol use was defined per NAPS2 study. Serum trypsin levels, pancreatic stone(s) and duct stricture were evaluated as Ffactors associated with DPCF during ERCP were evaluated using univariable and multivariable logistic regression analysis.

RESULTS

Among 213 patients diagnosed with definite CP, 104 patients underwent trypsin measurements and ERCP, of whom 42 (40.4%) had low/undetectable serum trypsin levels and 37 (35.6%) had DPCF during ERCP. There were no significant differences between patients with and without DPCF low/ undetectable and normal trypsin levels with regards to age, gender, etiology, smoking, and pancreas divisum. Patients with DPCF were more likely to have low trypsin levels (68% vs. 25%, $p<0.0001$), obstructing stones (86% vs. 57%, $p=0.02$), and strictures (69% vs. 30.9%, $p=0.001$) compared to those without DPCF. Patients with low/undetectable trypsin had significantly higher rates of heavy alcohol use (61.1%) ($p=0.006$) and calcifications (51.4%) ($p=0.002$) detected on CT scan or EUS. A total of 6 (54.5%) out of 11 patients who underwent ESWL after failure of ERCP, had successful deep pancreatic cannulation on subsequent ERCP. A low /undetectable serum trypsin level was significantly associated with DPCF in the both the univariable (OR: 6.13; 95% CI: 2.5-14.8; $P<0.001$) and multivariable (OR: 5.99; 95% CI: 2.13-16.83; $P=0.001$) analysis after adjusting for obstructing stones and stricture.

CONCLUSION

Preprocedural low serum trypsin levels independently predict DPCF during ERCP in patients with chronic pancreatitis. Consideration of ESWL prior to ERCP may increase successful deep pancreatic cannulation rates.

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Evaluating the Association between Hidradenitis Suppurativa Disease Activity Scores and Marijuana Use

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic, recurrent, inflammatory disease of the apocrine sweat glands, characterized by recurrent abscessing inflammation. The disease affects 1-4% of the population and has no known cure. HS has several known risk factors, one of which is tobacco. Smoking is strongly correlated with disease activity in HS, and thus all patients are counseled to stop smoking.

Pain is common in HS and patients often use marijuana for pain management; however, the impact of marijuana on disease activity has not been investigated. The purpose of this study is to investigate the relationship between marijuana use and HS disease activity.

METHODS

This research was conducted through the Wound Etiology and Healing Study (WE-HEAL Study), an observational biospecimen and data repository approved by The George Washington University IRB (041408). All subjects gave informed consent for longitudinal data collection while receiving treatment according to standards of care. Baseline smoking and marijuana (MJ) use were documented from history obtained by the physician at initial visit. MJ use was a binary variable; cigarette smoking was categorized as current, former or never, and quantified. Disease activity scores including Hurley stage, Hidradenitis Sartorius Score (HSS) and Active Nodule (AN) count are documented at baseline and subsequent visits. Statistical analysis was performed using GraphPad Prism (Version 5, GraphPad, USA) and $p < 0.05$ was considered significant.

RESULTS

This study used the 64 subjects enrolled in the WE-HEAL study with HS. There was no significant difference in age, sex, race, body mass index or disease duration in the MJ users ($n=9$) compared to the MJ non-users ($n=55$, $p > 0.05$ for all variables) and pain scores were comparable. There were no significant differences in disease activity at enrollment between the MJ users and non-users based on Hurley stage ($p=0.399$), HSS ($p=0.589$) or AN count ($p=0.32$). However, HSS and AN count tended to be higher in MJ users.

DISCUSSION

This study has several notable limitations. Firstly, MJ exposure was determined by patient report and exposure was not quantified, meaning under reporting of exposure was possible. Secondly, the number of MJ users in this study is small, limiting our ability to identify significant differences. Finally, the impact of MJ on disease activity in patients receiving other treatments for HS was not investigated.

CONCLUSION

The longitudinal observational cohort of HS patients followed in the WE-HEAL study is a unique population for investigating drivers of disease activity in HS.

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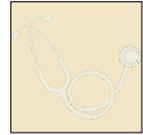
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Price Variation of Common Dermatologic Medications and an Opportunity to Help Patients Save Money by Influencing How They Shop

IMPORTANCE

High out-of-pocket drug expenditures are common in dermatology. Patients may not be aware that prices vary among pharmacies and may make choices that end up costing them more at the register.

OBJECTIVES

- (1) Compare the prices of commonly prescribed dermatologic medications at local pharmacies.
- (2) Assess patient awareness of local drug price variation and the factors that influence pharmacy choice.
- (3) Determine the role of patient price education on influencing perception and predicted shopping habits.

METHODS

We obtained costs of medications frequently prescribed in dermatology and internal medicine through unannounced interviews with pharmacists at 8 local dispensaries (3 independent, 2 chain, 2 retail, and 1 grocery store). Between July and August 2016, we administered a cross-sectional anonymous survey to adults (Age ≥ 18 and literate in English) visiting outpatient clinics at the George Washington University Medical Faculty Associates. After respondents reviewed a handout of local prescription drug prices, they were asked follow-up questions. Investigators administered 287 surveys to a convenience sample of adults and 218 respondents answered enough questions to be included in our statistical analysis.

RESULTS

Our findings revealed that prices of commonly prescribed dermatologic medications vary widely among local pharmacies: clobetasol lotion (median \$289.96, interquartile range \$100.56), tretinoin cream (median \$208.64, interquartile range \$27.00), and fluocinonide cream (median \$738.79, interquartile range \$347.19). In our survey population, 73.4% (n=157) felt the price of their medications was “roughly the same at every drugstore” or indicated that they were unsure. When considering a cost savings of \$10-25, 65% of respondents would switch pharmacies if the distance were the same, and 21.3% would switch if the distance was 45-minutes longer. After price education, respondents’ intended frequency of researching price online, calling a pharmacy to ask about price, and comparing the price between pharmacies before filling a prescription all increased, compared to prior self-reported frequencies (p<0.001).

CONCLUSIONS

This study suggests that price education will ultimately make patients more aware of disparities in medication costs. As the pharmacy distance increased, respondents were less likely to consider that alternate pharmacy, despite cost savings. However, brief price education was found to significantly change attitudes toward filling prescriptions and perceptions regarding local retail drug prices. Respondents intended to increase the frequency with which they research drug prices (both online and by phone) and compare prices among local pharmacies before filling their prescription. Thus, knowledge of drug pricing may be useful in creating cost savings for patients.

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Pathologic Changes in the Long Head of the Biceps Tendon

INTRODUCTION

The extent to which the long head of the biceps brachii (LHB) tendon contributes to anterior shoulder pain in the setting of rotator cuff syndrome is controversial. In the United States biceps tenodesis is an increasingly favored treatment option for those patients with rotator cuff syndrome and anterior shoulder pain with the presumption that inflammatory or degenerative disease of the LHB is contributing to the pain. However, there is little evidence on intraoperative examination of the LHB that facilitates the decision to pursue tenodesis. Previous research has suggested LHB inflammation, degenerative change, and vascular insufficiency may contribute to anterior shoulder pain in patient's with rotator cuff syndrome. Further understanding of the pathology as well as location of the pathology may better inform the therapeutic etiology of pain relief from a tenodesis as well as the indications for tenodesis. The goal of this study was to further characterize the pathology and location of the pathology in the LHB tendon in the setting of patients undergoing arthroscopic rotator cuff repair and tenodesis.

METHODS

All patients who provided informed consent and underwent arthroscopic rotator cuff surgery which included suprapectoral biceps tenodesis between 7/2014-12/2016 from one orthopedic surgeon's patient population were included. The biceps tendon specimen was harvested with an average length of 3.59cm. Tendon samples were cross sectioned into three zones (1-3) and examined for degree of inflammation, degenerative change and papillary tenosynovitis. A four-graded scale was used to describe the pathology: 0-3 or none, slight, moderate, and severe.

RESULTS

53 patients were included. 21 with rotator cuff tears (RCTs). 32 without tears. 42/53 patients had higher than grade 1 papillary tenosynovitis. Grade 2 or higher degenerative change was seen in 34/53 patients. Of these 30 had proximal degeneration, and 14 had distal degeneration. A higher degree of degenerative change was found in tendons from patients with a RCT. Of patient's with concurrent RCTs 79% had greater or equal to grade 2 degeneration. Only 33% of tendons without RCTs had greater or equal to grade 2 degeneration.

CONCLUSION

Regardless of whether there is a concurrent RCT significant inflammation is not found in the LHB in patient's undergoing arthroscopic surgery for rotator cuff syndrome. However, degenerative change of the LHB is more likely to be found in patient's with full thickness RCTs. Degenerative change is more likely to be found in the proximal tendon versus the distal tendon.

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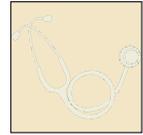
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Can Honey-Thick Liquids Cause Hypernatremia In Elderly Hospitalized Patients?

BACKGROUND

Although honey-thick liquids (HTLs) are commonly used in patients with dysphagia to minimize aspiration, their clinical benefit is not well-established in the literature. Past research also suggests that many patients on HTLs fail to meet daily fluid requirements and are prone to dehydration. We present 2 cases of patients on a general medical ward who developed hypernatremia within 24-72 hours of initiating HTLs, a complication not previously described in the literature.

Case 1

An 88-year-old man with HIV and diabetes was admitted to the medical ward after a fall. He was treated for UTI and delirium and recommended for subacute rehabilitation. On hospital day 13, he was noted to cough with meals, prompting evaluation by speech language pathology (SLP), who recommended changing thin liquids to HTLs. Within 24 hours, serum sodium increased from 144 to 152 mg/dL, eventually peaking at 165 mg/dL; correction was hampered by poor IV access. His course was further complicated by AKI and aspiration pneumonia. He died on day 22.

Case 2

An 80-year-old man with diabetes, remote PE and a recently discovered liver mass was admitted for debility, AKI, and elevated INR. AKI and INR were corrected and he remained inpatient for liver biopsy and subacute rehabilitation placement. SLP recommended changing thin liquids to HTLs on day 7. Serum sodium then increased for 7 consecutive days, peaking at 153 mg/dL. He later developed AKI and aspiration pneumonia and died on day 16.

DISCUSSION

Inadequate free water intake is a common cause of hypernatremia in the elderly. The patients above developed significant hypernatremia after starting HTLs, which likely decreased their free water intake; other etiologies, such as GI/renal/insensible losses, or use of hypertonic solutions, were absent. AKI may have occurred for similar reasons. HTLs may decrease free water ingestion for numerous reasons, such as longer time needed to drink HTLs, suppression of appetite due to poor taste and/or early satiety, or decreased access to HTLs compared to regular water in a hospital setting.

CONCLUSION

HTLs in older hospitalized patients may decrease free water intake and induce hypernatremia. Previous research on HTLs has not established a direct link to hypernatremia. Given the poor outcomes in the cases above, hypernatremia as a potential consequence of HTLs warrants further study.

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Vitamin D Receptor Polymorphisms are Associated with Baseline Muscle Strength and Response to Strength Training

BACKGROUND

VDR polymorphisms are associated with performance outcomes including hand grip strength and quadriceps strength. However, the positive associations identified in several of these studies have not proven reproducible when evaluated in other cohorts.

OBJECTIVE

Given persistent ambiguity regarding the influence of vitamin D receptor polymorphisms on muscle strength, we chose to evaluate the influence of five previously studied VDR variants (A1012G/ rs4516035, Fok1/ rs2228570, Ddel/ rs3782905, Bsm1/ rs1544410, Taq1/ rs731236) on a broader range of muscular performance measures in two cohorts of young adults. Studying the genetic determinants of muscle strength development may create the potential to predict adults who are more likely to suffer from sarcopenia, an age-related loss in muscle mass and strength that has been associated with loss of independence and poor health outcomes in the elderly.

METHODS

Two cohorts of young adults, *The Functional Single Nucleotide Polymorphism Associated with Human Muscle Size and Strength* (FAMuSS) and *Assessing Inherited Markers of Metabolic Syndrome in the Young* (AIMMY), were genotyped using Illumina Multi-Ethnic Genotyping Arrays (MEGA). All outcomes were adjusted for age and tested in gender-specific cohorts using both additive and dominant genetic models. ANCOVA models were used to analyze the relationship between genotype and several muscle strength phenotypes.

RESULTS

In FAMuSS, males with at least one copy of the rare allele of rs2228570 (Fok1) had significantly greater baseline MVIC strength in the exercised arm ($p=0.049$), but lesser 12-week change in whole muscle volume of the exercised arm ($p=0.034$) than those with only the common allele. In AIMMY, Caucasian females with at least one copy of the rare allele of rs2228570 (Fok1) showed greater right hand grip strength ($p=0.035$), while African American females with the rare allele of rs4516035 (A1012G) ($N=11$) showed greater left hand grip strength ($p=0.046$). The Fok1 site thymine/cytosine polymorphism alters an ACG codon, resulting in an earlier upstream start codon that affects transcriptional activity.

DISCUSSION

The current study extends our knowledge of VDR variants influencing muscular strength by including an African American cohort, and exploring additional muscle strength phenotypes: biceps size and maximum voluntary isometric contraction (MVIC), and the functional response to a 12-week strength training program. This validation study solidifies the connection between VDR polymorphisms and muscle strength by extending the relationship to biceps strength and response to a 12-week strength training program.

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Comparison of DLP-Based Effective Dose to Monte Carlo-Based Effective Dose in Low Dose Chest CT's

INTRODUCTION

Lung cancer is very difficult to detect during its early stages, as outward symptoms are not typically expressed early in the disease process. Advances in low dose CT have made it possible to screen high-risk patients and make earlier diagnoses. It is important to strike a balance between radiation exposure and image resolution, and the recommended effective dose (ED) of radiation for these scans is 1.5 mSv, much lower than the 8 mSv dose of a typical diagnostic chest CT scan. The purpose of this study was to compare the rapid formulaic dose length product (DLP)-based method of calculating ED to the Monte Carlo-based method, which is regarded as the gold standard.

METHODS

This was a HIPAA compliant retrospective study. Dose data from 85 non-contrast low dose chest CT's used for lung cancer screening were collected. Monte Carlo simulated organ based effective dose (ED_{MC}) was calculated using Radimetrics software, a commercially available radiation dose tracking software. The DLP-based effective dose ($ED_{DLP,B}$) was calculated using the formula $ED = DLP * k$, where k is the conversion coefficient, which are widely published. A k value of 0.015 was used for both sexes (k_B), and female and male specific k -coefficients of 0.019 (k_F) and 0.011 (k_M) were also used respectively. ΔED was calculated as $mean ED_{DLP} - mean ED_{MC}$; and $\% \Delta ED$ was calculated as $(mean \Delta ED / mean ED_{MC}) * 100$. ED_{MC} and ED_{DLP} were compared using Wilcoxon signed rank test (WSRT) using k_B , k_F and k_M to calculate ED_{DLP} . Modified Bland-Altman plots were created, comparing ΔED to ED_{MC} , and $\% \Delta ED$ was also plotted against patient diameter.

RESULTS

There was statistically significant difference between ED_{MC} and $ED_{DLP,B}$ ($p < 0.0001$) when using k_B (0.015) coefficient, although this was heavily influenced by gender. $ED_{DLP,B}$ underestimates ED_{MC} by a mean of 31% in women ($p < 0.0001$). There was no difference between ED_{MC} and $ED_{DLP,B}$ in male patients ($p = 0.3173$). ED_{DLP} underestimated ED_{MC} by 13% in women when using the gender specific k_F ; this difference was significant ($p < 0.0001$). ED_{DLP} underestimated ED_{MC} by 28% in men when using the gender specific k_M ; this difference remained significant ($p < 0.0001$). $\% \Delta ED$ is also dependent on patient diameter.

CONCLUSION

DLP-based calculation of ED using the gender-neutral k -coefficient underestimates ED by 31% in women; use of female-specific k -coefficient decreases this underestimation to 13%. This should be factored into CT protocol development of low-dose chest CT's in women. Gender-neutral k -coefficient is adequate for DLP-based ED calculation in men.

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Utilization of Ultrasound for Diagnostic Evaluation and Management of Peritonsillar Abscesses

PURPOSE OF REVIEW

We outlined the management of peritonsillar abscess (PTA) through the use of ultrasound, an imaging modality that continues to emerge as a diverse diagnostic and treatment tool. Our review compares the use of ultrasound to alternative diagnostic modalities, particularly computed tomography (CT). Further, the review evaluates how ultrasound can be used to help facilitate guided drainage of PTA and serve as a suitable alternative to more invasive management options.

RECENT FINDINGS

Studies over the past five years have demonstrated that the initial management of PTA with ultrasound is a more cost-efficient and lower-risk option than imaging with CT. Ultrasound possesses great specificity for PTA and may be more diagnostically accurate than previously thought. Ultrasound is particularly well tolerated in children and adults, avoids radiation exposure, as well as minimizes false positive aspirations. Additionally, the ability to utilize ultrasound from different approaches allows for flexibility in the management of PTA.

SUMMARY

These findings illustrate that ultrasound is being increasingly considered in the management of stable patients presenting with PTA.

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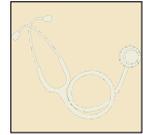
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Relationship between Educational Level and Disease Activity in Scleroderma and Systemic Lupus Erythematosus

INTRODUCTION

Socioeconomic inequalities are important factors which impact healthcare outcomes. Educational level is a major driver that facilitates patient's ability to navigate the healthcare systems and to engage with multidisciplinary support services. Scleroderma and systemic lupus erythematosus (SLE) are two autoimmune diseases in which the immune system attacks healthy tissues in the body. The purpose of the current study was to investigate the relationship between education levels in patients with SLE and scleroderma and disease activity scores using validated measures.

METHODS

This research was conducted through The STOP Scleroderma Study and the GW Lupus Study. These two longitudinal observational, biospecimen and data repositories are approved by The George Washington University IRB (051427 and 031614 respectively). All subjects gave written informed consent for longitudinal collection of their data while they receive treatment according to standard of care. SLE outcomes are measured with the following activity report scoring sheets: Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), Systemic Lupus Activity Questionnaire for Population Studies (SLAQ), and Systemic Lupus International Collaborating Clinics classification criteria (SLICC). Scleroderma activity is measured using the Medseger Disease Severity Index, the modified Rodnan skin score (MRSS), and the Scleroderma Health Assessment Questionnaire (S-HAQ). Statistical analysis was performed using GraphPad Prism (Version 5, GraphPad, USA) and $p < 0.05$ was considered significant.

RESULTS

Analysis included 54 patients from STOP Scleroderma and 16 from the GW Lupus Study. The Lupus cohort was 50% African American, whereas the STOP scleroderma cohort was only 24.1% African American consistent with known demographic differences between the diseases. Both cohorts were predominantly female (93.7% of Lupus and 87% in Scleroderma).

Highest educational level achieved did not differ with demographics in either cohort. On the Medseger Severity Scale, scores were better in patients who had achieved higher levels of education. The mean scores for high school, undergraduate, and post-graduate groups were 7.33 ± 5.56 , 4.11 ± 2.88 , and 2.61 ± 2.48 , respectively ($p = 0.0271$). Similarly, the mRSS scores for high school, undergraduate, and post-graduate groups were 19.33 ± 6.60 , 5.21 ± 3.64 and 5.00 ± 6.056 , respectively ($p = 0.0002$). Patient reported scores on the S-HAQ are 1.31 ± 0.753 , 0.305 ± 0.372 , and 0.331 ± 0.600 , respectively ($p = 0.0035$).

We were not able to identify differences in lupus disease activity scores based on educational group, but this was likely due to the very small sample size in the SLE cohort.

CONCLUSION

In the autoimmune disease scleroderma, the highest level of education achieved is correlated with disease activity score. This finding merits further investigation.

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Rib Plating Does Not Improve Long-Term Quality of Life

INTRODUCTION

Rib fractures are associated with significant morbidity and mortality. While studies on patients undergoing rib plating demonstrate decreased short term pain as well as need for and duration of mechanical ventilation, no studies have evaluated long term benefit. We evaluated the effects of rib plating on patient quality of life (QOL) and hypothesize that long-term QOL is similar between patients that did and did not undergo plating.

METHODS

A retrospective analysis was performed from 2012-2016 for patients with ≥ 3 rib fractures that were >90 -days from injury who did and did not undergo plating. Patients were plated primarily for respiratory failure or refractory pain. A Medical Outcomes Short Form 36-Item (SF-36) phone survey was conducted to assess QOL. Demographics, injury characteristics, and QOL were compared between groups. Multivariable analysis was performed to identify predictors of QOL.

RESULTS

251 patients were included (22 plated, 229 unplated). Twelve plated and 45 unplated patients completed the SF-36 survey with no differences in average time from injury (732 ± 264 days, 822 ± 400 days, $p=0.47$). Demographics were similar between groups; however, plated patients had higher ISS (25.9 ± 11.4 , 17.4 ± 7.9 , $p=0.004$) and worse overall QOL (59.7 ± 25.6 , 77.9 ± 18.3 , $p=0.007$) and physical/health related QOL (55.5 ± 27.6 , 75.8 ± 22.5 , $p=0.011$). After controlling for demographic and injury characteristics, plated patients had significantly worse physical/health-related QOL ($p=0.006$) and a trend towards worse overall QOL ($p=0.06$).

CONCLUSIONS

Rib plating does not improve quality of life ≥ 3 months following injury. Further work is needed to identify select subgroups that might benefit from plating in the long-run.

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Pediatric Peritonsillar Abscess: Outcomes and Cost Savings from Using Transcervical Ultrasound

BACKGROUND

Peritonsillar abscess (PTA) is the most common infection found in the head and neck. Adolescents and young adults are particularly susceptible to developing PTA. However, clinical impression alone often poorly differentiates between true abscess and acute tonsillitis. Over the last two decades, the introduction of ultrasound in the emergency department (ED) has proven to be an invaluable diagnostic tool that is both highly sensitive and specific.

OBJECTIVE

The first objective was to analyze clinical outcomes of children stratified by ultrasound into three diagnoses: acute tonsillitis, peritonsillar phlegmon, and abscess. The second objective was to compare clinical outcomes and financial impact between children who underwent ultrasound protocol to those who did not. We hypothesized transcervical ultrasound is cost effective for diagnosis and an option for reducing radiation exposure in the pediatric population.

METHODS

Children with PTA diagnosed in the ED were enrolled during a two year period for transcervical ultrasound evaluation. The ultrasound probe was placed underneath the mandible to visualize appropriate anatomy. Images were then analyzed by a blinded radiologist and categorized as 1) abscess, 2) phlegmon, or 3) tonsillitis. Data from a cohort of patients with PTA who did not receive ultrasound were collected from retrospective chart review. Outcome variables were analyzed using multivariate logistic regression.

RESULTS

Seventy-eight children were enrolled in the ultrasound protocol, compared to 101 children evaluated using traditional methods. Only 1/3 of patients presumed to have PTA by ED staff had ultrasound findings consistent with abscess. Overall treatment failure rate was 8% requiring re-admission or surgical intervention for abscess. Length of stay, surgical drainage, and radiation exposure from CT scans were reduced significantly in the ultrasound group ($p < 0.006$). Differences in readmission rates and mean charges between the two groups were not significant.

CONCLUSIONS

Based on our findings, the ED was accurate in diagnosing true abscess in only 1/3 of cases. The ultrasound group had significantly lower length of stay, rate of procedures and radiation exposure from CT scans compared to the pre-ultrasound group. No difference in readmission rates between the two groups was demonstrated. Despite the lack of difference in cost, the fees analyzed did not include ED charges, facility fee, medications, radiology, or anesthesiology charges for sedation associated with pediatric CT scans. If these cost variables were tabulated, we anticipate significant cost savings in the ultrasound group. Transcervical ultrasound is a safe, cost-effective, and accurate modality to diagnose PTA.

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Platelet Count Increase Seen with Ledipasvir-Sofosbuvir Combination Treatment of Chronic Hepatitis C in Patients with Thrombocytopenia

BACKGROUND

Thrombocytopenia (TCP) is commonly seen in chronic Hepatitis C (HCV). Ledipasvir-sofosbuvir (LDV/SOF) is a novel, fixed-dose anti-HCV combination that has shown high sustained virologic response (SVR) rates. However, since much remains to be learned about the natural history of TCP following LDV/SOF treatment, we set out to examine platelet (PLT) counts in thrombocytopenic patients with chronic HCV before, during, and after treatment with LDV/SOF.

METHODS

This is an IRB-approved, retrospective study of patients diagnosed with chronic HCV who received LDV/SOF between November 2014 and April 2016 at the Washington DC Veterans Affairs Medical Center. Patients who had PLT counts less than or equal to $150 \times 10^9/L$ for at least 6 months prior to treatment and completed therapy with LDV/SOF were included. Patients diagnosed with heparin-induced TCP; disseminated intravascular coagulation; medication-induced TCP; sepsis; as well as those who received PLT transfusion or thrombopoietic agents were excluded. PLT counts were collected at baseline (within 6 months prior to the start of therapy), during treatment, and throughout the follow-up period until the last follow-up, initiation of a new HCV medication, liver transplant, or death. Patients were categorized into 3 groups: mild TCP ($100-150 \times 10^9/L$), moderate ($50-99 \times 10^9/L$), and severe ($<50 \times 10^9/L$). Paired t-test was used to compare pre-treatment, on-treatment (week 4), and the last measured PLT counts. Multivariate regression analysis was used to determine the baseline variables associated with improvement in PLT counts. All registered PLT counts from the start of therapy were included in repeated measurement analyses to assess the evolution of PLTs over time.

RESULTS

Inclusion criteria were met in 244 patients (median age 64, 98% male, 88.9% African American). HCV genotypes were 1a (77.4%) and 1b (22.6%). The median follow-up from treatment start was 13 months. Treatment duration was 8 weeks (13.9%), 12 weeks (69.7%), or 24 weeks (16.4%), all at the fixed dose of LDV 90 mg and SOF 400 mg once daily. SVR at 12 weeks (SVR12) was attained in 159 patients (65.2%) while 67 patients (27.5%) had a documented undetectable viral load earlier than 12 weeks from treatment completion with no further testing. Eight patients (3.3%) failed treatment and 10 (4.1%) were lost-to-follow-up. The mean pre-treatment PLT count was $114 \times 10^9/L$ (22-150). The on-treatment and last measured PLT counts were significantly higher than the baseline PLT count ($129 \times 10^9/L$, $p < 0.001$ and $144 \times 10^9/L$, $p < 0.001$ respectively). The increase from the on-treatment to the last measured PLT count was also statistically significant ($p = 0.008$). The last measured PLT counts were on average $32.8 \pm 66.7\%$ higher than the baseline and 31.6% of patients had normal last measured PLT counts. The increase in PLT count was observed for all three TCP groups: mild (73.4%): from $129 \times 10^9/L$ at baseline to $149 \times 10^9/L$ during treatment ($p < 0.001$) to $160 \times 10^9/L$ after ($p = 0.045$); moderate (24.2%): from $75 \times 10^9/L$ before to $89 \times 10^9/L$ during ($p = 0.004$) to $112 \times 10^9/L$ after ($p = 0.027$); severe (2.5%): from $38 \times 10^9/L$ before to $64 \times 10^9/L$ during ($p = 0.003$) to $97 \times 10^9/L$ after ($p = 0.234$). Multivariate regression analysis was performed including the following variables: age; gender; HCV genotype; baseline PLT count, albumin, bilirubin, and AST/ALT; history of severe alcohol abuse; HIV coinfection; Hepatitis B coinfection; presence of splenomegaly; presence of cirrhosis; treatment duration and reaching SVR12. It showed that reaching SVR12 is associated with a faster increase in PLT count ($p = 0.022$). Repeated measurement analyses showed a gradual and linear increase in PLT counts from the start of therapy for the entire cohort ($p < 0.001$) as well as in every TCP group: mild ($p < 0.001$), moderate ($p = 0.001$) and severe ($p = 0.015$).

CONCLUSION

LDV/SOF is associated with an increase in PLT counts in chronic HCV patients with TCP. This desired effect becomes apparent even before the conclusion of therapy. It is thus tempting to correlate the increase in PLT count with LDV/SOF-associated quick eradication of HCV soon after treatment initiation. Whether that is due to elimination of HCV-associated bone marrow suppression and autoimmune TCP or other not yet known mechanisms, these results are tantalizing but would require longer follow-up. Larger prospective studies are needed to ascertain these results and uncover potential mechanisms.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Thyrotoxic Periodic Paralysis

Thyrotoxic periodic paralysis (TPP) is characterized by abrupt onset of hypokalemia and paralysis secondary to thyrotoxicosis (1). The hypokalemia is a result of intracellular shift of potassium due to sensitization of the sodium/potassium (Na⁺-K⁺) ATPase. TPP is most commonly seen in people of asian decent, and over 95 percent of TPP cases occur in men. We present a case of TTP presenting in an african american female.

41-year-old women of African American descent with a past medical history of Grave's disease on methimazole, sickle cell trait, and bilateral kidney stones status post lithotripsy presented with worsening bilateral leg cramping and generalized weakness of 2 days duration. She denies localized weakness, numbness, or change in sensation. Denies fever, chills, rash, nausea, vomiting, abdominal pain, change in bowel habit, or urinary symptoms. Her endocrinologist reduced the dose of methimazole four weeks prior. Patient had two prior episodes of hypokalemia and weakness in the past year. Found to have decreased potassium of 2.7 mmol/L and a decreased thyroid stimulating hormone level of 0.81.

Hypokalemic periodic paralysis is composed of a class of disorders with episodic muscle weakness associated with hypokalemia from acute shift of potassium into cells. Hypokalemic periodic paralysis may be familial caused by a mutation in the Cav1.1 skeletal muscle voltage-gated Ca²⁺ channel or the Nav1.4 Na⁺ channel. Nonfamilial periodic paralysis such as thyrotoxic periodic paralysis (TPP) and sporadic periodic paralysis (SPP), which are caused by sporadic mutations and are more common among Asians and Hispanics. The incidence of TTP is 10-20 times higher in asian populations compared to non-asian populations where the incidence is 0.1%-0.2%.

In TTP, there is an increase in the activity of Na⁺-K⁺ ATPase pumps in skeletal muscle. Both thyroid hormone and b₂-adrenergic agonists can increase Na⁺-K⁺ATPase activity by up-regulating its production and increasing the production of intracellular cAMP, respectively. TPP is also known to occur predominately among males despite a higher incidence of thyrotoxicosis in women, suggesting the potential role of androgen on Na⁺-K⁺ ATPase activity. Episodes are found to be aggravated with exercise and stress possibly due to an increase in beta-adrenergic response. These episodes can be prevented by treating the patient's thyroid disease hence preventing hyperthyroid states and with the use of propranolol to reduce the beta-adrenergic activity. Moreover, potassium supplementation and spironolactone have been shown to decrease these episodes.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Crohn's Disease Patients More Frequently Utilize the Emergency Department and Physician Offices than Ulcerative Colitis Patients

BACKGROUND

Though there are many overlapping features of clinical presentations among Inflammatory Bowel Disease (IBD) patients, there are key differences between Crohn's disease (CD) and Ulcerative Colitis (UC) that make CD more prone to severe symptomatology. CD can affect any part of the gastrointestinal tract, the full thickness of the bowel wall, and have skip lesions, whereas UC is limited to the colon, affects only the mucosa, and manifests as continuous colonic inflammation. CD patients have been observed to have a significantly decreased health-related quality of life compared to UC patients, and their quality of life is directly correlated with disease activity. Our study aim was to evaluate health care utilization between CD and UC patients.

METHODS

Using electronic health records, we performed a retrospective review of IBD patients at an academic medical center over six months to evaluate the health care utilization between CD and UC patients. All IBD patients were under the care of faculty gastroenterologists. Data regarding demographics, IBD subtype, ER visits, physician office visits, phone calls, and email communications were compiled into a database while maintaining subject confidentiality. Statistical analysis was conducted using a two-tailed Fisher's Exact Test with a significance set at $p < 0.05$.

RESULTS

Out of 831 health care utilizations, 452 (54%) were from CD patients. CD patients had 35 (8%) ER visits, while UC patients had 11 (3%) ER visits ($p = 0.0022$). CD patients had 251 (56%) physician office visits, while UC patients had 178 (47%) physician office visits ($p = 0.0148$). UC patients had 134 (35%) email communications, while CD patients had 108 (24%) email communications ($p = 0.0003$). There were no statistically significant differences in phone calls between CD and UC patients.

CONCLUSION

Our data indicate that CD patients utilize significantly more in-person health services (i.e. ER visits and physician office visits) compared to UC patients. This finding supports the severe symptomatology experienced by CD patients as they likely seek more immediate medical attention than other IBD patients. We also observed that UC patients, however, utilize more email communication services. This further supports a less urgent need for medical attention among UC patients as they may experience less severe symptoms. It is also possible that UC patients have earlier recognition of their symptoms or a heightened awareness of their disease process. Our study emphasizes the need for improved anticipation of the health care needs of CD patients to ultimately reduce costs related to IBD treatment.

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Outcome Ketamine Infusions: Is There a Difference Between 1- and 3-Day Infusions?

INTRODUCTION

Chronic pain impacts many aspects of a patient's quality of life (QOL). Ketamine is a NMDA receptor antagonist that has been used for neuropathic pain. This study aims to: (1) evaluate the impact of outpatient ketamine infusions on pain and QOL with a larger sample size than our previous study; (2) determine if there is a difference in results in patients receiving 1 or 3-day infusions; and, (3) examine whether repeated infusions have an influence on outcomes.

METHODS

With IRB approval, 118 patients completed the basic pain inventory (BPI) to rate, on a scale from 0 to 10, their pain and the degree pain interfered with QOL (general activity, walking, work, relationships, mood, sleep, and enjoyment of life). The BPI was completed prior to 1 or 3-day infusions and was repeated 2-4 weeks after infusions. Paired two tailed t-tests and random effect mixed models were used to compare post and pre-infusion scores.

RESULTS

There was statistically significant improvement ($p < 0.05$) in pain, enjoyment of life, general activity, mood, work, relationships, and sleep, but not walking ($p = 0.2419$). There was no significant difference in outcomes between 1 and 3-day infusions. However, this may be overstated, as there was a small sample of 1-day infusions. Repeaters had significant cumulative improvement in enjoyment of life ($p = 0.0132$) and relationships ($p = 0.0092$) with increased number of repeated infusions.

CONCLUSION

1 and 3-day outpatient ketamine infusions improve pain levels and QOL and may provide cumulative benefits with repeated infusions in patients with chronic neuropathic pain.

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Outcomes of Hip Arthroscopy in the Older Adult: A Systematic Review of the Literature

BACKGROUND

The indications for hip preservation surgery have expanded to include treatment of hip pathology in older adults. While several studies have examined the efficacy of hip arthroscopy in the setting of osteoarthritis, there has been no review of outcomes in older adults.

PURPOSE

To review the outcomes of hip arthroscopy in older adults and identify factors associated with treatment failures.

STUDY DESIGN

Systematic review.

METHODS

PubMed, EMBASE, and the Cochrane Library were searched through March 2016 for studies reporting outcomes of primary hip arthroscopy in patients older than 40 years. Inclusion in the review was based on age, patient-reported outcome (PRO) measures, and duration of follow-up. Two authors screened the results and extracted data for use in this review. Standardized mean difference was calculated to estimate effect size for PRO scores within studies.

RESULTS

Eight studies with 401 total patients undergoing hip arthroscopy for femoroacetabular impingement (FAI) or labral tears were included in this review. Seven of the 8 studies reported favorable PRO scores and significant postoperative improvement with moderate to large effect size. The included studies demonstrated a trend toward higher effect sizes with an increasing percentage of labral repair compared to isolated labral debridement. The complication rate was comparable to that of previous reports involving younger patients; however, the overall reoperation rate was 20.8%. Conversion to hip arthroplasty ranged from 0% to 30%, with an overall conversion rate of 18.5% at a mean time of 17.5 months following arthroscopy. The most common risk factors for conversion to arthroplasty were low preoperative PRO scores and advanced arthritis.

CONCLUSION

Hip arthroscopy appears to be a safe and efficacious treatment for labral tears and FAI in older patients who do not have significant underlying degenerative changes. However, in this population, there is a significant proportion of patients who eventually require hip arthroplasty. Outcomes may be affected by type of treatment (ie, labral debridement vs repair). Additional high-quality studies are needed to understand how these factors affect outcomes.

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Prevalence of Prothrombotic Gene Mutations in Hidradenitis Suppurativa

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic, recurrent, inflammatory disease of the apocrine sweat glands, characterized by recurrent abscessing inflammation. The disease affects approximately 1-4% of the population and there is currently no known cure. Many patients with HS undergo extensive reconstructive surgery requiring skin grafts. Since skin grafts are more likely to fail in patients with underlying prothrombotic states, the purpose of this study is to determine the prevalence of MTHFT C677T, Factor V Leiden (FVL), Plasminogen activator inhibitor-1 (PAI-1), and Prothrombin gene-Factor II (Pro2) procoagulant gene mutations in HS and the impact of these mutations on disease activity score.

METHODS

This research was conducted through the Wound Etiology and Healing Study (WE-HEAL Study), an observational bio-specimen and data repository approved by The George Washington University IRB (041408). All subjects gave written informed consent for longitudinal collection of their data while they receive treatment according to standard of care. Laboratory data was collected including procoagulant gene mutation (MTHFT C677T, FVL, PAI-1, and Pro2). Disease activity scores including Hurley stage, HSS and AN count are documented at baseline and every clinic visit.

RESULTS AND DISCUSSION

At the time of data lock there were 64 subjects enrolled in the WE-HEAL study with HS. There was no significant difference in age, sex, race, pain, body mass index or smoking status in patients with MTHFR mutations, PAI-1 mutations, FVL, Pro2 or no mutations. Of the patients who were tested for MTHFR, 73% were negative, 23% were heterozygous, and 4% were homozygous. The reported prevalence is 33% heterozygous and 8% homozygous in the population. FVL was negative in all 46 patients. The FVL allele has been reported to be present in 5% of Caucasians and virtually absent in all other races. In patients tested for the PAI-1, 44% tested negative, 42% heterozygous, 26% homozygous. Similar to reported values of 33%, 40%, and 26% respectively in healthy controls. The Pro2 mutation was 2% heterozygous compared to reported values of 0.4-4%.

There were no significant differences in baseline disease activity scores and ultimate healing outcome when comparing negative, heterozygous, and homozygous MTHFR patients. Similarly, there were no significant differences in disease activity scores when comparing negative, heterozygous, and homozygous PAI-1 patients.

CONCLUSION

In this longitudinal observational cohort of HS patients, genetic prothrombotic states were no more common than expected for prevalence of the mutations in the general population and presence of mutations did not correlate with disease activity scores.

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A Case Study of Rumpel-Leede Phenomenon

Rumpel-Leede phenomenon (RLP), also known as acute capillary rupture syndrome (ACRS), is a rare occurrence where distal dermal capillaries rupture in response to a proximal compressive force, such as a blood pressure cuff or tourniquet. This phenomenon has been reported to occur in states of vascular fragility such as long-term steroid use, hypertension or diabetes mellitus. Here, we provide a report of RLP occurring secondary to tourniquet application in a 26-year-old woman with adult-onset Still's disease (AOSD) and a recent drug rash. In this case, the cause of the phenomenon is most likely multifactorial. Likely contributing factors include long-term steroid use for the treatment of AOSD, and increased vascular permeability secondary to the drug rash. Patients and clinicians should be aware that the treatment of AOSD may induce a state of capillary fragility and they should work together to minimize the risk of complications.

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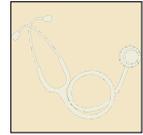
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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Is Prehospital Care Supported by Evidence-Based Guidelines? An Environmental Scan and Quality Appraisal using AGREE II

INTRODUCTION

The Institute of Medicine (IOM) has recommended that high-quality, evidence-based protocols be developed for emergency medical services (EMS). The National Association of EMS Physicians (NAEMSP) has outlined a strategy that will see this task fulfilled, consisting of multiple working groups focused on all aspects of guideline development and implementation. This group has been tasked with creating a needs analysis for evidence based guidelines in prehospital care. A first step, and our current objective is to catalogue and appraise current guidelines targeting EMS providers.

METHODS

A systematic search of the literature was conducted in MEDLINE (1175), EMBASE (519), PubMed (14), Trip (416), and guidelines.gov (64) through May 1, 2016. Two independent reviewers screened titles for relevance to prehospital care, and then abstracts for essential guideline features, including a systematic review, a grading system, and an association between level of evidence and strength of recommendation. All disagreements were moderated by a third party. Citations meeting inclusion criteria were appraised with the AGREE II tool, which looks at six different domains of guideline quality, containing a total of 23 items rated from 1 to 7. Each guideline was appraised by three separate reviewers, and composite scores were calculated by averaging the scaled domain totals.

RESULTS

After primary (kappa 97%) and secondary (kappa 93%) screening, 49 guidelines remained for full review. Three guidelines obtained a composite score of > 90%, the topics of which included aeromedical transport, analgesia in trauma, and resuscitation of avalanche victims. Two guidelines scored between 80% and 90%, the topics of which included stroke and pediatric seizure management. One guideline, splinting in an austere environment, scored between 70% and 80%. Nine guidelines scored between 60% and 70%, the topics of which included ischemic stroke, advanced cardiovascular life support, hemorrhage control, intubation, triage, hypothermia, and fibrinolytic use. Of the remaining guidelines, 14 scored between 50% and 60%, and 20 obtained a composite score of < 50%.

CONCLUSION

There are very few evidence-based guidelines in EMS. Of those that are published, the majority fail to meet established quality measures. The field of prehospital care would benefit from a wider breadth of rigorously developed clinical practice guidelines.

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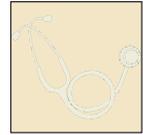
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An Analysis of Fixed Dose IV Recombinant Tissue Plasminogen Activator (rtPA) and Clinical Outcomes in Acute Ischemic Stroke Patients with Body Weight >100 Kilograms: Pooled Data from Three Randomized Clinical Trials

BACKGROUND

The ASA/AHA guidelines recommend a fixed dose of 90 mg of intravenous recombinant tissue plasminogen activator (rt-PA) for acute stroke patients weighing more than 100 kilograms (kg). Previous analyses in small studies have suggested that the magnitude of benefit with IV rt-PA is lower in patients with body weight >100 kg. We determined if body weight >100 kg (and receiving <0.9 mg/kg dose) independently influence patient clinical outcomes following IV rt-PA treatment.

METHODS

We pooled data from IV rt-PA treatment arms from 3 randomized controlled trials; National Institutes of Neurological Disorders and Stroke (NINDS) IV tPA study, Interventional Management of Stroke 3 trial (IMS-III) and Albumin Treatment of Acute Ischemic Stroke (ALIAS part 1 and 2). Patients demographic, stroke severity, comorbidities, hospital outcome and 90-day modified Rankin Scale (mRS) were compared between patients >100 kg and those ≤100 kg body weight (defined by estimated weight). Multivariate logistic regression model was used to identify independent effect of >100 kg body weight on 90-day favorable outcome (defined as mRS 0-2). An ordinal analysis of the mRS was also performed.

RESULTS

Among 977 patients treated with IV rt-PA, total of 111 subjects had body weight >100 kg (11% of all patients). The mean age (±SD) for the patients with weight >100 Kg was significantly lower (60±11 versus 68±13, p<0.001). Patients with weight >100 kg had higher rates of history of hypertension, diabetes mellitus, and hyperlipidemia. Patients with body weight >100 kg had longer period (days±SD) of hospitalization (11±14 versus 8±7, p=0.04). Compared with patients with ≤100 kg body weight, the rate of favorable outcome at 90 days was not significantly different among patients with >100 kg body weight [OR; (95% CI): 0.99 (0.91-1.04) p=0.91, after adjusting for potential confounders. The ordinal analysis did not showed any significant shift in the distribution of scores on the mRS in patients with >100 kg body weight (OR, 0.93; 95% CI, 0.64 to 1.37; P = 0.74).

CONCLUSION

Body weight >100 kg (and receiving <0.9 mg/kg dose) did not reduce the benefit of IV rt-PA treatment in acute ischemic stroke patients. Our results support the current recommendations in the ASA/AHA guidelines.

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Emergency Contraception Candidacy in the Pediatric Emergency Department

PURPOSE

The majority of adolescent pregnancies are unintended. Adolescents who access the emergency department (ED) for care may be at high risk for unplanned pregnancy. The purpose of this study was to identify the proportion of adolescent females presenting to an urban ED who may be candidates for emergency contraception (EC).

METHODS

This was a secondary analysis of a randomized control trial conducted in an urban pediatric ED designed to determine whether provision of clinical decision support derived from a computerized sexual health screening tool resulted in increased testing for sexually transmitted infections among adolescents (ages 14-19 years) at high risk for infection. We calculated the prevalence of adolescent females who met candidacy for emergency contraception and the proportion of EC qualifying females who were interested in speaking to a clinician about EC.

RESULTS

444 adolescent females were enrolled in this trial. The study population had a mean age of 16.25 years (SD +/- 1.65); 75.3% were non-Hispanic Black; and 25.5% were covered by private insurance. Overall, 210 (47.3%) of females were sexually active. 70 (33.3%) of those females reported vaginal intercourse within the last five days and were eligible for EC. Only 11 (15.7%) of eligible females, expressed interest in speaking with a clinician about EC (7 in intervention arm and 4 in usual care arm). Clinicians prescribed EC to 2 of 11 (18.2%) patients who expressed interest in EC receipt.

CONCLUSIONS

Although a large proportion of adolescents were eligible for EC, few expressed interest in speaking with a clinician about EC. However, a large proportion of adolescents who were interested in EC receipt did not receive EC. Further studies should investigate adolescent attitudes towards ED-prescribed EC and barriers to EC provision by clinical staff.

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Cranial bone grafting in the setting of infection: is it an absolute contraindication?

BACKGROUND

Surgical treatment of intracranial empyema often necessitates craniotomy with removal of a bone “flap” in order to allow exposure to the affected site, debride necrotic tissue, and drain loculated pockets of purulent fluid. After removal, the bone is avascular, rendering it more susceptible to bacterial infection and subsequent necrosis. Consequently, standard practices are to bank the bone flap in an ectopic subcutaneous site (e.g., abdominal wall) or cryopreservation for future re-implantation. Disadvantages to this include an obligatory secondary operation, as well as relegating the patient to a protective helmet. Here we report on a unique approach, with primary re-implantation of the bone flap at the time of initial craniotomy, with the hypothesis that a substantial proportion may have successful bony reconstruction without infection or loss of the bone flap.

METHODS

An institutional-review board approved retrospective review was performed of patients undergoing craniotomy for intracranial empyema at Children’s National Medical Center between 1997-2014. Those who had immediate bone flap re-implantation were included for study. Outcomes were determined by 1) persistent or recurrent infection/osteomyelitis, 2) long term bone healing versus resorption, and 3) requirement for future cranioplasty.

RESULTS

23 bone flaps in 21 patients were included for study. Average age was 10.7 years at craniotomy. Average follow up was 22.2 months. Average bone flap surface area was 36.1 ± 34.3 cm². The majority of the empyemas were secondary to sinusitis (82.6%). Patients were treated with an average of 5.4 weeks of susceptibility-targeted antibiotic therapy after drainage.

Of the 23 replaced bone flaps, 21 (91.3%) were successfully replaced. 15 (65.2%) required a single craniotomy in conjunction with antibiotic therapy to treat the empyema. An additional 6 (26.1%) required an average of 1.4 ± 0.7 (range: 1-3) intraoperative washouts with eventual clearance of infection. No patients developed clinical evidence of osteomyelitis. In the long-term, 2 patients (9.5%) developed partial bony resorption necessitating further reconstruction with autogenous split calvarium bone graft to restore continuity of the calvarium.

CONCLUSION

Immediate rigid replacement of the bone flap after craniectomy for drainage of intracranial empyemas is a reliable technique to provide autogenous reconstruction while minimizing bony resorption and the requirement for secondary cranioplasties, and carries a low complication profile.

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Patients with Scleroderma Sine Scleroderma Exhibit Lower Disease Activity Scores than Limited and Diffuse Scleroderma Patients

INTRODUCTION

Scleroderma is an autoimmune disease characterized by inflammation, vasculopathy, and fibrosis of skin, vasculature and internal organs. Scleroderma without extensive skin involvement is referred to as Scleroderma Sine Scleroderma; these patients have positive scleroderma autoantibodies and can develop internal organ involvement but usually have minimal or no skin involvement. The purpose of this study was to investigate differences demographics and disease progression between limited, diffuse and sine scleroderma patients.

METHODS

This research was conducted through the STOP Scleroderma Study. The STOP Scleroderma Study is a longitudinal biospecimen and data repository approved by the George Washington University IRB (051427). Subjects gave written informed consent for collection of their data. Demographics including, age, sex, and race were compared between the groups. Disease activity scores were also analyzed including modified Rodnan skin score (mRSS) and Medsger's severity score. Statistical tests including T-test, Fisher's Exact and Chi Square were performed using GraphPad Prism 5.0.

RESULTS

The analysis included 8 patients with scleroderma sine scleroderma, 26 patients with limited scleroderma and 15 diffuse scleroderma patients. Patients with scleroderma sine scleroderma were younger (mean age 44.66 ± 13.91), than diffuse (52.09 ± 13.90), and limited (60.58 ± 12.60) patients ($p=0.01$). However, there were no significant differences in race or sex. As expected sine patients had significantly lower mRSS (0 ± 0 in sine, compared to 12.43 ± 9.24 in diffuse, and 5.28 ± 4.29 in limited, $p<0.0001$). Medsger severity scores were also lower in patients with sine (0.143 ± 0.378) compared to diffuse (5.71 ± 3.85) and limited (3.125 ± 1.60 , $p<0.0001$). When examining the antibody profiles of sine patients, 87.5% had positive ANA, 37.5% had a positive Scl-70, 25% had a positive Centromere, and 12.5% had a positive RNP. Over longitudinal follow up, the mRSS did not change from baseline; however, Medsger severity score increased over follow up by 0.357 ± 0.67 . Peripheral vascular complications developed in 25% of patients and lung complications in 12.5% of patients.

CONCLUSION

Sine scleroderma patients are significantly younger than limited and diffuse scleroderma patients. Further, sine scleroderma patients present with a significantly lower baseline mRSS and Medsger score. Patients with positive scleroderma antibodies but minimal skin involvement should be followed long term in order to monitor for internal organ complications of scleroderma.

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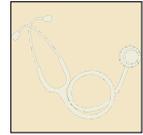
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Association of Hyponatremia and Fluid Status with Brain Injury in Newborns with Hypoxic-Ischemic Encephalopathy (HIE)

BACKGROUND

Cerebral edema plays an essential role in the pathogenesis of brain injury in HIE. While the role of hyponatremia and positive fluid balance in potentiating evolving cerebral edema has been described in pediatric and adult patients with brain injury, these factors have not been investigated in newborns with HIE undergoing therapeutic hypothermia.

OBJECTIVE

To evaluate the relationship between hyponatremia, fluid status and brain injury assessed by MRI in newborns with HIE.

DESIGN/METHODS

Data were collected as a part of an observational study evaluating biomarkers of brain injury in newborns with HIE. Plasma sodium (Na), Blood Urine Nitrogen (BUN), and creatinine levels were collected at 24 and 72 hours of life (HOL). Osmolarity (Osm), urine output (UOP), and fluid balance were calculated at corresponding timepoints. Severity of brain injury by MRI was assessed according to Barkovich (AJNR 1998) basal ganglia (BG) and watershed (WS) scores. Outcome was classified as normal (BG and WS=0), mild (BG<3, WS<4), moderate/severe (BG≥3, WS≥4), or died. Differences in Na and measures of fluid status were assessed by Kruskal-Wallis Tests. Receiver operating curves (ROC) were performed to identify cutpoints for each measure. Sensitivity and specificity of individual and combined fluid balance measures to predict death or moderate/severe brain injury were calculated.

RESULTS

Data were analyzed from 151 infants with HIE (mean BW 3.3±0.7 kg, GA 38.7±1.7 wks, median pH 6.95 (IQR 0.3), 56% male, 21% severe encephalopathy). Increasing severity of brain injury was associated with lower Na, UOP, and Osm, and higher BUN and positive fluid balance, particularly at 72 hours of cooling. Cutpoints with optimal sensitivity and specificity at 72 HOL were Na53.5ml, UOP 11.5 mg/dL, and Osm <279.5 and combining these factors resulted in the highest area under the ROC curve. Newborns exceeding all 5 factors had the lowest frequency (11%) of normal MRI, whereas newborns with no risk factors had the highest frequency (64%) of normal MRI. Conversely, the highest frequency of death was found among newborns with five risk factors (44%) while only 5% of infants with no risk factors died.

CONCLUSION

Lower Na, UOP, and Osm in conjunction with higher BUN and fluid balance are associated with brain injury in newborns with HIE. These readily accessible measures of fluid status can help identify infants in need of additional neuroprotective treatments after TH.

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Beneficial Effects of Oxytocin in Sleep Apnea

INTRODUCTION

Approximately 24% of males and 9% of females in the United States suffer from obstructive sleep apnea (OSA). OSA increases cardiovascular mortality fourfold yet current treatment with continuous positive airway pressure (CPAP) only lowers arterial pressure by 2mmHg. In addition CPAP therapy is not well tolerated and as such many patients are non-adherent. This prompted further investigation into developing novel a OSA treatment. Previous research has shown oxytocin is cardioprotective, preventing the hypertension that occurs in an animal model of OSA. This study aims to test the efficacy of intranasal oxytocin administration in humans with OSA.

METHODS

Eight patients diagnosed with moderate to severe OSA by a standard polysomnogram, were enrolled. These patients underwent a second polysomnogram preceded by the intranasal administration of 40 i.u. of OXT. Multiple physiological signals, including the EKG, EEG, oxyhemoglobin saturation, and respiratory airflow, were acquired by the Philips Respironics Alice 6 LDXN Sleep Diagnostic System. A registered polysomnographic technologists (RPSGT) manually scored the sleep study, identifying sleep stages, arousals, and marking the beginning and end of each apnea and hypopnea. Hypopnea is defined as reduction in ventilation of greater than 30% that results in arterial desaturation of 4% or more and lasting at least 10 seconds. Apnea is defined as a reduction in the peak signal excursion of greater than 90% and lasting at least 10 seconds.

RESULTS

Oxytocin increased the total sleep time from 414 minutes to 459 minutes ($p < 0.05$). The total sleep time (TST) is the total sleep interval excluding the wake sleep stages.

Oxytocin treatment decreased the respiratory event durations from 31.7 ± 2.4 seconds to 25.8 seconds ± 1.7 seconds (mean \pm S.E., $p < 0.05$). Further stratification revealed a decrease in the hypopnea duration from 33.5 ± 2 seconds to 27.3 ± 1.6 seconds (mean \pm S.E., $p < 0.01$).

The ratio of hypopnea events that were accompanied with arousals / all hypopnea events significantly ($p < 0.01$) decreased from 74.1 ± 3.7 % to 55.6 ± 5.3 % (mean \pm S.E.). Hypopnea events that were accompanied with arousals were defined as an arousal that occurs between the start of the event and up to 5s afterwards.

CONCLUSION

The administration of 40 i.u. of OXT has led to clinically significant changes in patients' sleep physiology by increasing total sleep while decreasing both respiratory events and accompanying arousals. These changes decrease severity of OSA and it is postulated that this will precipitate a decrease in cardiovascular mortality.

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A Case for Prophylaxis in Autoimmune-Related Interstitial Lung Disease

CASE

A 62-year-old man with a history of interstitial lung disease, hypertension, hyperlipidemia, and depression presented with shortness of breath. CT scan a year prior had first showed groundglass opacities in the periphery of bilateral lung zones suggestive of interstitial lung disease. Open lung biopsy 8 months prior had found small airway injury with OP and fibrotic NSIP. He was on high-dose steroids that were tapered then abruptly discontinued 2 months prior. Family history was significant for a sister with NSIP as well as mixed connective tissue disorder. Other medications included: Albuterol, fluticasone, tiotropium, lisinopril, metoprolol, furosemide, pravastatin, and duloxetine.

Vitals on admission were notable for T 99.1, BP 104/63, RR 18, HR 94, spO2 85% on oxygen. Physical exam revealed diffuse bilateral inspiratory crackles as well as 3+ bilateral edema. Labs included: WBC 9.75 K/uL, 14.8 hemoglobin g/dL, 140 platelets, creatinine of 1.4, and lactate 1.4 mEq/L. Further studies revealed a procalcitonin 2.23 ng/ml, LDH 1078 U/L, ANA 1:40 speckled pattern, and alpha-1-antitrypsin 229 mg/dl. Extensive rheumatological serology was otherwise unremarkable.

CT thorax revealed bilateral ground glass opacities. He was empirically covered with vancomycin, zosyn, azithromycin, valganciclovir, trimethoprim-sulfamethoxazole and then atovaquone due to worsening renal failure. Due to worsening respiratory failure, he was acutely intubated. Silver gram stain was positive for PJP and all medications were stopped except for atovaquone. Due to disease severity, he was switched to clindamycin and primaquine to complete course of treatment but ultimately the disease course of respiratory and renal failure proved fatal.

DISCUSSION

OP/NSIP overlap including autoimmune-related cases predisposes patients to unfavorable disease progression. This patient likely had an UCTD, which NSIP may be more commonly associated with. Evidence is controversial as to whether patients with autoimmune diseases on immunosuppression should be given PJP prophylaxis. This patient had multiple risk factors for presentation in acute respiratory failure including OP/NSIP as well as medication-related immunosuppression predisposing to PJP that often has delayed diagnosis in non-HIV patients. Evidence is mixed as to PJP colonization in interstitial lung disease. This patient, however, was likely colonized and had an immune reconstitution reaction to the PJP given the abrupt withdrawal of steroids. Given the variability of risk for PJP, strategies such as monitoring CD4 count or using PCP PCR may be helpful in risk-stratifying patients and risk and determining initiation or withdrawal of prophylaxis. Immunosuppressants should also be tapered slowly given the risks of immunoreconstitution disease.

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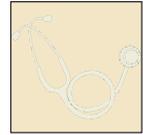
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Tamsulosin for Urolithiasis: A Review of the Recent Literature and Current Controversies

In the United States, urolithiasis affects approximately 1 in 11 people, and there is evidence that the prevalence is increasing. A relatively recent treatment strategy for urolithiasis involves using medical expulsive therapy (MET) to increase the likelihood of spontaneous passage of ureteral stones. The 2 leading drug classes for MET are alpha-1-adrenergic receptor blockers and calcium channel blockers. Tamsulosin, an alpha-1-adrenoceptor blocking agent, is thought to induce spontaneous stone passage by relaxing ureteral smooth muscle tone. However, tamsulosin has not been proven effective for increasing ureteral stone passage and is not approved by the Food and Drug Administration for this indication. There is a relative paucity of data on the efficacy of tamsulosin for urolithiasis, and of the published results, there are conflicting conclusions from the data. Because of the acute and often severe nature of symptoms from urolithiasis, emergency medicine physicians are frequently the first to diagnose and treat this condition. This has led to tamsulosin being frequently prescribed from the emergency department (ED) for off-label use without the support of high-quality evidence. If tamsulosin is proven effective, its use in the treatment of urolithiasis could offer several important advantages. The number of procedures, length of hospital stay, and health care costs after the initial ED visit could potentially be reduced. Tamsulosin may also increase patient satisfaction by reducing the invasive treatment and decreasing the time to stone passage. This review focuses on the efficacy of tamsulosin based on stone location, after shock wave lithotripsy, compared with other MET drugs and in the acute setting of the ED.

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Point-of-Care Ultrasound Utilizations in the Emergency Airway Management: An Evidence-Based Review

Point-of-Care Ultrasound (POCUS) is an increasingly sought-after and versatile tool for advanced airway management in emergency medicine. Recent publications evaluating POCUS in airway assessment, confirmation of tube placement, and readiness for extubation suggest POCUS offers superior diagnostic accuracy over traditional decision rules and direct visual assessment in the emergency department setting. Already a diagnostic workhorse in emergency care, POCUS offers the benefits of speed, ease and availability to airway management, and stands positioned to become the standard of care in emergency medicine. As a portable and cost-effective diagnostic adjunct, POCUS has similar potential utility for airway management in out-of-hospital and resource-poor clinical environments. In this article, we review the evidence-based recommendations on the use of ultrasound in pre-intubation assessment, intubation confirmation and the use of ultrasound in cases with potential surgical airway intervention.

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Videogame-Related Illness and Injury: A Review of the Literature and Predictions for Pokémon GO!

OBJECTIVE

Reports of videogame-related illness and injury soon emerged in the literature with the inception of videogame systems and subsequent development of novel gaming platforms and technologies. In an effort to better detail the impacts of these phenomena and provide recommendations for injury prevention as it relates to Pokémon Go and the larger world of augmented reality games, we conducted an extensive systems-based review of past trends in videogame-related illness and injury from the literature.

MATERIALS AND METHODS

A literature review using PubMed, Medline, and PsycInfo databases with search terms "Pokémon GO," "videogame injuries," "augmented reality injuries," and "Nintendo Injury" was performed. The search was limited to the English language, and the Boolean were used to combine the search terms.

RESULTS

The literature search yielded 359 peer-reviewed articles, 44 of which met the study criteria and included in the review. Seventeen additional popular press reports detailing injuries related to Pokémon Go were also incorporated. Videogame-related injuries and illness include both physical trauma as well as psychological and behavioral disorder with unique patterns of injury and illness linked to specific gaming platforms.

CONCLUSIONS

As videogames become increasingly advanced and immersive, they expose players to unique and often more serious injury and illness. Augmented reality games, such as Pokémon GO, are the next step in the evolution of this trend and likely portend a future in which many pathologic processes may become increasingly common.

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Survival After Profound Acidosis and Rhabdomyolysis Due to Dietary Supplement Use

Severe acidosis below a pH of 6.7 is rarely compatible with life. We describe a case of a 40-year-old man who presented to the emergency department with altered mental status and syncope. His initial arterial blood gas demonstrated a pH of 6.6 and a lactate of more than 20 mmol/L. The patient was intubated, started on sodium bicarbonate, and admitted to the critical care unit. During his hospitalization, he developed rhabdomyolysis with creatinine kinase reaching more than 158 000 IU/L and subsequent renal failure requiring hemodialysis. After an extensive evaluation, his presentation was attributed to dietary supplement use and exercise. With the widespread popularity of supplements and the limited regulation of the industry by the Food and Drug Administration, it is essential that emergency providers be aware of the potential for supplements to have adverse effects and appropriately counsel patients on the risks involved with dietary supplementation.

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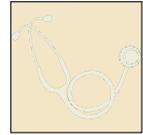
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Fluctuating Monoclonal Gammopathy Protein levels in Idiopathic Systemic Capillary Leak Syndrome

BACKGROUND

Idiopathic Systemic Capillary Leak Syndrome (ISCLS) is a rare condition characterized by hypotension, edema, and fluid extravasation with potentially life threatening complications including multi-organ failure. It can be difficult to diagnose and differentiate from other causes of hypotension in severely ill patients. There is no well-defined treatment guidelines for ISCLS, but there is evidence that high dose monthly intravenous immunoglobulin (IVIg) can successfully be used to prevent recurrences. Additionally, there are significant data suggesting an association between ISCLS and Monoclonal Gammopathy of Undetermined Significance (MGUS).

CASE PRESENTATION

We present a case of a 39-year-old male with a history of several hospitalizations due to acute cardiogenic shock, with intermittent periods of complete recovery, eventually diagnosed with ISCLS after four years. After diagnosing ISCLS, further work up revealed IgG lambda free light chain elevation on serum electrophoresis (SPEP) consistent with MGUS. His first SPEP result showed 1 g/dl of protein, followed by 0.4 g/dl several months later, and then 1.91 g/dl several months after that. The most recent measurement was made 6 days after the patient received his monthly IVIg dose. Typically, a monoclonal protein level fluctuation to a higher value would signal MGUS progression, but in a patient with ISCLS who has received recent IVIg infusion, other differential diagnosis was sought.

The differential diagnosis at this time included false positive SPEP given recent IVIg treatment. The half-life of IVIg is 20-30 days, so in theory this might be possible, but, given that IVIg is polyclonal IgG obtained from a large group of donors, we concluded it is unlikely to cause monoclonal M spike on SPEP. Other possibilities included protein extravasation into interstitial tissues secondary to the ISCLS. And finally, the fluctuating SPEP reflected a true change in monoclonal IgG for which additional work up might be necessary.

DISCUSSION

Data suggests that these patients progress to Multiple Myeloma at the same rates as non-ISCLS patients. Therefore, hematologists must follow these patients' SPEP values to monitor for progressive disease. Given the main stay of treatment for patients with ISCLS is monthly intravenous IVIg, this presents a challenge when interpreting the SPEP abnormal protein values. We would like to convey caution when interpreting the M protein and recommend conducting the SPEP testing prior to the monthly IVIg administration as this could possibly avoid unnecessary interventions in this population.

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The Latarjet Procedure for Anterior Glenohumeral Instability Recurrence in the Setting of the US Military; A Retrospective Case Series

INTRODUCTION

Glenohumeral (shoulder) instability is one of the most common pathologies seen by orthopedic sports medicine surgeons. The US Military is a unique, high-demand, physically active population with high rates of glenohumeral instability. Glenoid bone augmentation procedures are the gold standard treatment for recurrent anterior shoulder instability in the setting of glenoid bone loss greater than 15-20%. The Latarjet procedure, along with various modifications, is one possible stabilization procedure available to surgeons. However, complications and outcomes related to this procedure are not well understood in the military population. Therefore, the purpose of this study was to report complication rates, recurrent instability, and revision surgery following a Latarjet in the military population.

METHODS

The Military Health System Data Repository (MDR) was queried to identify all active duty military personnel who underwent a Latarjet procedure for recurrent anterior shoulder instability between January 1, 2004 and December 31, 2015. Following identification of these individuals, we collected demographic information, nature of the initial injury, prior history of surgeries on the affected shoulder, and outcomes, including complications, recurrent instability events, and revision surgery.

RESULTS

A total of 217 (212 male, 5 female; mean age = 26.2 years) patients were identified. The majority of procedures (52.3%) were performed on the dominant shoulder. Most patients (55.8%) experienced both subluxations and dislocations, while 27.2% and 14.8% reported only subluxations or dislocations, respectively. In 2.3% of patients, there was not clear documentation of a previous instability event. 59.0% of patients had a previous stabilization surgery and required revision to Latarjet, and 28.1% of patients had more than 1 previous stabilization procedure. Following the Latarjet, 8.8% reported a recurrent instability episode; the majority of these instability episodes were subjective subluxation events as opposed to frank dislocations. 11.1% of patients required an additional procedure after the Latarjet, most commonly a revision to the original procedure, as some did not report an actual instability event.

CONCLUSIONS

Indications for certain surgical procedures among military service requires high-impact physical activity that expose service-members to a higher risk of shoulder instability. In the presence of glenoid bone loss, the Latarjet is the most commonly used surgical procedure for glenoid augmentation. This study has demonstrated that despite an overall high demand occupation, recurrent shoulder dislocation rates are low and reliably restore shoulder stability. We recommend continued investigation of patient outcomes through a patient reported outcomes database and further clinical investigations.

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Extruded MIS Lateral Interbody Fusion Cage and Revision: A Case Report

Our findings suggest that revision with an ALIF procedure after failed MIS lateral interbody fusion (LLIF) provides the proper exposure and stability to avoid recurrent cage migration. With few exceptions, the LLIF procedure is a safe and effective method of reduction for spondylolisthesis and symptoms of stenosis. Complications are rare, but include lumbar plexus injuries, anterior thigh pain, psoas weakness, retroperitoneal hernias and hematomas. There have been few reported cases of failed / extruded hardware. We report one case of an extruded LLIF cage and the subsequent treatment and revision procedures. In this case, a 70-year-old female underwent an L4-5 lateral interbody fusion for stenosis and acquired spondylolisthesis. Postoperative X-rays showed excellent placement and alignment of the cage. Three weeks after her index procedure, she complained of persistent pain and right lower extremity radicular symptoms that had consistently worsened. Repeat X-rays showed complete lateral extrusion of the cage. She returned to the operating room where she had her hardware removed anteriorly and was revised to an L4-5 anterior lumbar interbody fusion without complication, and at most recent follow up, she is asymptomatic with proper hardware positioning.

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Incidental Hydrocele Rupture During Vasectomy: A Case Report

INTRODUCTION

Physicians perform vasectomies routinely for male sterilization and birth control. Vasectomy protocol is well established involving isolation and ligation of the vas deferens. The number of vasectomies are estimated in the hundreds of thousands yearly. A hydrocele is a fluid collection around a testicle. Hydrocele rupture during vasectomy is a relatively uncommon occurrence.

CASE

34 yo M with no significant PMH presents for elective vasectomy. No previous urologic issues in the past. Patient consented to procedure and all questions answered.

Patient underwent vasectomy. The vas on the left was successfully ligated and cauterized. Immediately upon reduction of the left sided vas, approximately 50cc of clear/yellow fluid rushed out of the scrotum, and then quickly ceased. No further leakage afterwards. No incisions were made in the proximity of the urethra. This was verified by the providers. After observation for several minutes, it was deemed that this fluid was likely secondary to a hydrocele. Vas ligation and cautery on the right side proceeded without any difficulty or complication.

Patient vas samples were obtained and sent to pathology. The samples showed right and left vas deferens with complete cross section of lumens identified. UA obtained post vasectomy was negative (color yellow, clear, negative for glucose, protein, bili, urobili, pH 7, blood, ketones, nitrite, leukocyte esterase, specific gravity 1.012). This was done to ensure integrity of urinary tract. Patient seen for f/u 3 days after procedure with no complications (no fevers, chills, scrotal pain, scrotal swelling, or ecchymosis). Patient did not obtain 6 week semen analysis post op.

DISCUSSION

This case demonstrates the importance of understanding hydrocele as a potential rare complication during vasectomy. If a practitioner suspects hydrocele rupture, he or she should note the quality and amount of fluid as well as rule out other potential causes of fluid leak including the urinary tract or vasculature. Hydrocele rupture is typically a benign intraoperative complication with no major post op complications. Understanding hydrocele rupture during vasectomy will help practitioners react to hydrocele rupture during vasectomy in a efficient and professional manner, with proper work up and follow up.

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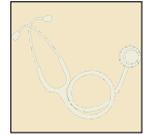
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Validation of a Genetic Risk Score Based on Single Nucleotide Polymorphisms Implicated in Adult Bone Fragility and Associated with Pediatric Bone Density

BACKGROUND

Osteoporosis and associated fragility fractures are a major health concern in the United States. 1 in 2 women and 1 in 4 men will suffer a fragility fracture in their lifetime. Depending on the skeletal site, peak bone mineral density (BMD) is not attained until at least early adulthood, thus it is possible that with early identification and optimization of modifiable factors, the incidence of osteoporosis and its damaging effects can be mitigated.

OBJECTIVE

We set out to validate a genetic risk score (GRS) comprised of 63 SNPs associated with adult bone fragility and/or low BMD, previously shown to be significantly associated with BMD z-score in children in two previous studies. Our goal was to assess whether application of the GRS could be extended to include a wider range of age and bone phenotypes.

METHODS

Data from three cohorts were included in our analysis. Two cohorts were comprised of healthy Caucasian young adults, and one of African American children. SNPs were genotyped using Illumina Multi-Ethnic Genotyping Arrays (MEGA), with data quality checks performed in Genome Studio and Plink. Phenotypes analyzed vary by cohort, and include BMD measures from DXA, as well as relatively novel measures such as robustness. The GRS was calculated for each subject as a percentage of risk alleles. To assess any relationship to bone phenotypes, linear regression models were performed in gender specific cohort and with age added as a covariate.

RESULTS

None of the phenotypes evaluated showed a significant linear relationship with the GRS at the 0.05 significance level, but the relationship between GRS and BMD appeared to trend toward significance in the cohort whose subjects were most like those analyzed in previous studies. Our other cohorts offered an opportunity to discover novel GRS-bone relationships such as robustness, and to test the GRS for the first time in an African American cohort, so it was not surprising to us that no relationships were found. Further investigation will focus on why the GRS was unable to predict BMD in our cohorts.

DISCUSSION

While our study was not able to validate the use of the GRS as a tool to predict measures of bone quality, we did find some interesting patterns showing differences between genders and between those of differing ethnic backgrounds. These factors will be important to consider as the GRS strives to become a clinically useful tool.

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Correlation of fetal MRI findings and need for postnatal VP shunt in children born with Myelomeningocele

INTRODUCTION

Myelomeningocele occur in about 3.4 per 10,000 births in the United States. Fetal MRI is being increasingly used after diagnosis to give detailed pictures of the anatomy. However, the long term prognostic value of fetal MRI is not well understood. In this study, we examined the degree of prenatal ventricular dilatation measured by MRI in fetuses with MMC and correlate to the need for postnatal ventriculoperitoneal (VP) shunt by 12 months of age.

METHODS

This was an IRB approved, retrospective study. We examined MRI imaging (n=24) of fetuses (mean 24 weeks gestation) diagnosed with myelomeningocele. Only fetuses that were carried to term were included in the study. Ventriculomegaly was evaluated on images by measuring lateral ventricle size at the frontal horns. Additional measurements and features included evaluation of 3rd and 4th ventricular dilatation, hindbrain herniation, and cisterna magna. Patients were evaluated for whether they had a VP shunt placed by one year of age.

RESULTS

Mean prenatal ventricle size was greater for patients who received a VP shunt postnatally compared to those who did not receive a VP shunt (p15mm, 100% (n=4) went on to receive a VP shunt postnatally. For fetuses with ventricle sizes 5-10 mm, 50% (n=12) went on to receive a VP shunt, and for fetuses with ventricle sizes 10-15mm, 37.5% (n=8) received a VP shunt postnatally. No significant correlation was found between 3rd and 4th ventricular dilatation and postnatal VP shunt placement. Absence of cisterna magna on fetal MRI was found to be a statistically significant predictor (p<0.05) of postnatal VP shunt placement.

CONCLUSIONS

This study correlated prenatal ventricular size on fetal MRI with potential need for a VP shunt by one year of age. All fetuses with prenatal ventricle size greater than 15 mm required a VP shunt by 1 year of age. The results of this study could be used to help guide the clinician in evaluating prenatal MRIs and in counseling parents.

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Secondary Myelofibrosis with Pericardial Extramedullary Hematopoiesis: A Unique Case of Polycythemia Vera Progression

PURPOSE

The purpose of this case study is to illustrate the unique occurrence of progression of polycythemia vera into secondary myelofibrosis with resultant pericardial EMH, while making a theoretical connection to JAK 2 mutation.

CASE REPORT

A 71-year-old Ethiopian man with a history of polycythemia vera diagnosed 4 years previously, maintained on hydroxyurea, presented to the emergency room with worsening shortness of breath with associated dry cough, anorexia, and night sweats of 3 weeks duration. A complete blood count showed a modestly elevated leukocyte count of 15×10^9 cells/L, hemoglobin of 9 g/dl, and platelet count of 654,000/L. The peripheral blood smear showed marked neutrophilia with mild bandemia, the erythroid lineage was notable for rare nucleated red blood cells and occasional teardrop cells. A bedside echocardiogram in the emergency room revealed a large pericardial effusion with features concerning for pericardial tamponade. After a formal follow-up echocardiogram confirmed hyperdynamic systolic function with an ejection fraction of 70%, patient was emergently taken to the operating room for a left anterior thoracotomy and a pericardial window. He was found to have dense pleural adhesions, with 700ml of sanguinous fluid drained from the pericardial space. Evaluation of the pericardial fragments and pericardial fluid revealed presence of hematopoietic elements (both myeloid and erythroid precursors) suggestive of clonally proliferative hematopoietic cells. Extramedullary hematopoiesis (EMH) with concomitant anemia was suspicious for evolution of his polycythemia vera to myelofibrosis and possibly leukemic transformation. The patient subsequently underwent a bone marrow biopsy with pathology consistent with post polycythemia vera myelofibrosis. JAK2 V617F mutation was detected while BCR-ABL gene was negative on the peripheral blood.

CONCLUSION

This interesting case report illustrates an important, mysterious connection between post-polycythemic myelofibrosis, EMH involving the pericardium with resultant tamponade or pericardial effusion, and JAK2 mutations. As only 8 cases of pericardial EMH have been reported, with less than half of these evaluated for JAK2 mutations, it is still unknown whether this case could be generalized. This case highlights an unusual etiology for pericardial effusion and tamponade, and further research should be considered with regards to JAK2 mutations in cases of myelofibrosis.

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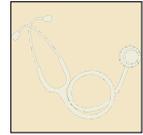
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Impact of Clavicle Fractures on NFL Athletes Return and Performance

BACKGROUND

Clavicle fractures in the National Football League (NFL) have gained significant attention in recent years due to their impact on high profile athletes; however, little data has been published on long-term player performance data.

PURPOSE

To define the time to return to play following clavicle injuries in the NFL and to evaluate the quantitative effect on athletic performance.

STUDY DESIGN

Retrospective Cohort Study; Level of evidence, 3.

METHODS

Data on NFL players who sustained a clavicle fracture were collected from 1998 through 2015. Outcomes data included time to return to play, yearly total yards, and touchdowns for offensive players, and yearly total tackles, sacks, and interceptions for defensive players. Number of games missed and time to return to play after injury were collected for all players. Using previously accepted methodology with a modification to account for number of games played, offensive power rating ($OPR = ([total\ yards/10] + [total\ touchdowns \times 6])/\# \text{ games played}$) and defensive power rating ($DPR = (total\ tackles + [totals\ sacks \times 2] + [total\ interceptions \times 2])/\# \text{ games played}$) were calculated for pre-injury and post-injury seasons. Offensive and defensive control groups consisted of position-matched NFL athletes who competed in the 2013 NFL season without an identified clavicle injury.

RESULTS

The study group was composed of 20 players who sustained a clavicle injury. 17 (85%) returned to season competition during the study period; however, 3 players did not play for an entire season after injury and were thus excluded. The remaining 14 players included 12 offensive and 2 defensive players. Athletes returned to competition after a median of 3.47 months following injury and missed a median of 8 games. Analysis of pre- and post-injury athletic performance revealed no statistically significant change after return to sport. There was a downward trend in post-injury ratings for quarterbacks, running backs and offensive players as a whole. Wide receivers had increased ratings post-injury. Defensive players had higher post-injury ratings. In the control groups, all offensive and defensive positions, except for quarterbacks, showed a downward trend before and after the index season; however, none of the differences in power rating trends were statistically significant.

CONCLUSION

While there were some changes in trends in both the offensive and defensive power ratings post-injury, there was no statistically significant difference in power ratings before and after injury as compared to the controls. In conclusion, other than the impact of missing a median of 8 games, clavicle fractures appear to have no impact on NFL player performance.

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Validation of a Risk Score Calculator for Patient Discharge

Despite public awareness of the increased number of opioid related deaths, opioid use has remained constant over the last decade. Established demographics of populations predisposed to abuse are clear, however, presently there are no well-defined screening methods. A model predicting risk of discharge from the pain clinic had previously been calculated using data from the GW pain center. Variables examined included smoking, back pain, employment status, type of insurance, drug abuse and referral source. The purpose of our study was to see if this equation did indeed predict risk of discharge in a separate group of patients. With IRB approval, 26 subjects dismissed from clinic over a 13-month period were identified and 25 patients seen during the same time period were randomly selected as control. Subject risk factors were identified based on chart review of risk model characteristics. The risk of involuntary discharge was calculated using the previously developed risk stratification model. Data were divided into ordinal risk quartiles and analyzed using chi-square analysis. Among the 51 patients in the validation sample who had non-missing data for all components of the risk model, 26 (51%) were discharged involuntarily. The rate of involuntary discharge by quartiles of risk score were 8%, 54%, 56%, and 76%, for quartiles 1 to 4, respectively. The association between risk score quartile and being involuntarily discharged was strong ($\phi=.51$) and significant ($p=.004$). The odds of being involuntarily discharged for those in the highest versus lowest risk quartile were 35.75 (95% confidence interval 3.47-368.83). Risk scores may be helpful in identifying patients at risk for opioid abuse and discharge from a pain clinic. In a previous study based on our patient population, we calculated a risk score based on patient characteristics significantly associated with discharge. These were illicit drug use, unemployment, disability, smoking and low back pain. In this study, we found a significant association between the risk score calculated in subsequent patients discharged and therefore validated the risk score calculation for our patient population.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

No Pain, No Gain: Renal Infarction Following Anabolic Steroid Use

INTRODUCTION

Anabolic-androgenic steroids (AAS) are used for performance and physical enhancement. While potential cardiotoxicity and hepatotoxicity of AAS have been described, there are fewer reports of vascular events.

CASE PRESENTATION

A healthy 41-year-old man presented with acute left flank pain. He reported using dimethazine (DMZ), an AAS available in commercial supplements, for one week prior to presentation. He denied using other supplements or recreational drugs. Exam was notable for above average muscle bulk and left flank tenderness. Labs were grossly within normal limits. Computed tomography angiography of the abdomen showed multifocal left kidney infarcts.

Extensive workup was obtained to determine the etiology of the infarct. Magnetic resonance angiogram (MRA) of the renal vasculature showed no anatomic abnormalities and a computed tomography angiogram of the aorta showed no thrombus or atheroma. Transthoracic echocardiogram did not show any thrombus or demonstrate a patent foramen ovale. Hypercoagulable laboratory workup was negative including normal antithrombin III, normal protein C and protein S function, normal C3 and C4, and absence of Factor V Leiden. ANA, rheumatoid factor, MPO, anti-scleroderma, anti-proteinase, anti-centromere, anti-DS SNA, anti-SSA, anti-SSB, JAK2 mutation analysis and paroxysmal nocturnal hemoglobinuria flow cytometry were negative. Homocysteine was mildly elevated to 21. Notably, patient's testosterone was low at 34 and his LH was low at 2.2, but FSH was normal at 2.65.

Patient was started on a heparin drip, and transitioned to rivaroxaban upon discharge with outpatient hematology follow up. He was counseled on the risks of AAS.

DISCUSSION

Given the negative hypercoagulability workup, it is likely anabolic steroid use caused this patient's renal infarcts. Though he endorsed supplement use for one week, his suppressed testosterone and sex hormone axis suggested chronic use of anabolic steroids.

To our knowledge, there are only a handful of reported cases of arterial thrombosis in the setting of steroid use and only one other reported case of renal artery infarct. As in our case, the diagnosis was made after a negative hypercoagulability workup. Studies have shown that AAS use can cause a hypercoagulable state by increasing platelet production and aggregation via increased thromboxane A2 and decreased prostacyclin. Other studies have demonstrated increased collagen and fibrin deposition in blood vessels leading to increased vascular reactivity.

Our case highlights the importance of considering AAS use in otherwise healthy individuals with unexplainable vascular events, and the need for increased counseling about AAS, including their rare but serious side effects.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Conscious Sedation Simulation Course for Medical Providers and Its Effect on Decreasing Procedural Sedation-Related Complications in the ED

This study aims to improve training and decrease complications related to conscious sedation (light anesthesia to decrease pain during painful procedures). Conscious sedation is an integral part of an Emergency Medicine physician's scope of practice, and residents are required to have performed a minimum of 15 conscious sedation procedures prior to graduation. At GW, resident training has typically included lectures/didactics, an occasional simulated case during the routine simulation training days, and hands on training/supervision in the ED. However, no dedicated conscious sedation curriculum exists, and the experience of residents in the program is variable. The investigators plan to develop a 4 hour integrated didactic and simulation curriculum for conscious sedation, and evaluate the effectiveness of the curriculum on resident knowledge, self-efficacy, and assess for impact on clinical outcomes (if any).

The educational component will be conducted during a regularly scheduled grand rounds as a part of the residency curriculum. Residents will be provided with session pre-reading, complete a demographic survey and knowledge pretest, participate in the simulation training session, and then take a written post-test. A conscious sedation skills station will be included in the annual resident mock oral boards session to assess post course skill retention. Participants will be asked to provide anonymous feedback regarding the efficacy of the training.

In addition, the investigators seek to extract clinical (Emergency Dept) conscious sedation data by reviewing charts from six month timeframes before and after the course is taught, to determine if there is an impact on clinical performance. Although a measurable change in complication rates is unlikely, smaller variations (such as duration of monitoring, degree of oxygen desaturation) may provide insight into whether the course has changed clinical practice. This course will ideally become a fixed part of the residency education curriculum, and later could be applied to any medical provider from any specialty (CME course) with tailored cases related to their practice.

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SCHOOL OF NURSING

Integrating Social Determinants of Health in Health Care Education: Using Simulation Based Learning to Prepare Nurse Practitioner Students

BACKGROUND/PURPOSE

Social determinants of Health (SDH) are conditions in which people are born, work, live, and age, and the policies, agendas, norms, and political systems that impact conditions of daily life. SDH should be an integral component of health professional education. Providers need the knowledge, skills, and motivations to address and act on these factors. The study purpose was to test the impact of a simulation intervention on improving Adult-Gerontology Primary Care Nurse Practitioner (AGPCNP) and Family Nurse Practitioner (FNP) student knowledge and confidence of enacting SDH in their clinical practices.

METHODS

A quasi-experimental pretest-posttest design was used. Students participating in Objective Structured Clinical Examinations (OSCE) were assigned to the control or experimental group based on their OSCE itinerary. Before the OSCE, subjects read an article on SDH. At the simulation center, subjects completed a 3-item confidence and a 10-item knowledge pre-test, developed by the research team and assessed for content validity by three experts. The experimental group then received a SDH-centered simulation, while the control group received a non-SDH simulation. Both groups then completed the confidence and knowledge post-tests.

RESULTS

Subjects ($N = 118$: Control $n = 57$, Experimental $n = 61$) were predominantly female (87%), age 20-50 (92%), Non-Hispanic/white (74%), and had practiced on average seven years. After the intervention, the control group statistically significantly improved on confidence ($p = .03$) but not on knowledge, while the experimental group improved on both ($p = .02, p = .00$). For both groups, confidence was correlated with overall years in practice ($r = .20, p = .05$) and practice in a health professions shortage area ($r = .21, p = .05$).

IMPLICATIONS

SDH-centered simulation based learning is an effective way to increase students' knowledge and confidence in using tenets of SDH in assessing, developing and implementing plans of care for patients. Further testing of the instruments is needed to establish validity and reliability before larger studies are conducted. Future research is needed to examine the sustained use of SDH after graduates enter practice.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Change is Slow, but Apathy is Devastating/Challenging Medical Education in Health Policy & Criminal Justice/Curriculum Development: Incarceration & Health 101

BACKGROUND

Incarceration rates and health disparities in the U.S. prison population are rising at staggering proportions. As future physicians, it is crucial for medical students to develop a working knowledge of the criminal justice system and the agency of the health care provider working within the backdrop of this system. It is nearly statistically impossible that a current medical student/future physician will not care for a patient affected by a history of incarceration in their lifetime. Combining persons in jail, under parole, and in supervised probation, 1 in every 31 adults, or 3.2% of the U.S. population lives under a form of correctional control. One in three black males can expect to be imprisoned in his lifetime. The number of incarcerated persons in America has more than quadrupled in the past 30 years. Contributing factors to incarceration include a myriad of health-related issues including but not limited to dire rates of mental health illness, substance use disorders, and histories of violence against vulnerable populations. Incarcerated persons are disproportionately vulnerable to contraction of infectious diseases and experience unequal access to quality health care services. This issue cuts across all disciplines - evidence-based medicine is not immune, but rather exceptionally accountable.

The multidisciplinary nature of mapping the criminal justice system as it pertains to health lends itself to utilization of the assets within University communities—where Schools of Medicine, Public Health, Public Policy and Law coexist in natural symbiosis. The objective of this project was to draft a proposed outline of medical school topics that would befit a curriculum to address incarceration and its intersection with medicine, public health, health policy, healthcare delivery and health advocacy.

METHODS

The project was divided into a two-part design—theory and practice. First, a compilation of evidence-based research, health policy legislation and community organizations related to criminal justice and health were evaluated. Second, meetings within various University department leaders were scheduled to discuss the feasibility of curriculum implementation as well as to assess service-oriented fieldwork opportunities.

RESULTS

Integrating a two-part design to curriculum adaptation was only partially productive. The use of a conceptual framework to organize evidence-based research and focus on strengthening relationships with local prison health providers in the D.C. community yielded an overwhelmingly positive response. This integrated model of research will serve as a foundation upon which continued support for future endeavors will rest. An online “home” for this information was initiated within the Himmelfarb Library services.

However, implementation of the proposed design was limited by administrative approval and scheduling. Prioritization of pre-clinical curriculum topics that mirror USMLE Step 1 content and an accelerated pre-clinical curriculum restricted the will to integrate this topic into the pre-clinical curriculum hours.

CONCLUSION

Further research is warranted to evaluate resources vested within the larger University community that would provide support for a multidisciplinary approach to the integration of a criminal justice and health curriculum. In the nation’s Capital of Washington D.C., it is imperative to utilize the abundant resources at our disposal to complement our pre-clinical and clinical education in these formative years with the study of health policy, healthcare delivery, health advocacy and the complex bioethical conundrums ripe within the context of the criminal justice system. Future physicians will undoubtedly face many social, structural, and personal challenges in the care of this vulnerable population. We owe it to our patients to be prepared. Change is slow, but apathy is devastating.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Use of Ultrasound to Teach Living Anatomy to Graduate Students

INTRODUCTION

Ultrasound technology is used to reinforce gross anatomy instruction in many clinical medical programs. However, these techniques have not transferred into common practice for anatomy instruction in non-clinical graduate level courses. The addition of opportunities to explore living anatomy through ultrasound sessions is an innovative approach of learning basic anatomy, and may improve student engagement. These sessions could help students transfer the anatomy that they learn in lectures onto a living, moving body, providing a clear view of local anatomy in real time to assist with spatial understanding and knowledge retention. Our main objective of this study is to determine the efficacy of the ultrasound sessions to achieve better student understanding and retention of gross anatomy.

METHOD

We tested our hypothesis by using metric analysis of student anatomy knowledge after they participated in the course. Graduate students were recruited who previously completed ANAT6181 (graduate Human Gross Anatomy course) at The George Washington University, and participated in three two hour ultrasound workshops. The students taking the class this Spring will also be recruited at a later time point. The implementation and analysis of a detailed survey including both ratings and written comments will be done. Exam scores will also be assessed to evaluate learning.

RESULTS AND FUTURE DIRECTION

Preliminary results from the end of the semester exams and preliminary comments demonstrate an appropriate level of understanding of basic anatomy and a great enthusiasm for this method of learning. More data needs to be collected and analyzed in order to recommend this new approach to graduate students learning in Gross Anatomy.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Graduate Students in a Hybrid Microscopic Anatomy Course

INTRODUCTION

In a world that is becoming more dependent on technology, the implementation of online and computer resources is permeating graduate medical education. As curricula evolve and classes reformat, histology or microanatomy has been a discipline highly influenced in medical education programs. A growing trend is that many institutions are now offering an online resource of digitized histological images as opposed to the traditional glass light microscope preparations. Previous studies have reported equal if not improved performance and benefits of these online histology resources such as slide consistency, flexibility, ease of use, and efficiency of faculty time. An online, interactive histology atlas has been developed for undergraduate, graduate, and medical students at George Washington University in Washington, D.C. This online resource offers numerous digital preparations in reference to the in-class teaching syllabus of the clinically relevant organ and tissue systems. The atlas both teaches structure and proper identification techniques, but also offers accompanying texts containing background information and image clarification. Furthermore, the online resource offers testing and labeling practice to enhance the learning process. As a cornerstone of every medical student's training, this study wishes to evaluate the efficiency, reception, and helpfulness of the online resource.

METHODS

We evaluated such measures by anonymously surveying the 2016 fall cohort of graduate students in George Washington University's Graduate Certificate of Anatomical and Translational Sciences (GCATS) and Masters of Anatomical and Translational Sciences (MATS) programs. The survey was centered on the students' use, thoughts, and feedback of the online histology atlas that was created with an asynchronous instructional design using adult learning theory. The practical exam grades were also looked at to assess learning of the material.

PRELIMINARY RESULTS AND CONCLUSIONS

A preliminary survey found that 66% of students thought the atlas very useful, 75% stated the online laboratory exercises to be an effective use of time, and 100% mentioned the online component enhanced their learning of the material. Students scored very well on the final practical exam in the course. Given the feedback from our survey, combined with other studies' findings, we hope to implement changes to make the online laboratory more effective for student use and to enhance the overall learning dynamic for histological study.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Defining the Foundations of and Parameters for Clinical Public Health

The evolving U.S. health care system is increasingly expanding the scope of practice for health care providers. Today's providers must be both excellent clinicians to their patients and physician leaders for their communities. In response to these changes, GW SMHS is integrating a curriculum in Clinical Public Health into our medical education program. Clinical Public Health, the application of principles of public health, population health, and leadership to medical care and health systems decision-making, provides tools that are required of health care providers who practice in 21st Century health care systems as they assume roles as clinicians, problem-solvers, community leaders, researchers, team members, and advocates.

To guide continued GW SMHS Clinical Public Health curriculum development and to foster continuous quality improvement efforts, this project researched current models of medical/health education that incorporate public health/population health and the evolving scope of practice of clinicians through literature reviews, environmental scans, and interviews with experts.

The literature review identified core competencies including bioethics, health disparities, inter-professionalism, social determinant, health law and policy, biostatistics and epidemiology. This range of topic begs the question how to teach each one to enough depth that future clinicians are equipped to practice them in a clinical setting. In addition, literature review highlighted models of medical/health curriculums incorporating public health principles. The environment scan involved researching various efforts and programs in existence using creative approaches to teach these core competencies, as well as identify experts behind these programs to interview. The interviews with experts in the field of clinical public health elucidated the practicality of implementing these programs, the challenges and limitations and resources required to move these models from the theoretical to reality.

Applied and experiential learning was found to be the most favorable model for teaching students key clinical public health competencies. This project discusses the approaches, challenges and outcomes of program enriched with experiential learning. A major limitation was the trade of between breadth of knowledge and depth with the experiential learning approach. In addition, given the novelty of these programs, it was difficult to find a measure of their success at teaching competencies to future clinicians and the impact on communities involved.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Medical Education Research without Active Student Participation: An Observational Study

Given that a major concern of medical education research is to identify and provide effective pedagogical methods for knowledge transfer to and acquisition by students, the purpose of this study was to determine the extent of **ACTIVE** medical student involvement in medical education research.

We selected four recognized academic medical education journals, *Medical Education*, *Medical Science Educator*, *International Journal of Medical Education*, and *Medical Education Online*, and abstracted data on both author demographic and geographic location of studies conducted from January 1996-December 2016. Only articles that pertained to medical school education were analyzed and information regarding first author gender, senior author gender, student author, and geographic location of study were noted.

A total of 2,416 articles pertaining to medical school education were examined. We found that irrespective of the journal, less than 10% of the published articles had student authorship. Of the articles that did have student authors, less than 5% consisted of female student authors, demonstrating a potential gender disparity in medical education research. Additionally, there is also a geographic disparity in student authorship with 62% of all student authors coming from North America, compared to less than 38% in all other regions.

Clearly, medical students are not active participants in medical education research. Therefore, medical education research needs a paradigm shift that not only highlights issues that concern educators but also include student perspectives in terms of issues and questions to be investigated and answered, respectively, thereby giving students a prominent role in medical education research and allowing both faculty and students to synergistically improve the quality of medical education research.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Preparing for The Baby Boom: Utilizing Mobile Applications to Keep Geriatric Patients Healthy

The United States' population is aging and aging fast. The 2013 US census reported that people aged sixty-five and older accounted for 44.7 million people and 14% of the total US population. With the aging of the baby boomer population, the number of elderly in the US is expected to more than double to an astonishing 98 million people by 2060 and will comprise approximately half of the US population.

In an effort to offset some of the financial, logistical, and infrastructural challenges that caring for a large geriatric population may present, it is important to focus on preventative medicine. This project explores the cross roads of technology and preventative medicine in an effort to lay the foundation for a mobile application, which will better enable physicians, patients, and caregivers to share real time information in the management of chronic disease.

The research presented is stage one of the project, in which basic tenants are identified upon which the mobile application will be based. Extensive literature reviews were conducted on various subjects including: telemedicine, traditional geriatric medicine, preventative geriatric medicine, prevalent and costly diseases among the elderly, the cost of caring for the elderly, and innovative ways to finance care. Shadowing experiences in these fields as well as physician interviews helped further shape the basic tenants.

Five basic tenants of my mobile application were identified and are briefly summarized below.

A successful product will:

1. lower the cost of healthcare by targeting the most prevalent and costly conditions among the elderly while also promoting overall healthy living.
2. lower the cost of healthcare by utilizing the app to facilitate independent living.
3. be economical enough for a consumer to pay for it out of pocket or should be medically necessary to be covered by Medicare or health insurances.
4. alleviate some of the unique challenges specific to geriatricians.
5. only succeed if the app is executed properly- both from a user perspective and also from integration with the end provider.

Future stages of this project will utilize these tenants to develop an app where patients can monitor all of their chronic conditions with physician oversight, maintain healthy living, and provide key medical and ancillary information to assist in independent living. This is all in an effort to prevent the progression of chronic diseases, improve quality of care and life, and alleviate the burden an aging population will have on society.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Validation of a Novel Cognitive Simulator for Orbital Floor Reconstruction

PURPOSE

The increasing focus on patient safety in current medical practice has promoted the development of surgical simulation technology in the form of virtual reality (VR) training designed largely to improve technical skills and less so for nontechnical aspects of surgery such as decision making and material knowledge. The present study investigated the validity of a novel cognitive VR simulator called Touch Surgery for a core maxillofacial surgical procedure: orbital floor reconstruction (OFR).

MATERIALS AND METHODS

A cross-sectional study was carried out on 2 groups of participants with different experience levels. Novice graduate dental students and expert surgeons were recruited from a local dental school and academic residency programs, respectively. All participants completed the OFR module on Touch Surgery. The primary outcome variable was simulator performance score. Post-module questionnaires rating specific aspects of the simulation experience were completed by the 2 groups and served as the secondary outcome variables. The age and gender of participants were considered additional predictor variables. From these data, conclusions were made regarding 3 types of validity (face, content, and construct) for the Touch Surgery simulator. Dependent-samples t tests were used to explore the consistency in simulation performance scores across phases 1 and 2 by experience level. Two multivariate ordinary least-squares regression models were fit to estimate the relation between experience and phase 1 and 2 scores.

RESULTS

Thirty-nine novices and 10 experts who were naïve to Touch Surgery were recruited for the study. Experts outperformed novices on phases 1 and 2 of the OFR module ($P < .001$), which provided the measurement of construct validation. Responses to the questionnaire items used to assess face validity were favorable from the 2 groups. Positive questionnaire responses also were recorded from experts alone on items assessing the content validity for the module. Participant age and gender were not relevant predictors of performance scores.

CONCLUSION

Construct, content, and face validities were observed for the OFR module on a novel cognitive simulator, Touch Surgery. Therefore, OFR simulation on the smart device platform could serve as a useful cognitive training and assessment tool in maxillofacial surgery residency programs.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Using an asynchronous learning module to augment clinical knowledge in relation to Focused Abdominal Sonography in Trauma

Focused Assessment with Sonography in Trauma (FAST) is an exam used by emergency personnel to assess the pericardial and peritoneal spaces for fluid. It has essentially replaced diagnostic peritoneal lavage as a noninvasive, rapid and easy to learn alternative to identify high-risk patients in cases of acute trauma. The primary goal of this project is to supplement an ongoing study to create and test a checklist, which novice sonographers will use while performing FAST. A multimedia asynchronous learning module centered on clinical knowledge was created to facilitate sonographers understand of the technique, limitations, pitfalls and clinical application. The development of the checklist will assist novice sonographers in minimizing mistakes while performing the bedside exam. The module—a two-part video with a narrated demonstration and PowerPoint—teaches novices how to use anatomic landmarks to perform the ultrasound quickly and effectively. While the results of this project are still pending, next steps are blending the checklist and module in order to improve novice sonographer's technical skill in performance of FAST examination as well as to augment their clinical understanding of it.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Bedside competency assessment of emergency ultrasound examinations using a mobile SurveyMonkey® SDOT tool

BACKGROUND

Bedside ultrasound (US) has become an important diagnostic tool in emergency departments (EDs), and is now mandated by the ACGME to be part of the curriculum for all emergency medicine (EM) residency programs. Various assessment tools are used to assess residents' competency in ultrasound, including: Objective structured clinical examinations (OSCEs), multiple-choice tests, online interactive examinations, standardized direct observation tools, practical examinations, and quality assurance (QA) review. At GW's emergency medicine residency, all US examinations performed in the ED are reviewed the following Monday in QA meeting and written feedback on each exam is provided to the residents. The primary goal of this study is to develop and utilize a mobile Standardized Direct Observation Tool (SDOT) to perform a real time bedside trainee evaluation and compare the results in a blinded fashion with the reference standard, the assessment of competency in the following week's QA meeting.

METHODS

In this prospective, observational study, a data collection tool was developed using SurveyMonkey® that contained evaluation items based on the CORD-AEUS: Consensus Document for the Emergency Ultrasound Milestone Project. Faculty from the Section of Emergency US in the Department of EM used the mobile-phone based data collection tool as a SDOT at the bedside when students, residents, and fellows were performing one of eight core US examinations. Data recorded included demographic data, exam-specific data, and overall quality measures (on a scale of 1-5, with 3 and above being defined as adequate for clinical decision-making), as well as interpretation and clinical knowledge. The US exam itself was recorded and uploaded to QPath®, GW University Hospital's HIPAA-compliant ultrasound archive. The following Monday, the examination was reviewed by a blinded member of the Section of Emergency US faculty for similar metrics, and the results were combined in a Microsoft Excel database. The agreement of examinations scored adequate (3 and above) in the two evaluation methods is the primary outcome.

RESULTS

To date, 78 surveys have been completed. The agreement between the two methods of competency assessment is good, with agreement in 72/78 (92.3%) of cases (2 inadequate [score of 1 or 2] and 70 adequate [score of 3, 4, or 5]). There was disagreement in 6/78 exams (7.7%).

CONCLUSION

Bedside SDOT by using a mobile SurveyMonkey® platform facilitates assessment of competency in emergency ultrasound by trainees, and correlates well with traditional assessment by asynchronous measures of competency as determined in weekly image review quality assurance.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Impact of a Student Led Rheumatology Interest Group on Medical Student Interest in Rheumatology

BACKGROUND

Based on data from the 2005 Rheumatology Workforce Study the demand for rheumatologists will continue to increase in the coming decades. Demand for rheumatologists outstrips the current supply of trained rheumatologists. The American College of Rheumatology has implemented several strategies to try to increase medical student interest in Rheumatology including programs such as Choose Rheumatology! The purpose of this observational study was to investigate impact of development of a student led Rheumatology Interest Group and the Choose Rheumatology! program on medical student interest in Rheumatology at a single institution.

METHODS

In April 2015 a student led Rheumatology Interest Group was established at our institution. As part of the inaugural meeting the "Choose Rheumatology!" team presented on careers in rheumatology, several faculty gave testimonials on why they had chosen Rheumatology, and patients spoke on the impact their rheumatologist had on their lives. Follow up meetings included a meeting on finding research projects and two joint injection workshops. To assess medical student interest in rheumatology we retrospectively collected data and following initiation of the interest group based on four parameters: the number of medical student abstract submissions to the GW Research Days, the number of medical students enrolling in the rheumatology elective, and the number of manuscripts published by faculty with medical students. In order to account for the variable time periods in the pre- and post-intervention groups, the mean number of student-rheumatology interactions per 6 months in the pre- and post-intervention periods was assessed for each parameter. Data analysis was performed using GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego, CA).

RESULTS

Student interest in the rheumatology elective significantly increased following the Interest Group intervention with a mean number of students per 6 months period ($p=0.021$). The number of abstract submissions also significantly increased ($p=0.017$). The number of manuscripts submitted by student-faculty dyads has also increased ($p=0.013$).

CONCLUSION

A simple and low cost intervention of development of a student led interest group coupled with a Choose Rheumatology! Campus visit has dramatically impacted student interest in Rheumatology at a single institution.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

“Fungus Amungus”—A Common Disease State that is Commonly Missed: A Survey-Based Study

BACKGROUND

Dermatophyte infections involving the skin, hair, or nails affect an estimated 25% of the world’s population, and accounted for 51 million outpatient visits over a ten-year period (1995-2004) in the United States alone. Dermatophytosis is routinely managed by dermatologists, though given the diversity of clinical presentations, is sometimes misdiagnosed, which can result in inappropriate therapy, worsening of symptoms, and even result in additional skin and soft tissue infections.

METHODS

An interactive survey of board-certified dermatologists was conducted at the 2016 Orlando Dermatology Aesthetic & Clinical Conference, during a seminar on superficial mycotic infections. The structure of the survey entailed reviewing a presentation of a clinical image followed by responding to a simple yes or no question: is this a fungal infection? Data was gathered anonymously via an audience response system and data tabulated using Microsoft excel.

RESULTS

In all, 13 cases were presented. Although the majority of the cases (8/13) were appropriately categorized by 50+% of the audience, this percentage decreased as accuracy of categorization increased. For example, in only 4 of the 13 cases did audience members accurately categorize the cases > 75% accuracy. Moreover, there was only one case for which 90+% of the audience appropriately categorized the case.

CONCLUSION

The study limitations included a lack of a measureable response rate and a small sample size, which prevent significant conclusions from being made. However, the results do emphasize the protean clinical nature of cutaneous dermatomycoses and the ease with which one may miss the correct diagnosis. Secondary syphilis, annular psoriasis, and pityriasis rosea are among just a few inflammatory skin diseases that can mimic dermatophyte infections as illustrated herein. As such, these data underscore the importance of continued medical education on dermatophyte infections as well as proper education and training on bedside diagnostic techniques such as potassium hydroxide during residency and beyond.

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MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH

Systematic Review of Associations Between Particulate Matter (PM_{2.5}, PM₁₀) and Cancer Risk

BACKGROUND

Particulate matter is a combination of solid and liquid particles suspended in air, and can contain dust, pollen, smoke, and other chemicals. Many studies have investigated a potentially deleterious effect on lung health as a result of PM_{2.5} and PM₁₀.

OBJECTIVE

To review and investigate the association between particulate matter exposures (PM_{2.5} and PM₁₀) and lung cancer, and the strength of the exposure.

METHODS

We included the first several steps of the Navigation Guide methodology and developed a PICOS/PECOS statement. We then searched for articles that fit our search criteria that illustrating a comprehensive overview of research pertaining to lung cancer incidence/mortality and PM_{2.5} and PM₁₀ exposures.

RESULTS

We identified 9 studies that met our inclusion criteria and 6 were included in this study. These studies found PM_{2.5} and PM₁₀ exposures increase the risk of lung cancer incidence and/or mortality from 1.16-1.27, and one study found an OR of 3.30 for the high frequency of cooking and 4.08 for solid fuel usage for cooking. None of the studies concluded that there was little to no effect on lung cancer incidence while the others found significant hazard and odd ratios for the relationship between PM_{2.5} and PM₁₀.

CONCLUSION

Based on the review of these articles, we concluded that these studies suggest PM_{2.5} and PM₁₀ have a moderate increase in the risk of incidence and mortality of lung cancer.

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Elevated Blood Pressure in Adults and Household Air Pollution Caused by Use of Unimproved Cookstoves: A Systematic Review

There is emerging evidence that household air pollution (HAP) created by the use of unimproved cookstoves using solid fuels (wood, crop residues, charcoal, coal, and animal dung) could be a risk factor for elevated blood pressure in adults. Numerous reviews have found a risk associated with ambient particle air pollution and cardiovascular disease and clinical research has shown pathways in which the body's response to irritating air pollutants can have effects on the cardiovascular system. These responses are inflammatory in nature and can lead to oxidative stress which has been shown to play a role in the physiology of hypertension, systemically high blood pressure. If ambient pollution is a risk factor for elevated blood pressure, then pollution created in the home from similar fuels is conceivably causing an added risk for elevated BP levels and perhaps cardiovascular disease if left unchecked.

This review aimed to summarize studies that have researched the association between indoor cookstoves and their fuels and the association with hypertension. PubMed, Scopus, and Cochrane Library were searched for articles pertaining to adults using unimproved cookstoves and the association with hypertension or elevated blood pressure. 10 articles were found within these guidelines and all found some significant evidence supporting the hypothesis that unimproved cookstoves increases the risk for elevated blood pressure, specifically in older women with higher BMIs.

Further research must be done to fully substantiate this hypothesis specifically longitudinal studies and intervention trials with longer follow up time. However, the research is being done regularly as this review was done months after a similar one was published with multiple new articles included.

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The Role of Health in the Perception of Climate Change Risk: An in-depth Qualitative Approach

BACKGROUND

Research has suggested that a health frame is critical to compel concern about, and action on climate change. However, the understanding of how health is important to these processes is largely unexplored. Using an in-depth qualitative approach, we explore how health informs the conception of climate change risk after exposure to episodes of a climate change documentary series which vary in the way that they frame climate change.

METHODS

59 participants (objective of 70) were recruited from five locations to watch one of four episodes of season two of Years of Living Dangerously, participate in an in-depth interview and complete a follow-up survey one month after the interview. The five locations were: Portsmouth, New Hampshire; Miami, Florida; Las Vegas, Nevada; San Francisco, California; Toledo, Ohio. Data were analyzed in QSR NVIVO.

RESULTS

Data collection is ongoing but preliminary findings show that interviewees' concerns about health effects shown in the episodes are often discussed in the context of proximate risks, whereas the potential for future health risks and other threats from climate change were generally framed as uncertain and distant. Additionally, health risk perceptions were not necessarily connected to climate change, but rather other environmental risks like particulate air pollution. In general, participants did not have a clear understanding (or had a limited understanding) of how climate change impacts human health. Finally, participants who viewed episodes with a health focus tended to mention health concerns more often than those who viewed episodes without an obvious health topic.

CONCLUSIONS

Health plays some role in shaping risk assessment of climate change, but must be raised explicitly and in an immediate rather than distant way in order for audiences to include it in their risk assessment process and to make the connection between effects of climate change and potential health effects.

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JOINT PA/MPH PROGRAM

Climate Change and Mental Health: A Systematic Review

BACKGROUND

With the dramatic increase in research on climate change over the past decade, an increasing number of studies have explored relationships between climate change and mental health. The 2016 U.S. Global Change Research Program's (USGCRP) report, *Impact of Climate Change on Human Health in the United States: A Scientific Assessment*, identified some of the most relevant scientific literature available at the time on the relationships between climate change and mental health in the U.S.

OBJECTIVE

This review a) examines pertinent climate change impacts on mental health; and b) systematically reviews published research relevant to climate change impacts on mental health and well-being made available since the USGCRP report.

METHODS

PubMed and Scopus were searched from all studies in English between 2014 and December 31, 2016. Only original empirical research published in English was included; studies referenced in the USGCRP report was excluded.

RESULTS AND DISCUSSION

Thirteen articles were identified that evaluated the relationship between climate or climate change and mental health. Of these 13, 5 studies evaluated temperature, 5 studies evaluated extreme weather events, 2 studies evaluated climate change broadly, and one study evaluated sea level rise as the exposure of interest. The specific mental health outcomes measured varied widely between the studies but included mood disorders, trauma- and stress-related disorders, suicide, and psychotic disorders. The studies generally found positive significant associations between increasing exposure to extreme weather events and temperature and increased risk for mental health disorders. Most of the studies lacked analysis of specific risk groups, but women were found in at least 2 of the studies to have significantly higher levels of mental health effects compared to men. Additional specific results and trends across the 13 studies, and recommendations for the design of future studies will be further detailed in the presentation.

CONCLUSION

Studies continue to associate climate events and changes, such as increasing temperature and extreme weather events, with an increased risk and prevalence of mental health disorders. Better understanding of how specific climate exposures may specifically impact mental health is important in targeting appropriate prevention and treatment interventions for specific risk groups and high risk geographical areas.

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Phytoestrogen Exposure During Infancy and Risk of Uterine Fibroid Development

BACKGROUND

Uterine leiomyomata (fibroids) are common, benign, smooth muscle tumors that primarily develop among reproductive-aged women. Fibroids are often associated with pelvic pain, heavy menstrual bleeding, and reproductive complications, thus accounting for a significant amount of hysterectomies each year. Although the pathogenesis of uterine fibroids is not well known, early-life exposures to hormonally active compounds, such as phytoestrogens, may affect uterine receptors to estrogen or progesterone that lead to fibroids.

OBJECTIVES

Here we report the results of four epidemiological studies which examined the association between early-life exposure to phytoestrogens contained in soy-based formula and increased risk of uterine fibroid development among premenopausal women.

DATA SOURCES

A comprehensive literature search was conducted using five peer-reviewed scientific journals, including: PubMed, Embase, Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Scopus. All four studies were prospective cohort studies.

Study eligibility criteria: For inclusion in this systematic review, studies included premenopausal women, aged 23-59 years old, exposed to soy-based protein formula within 6 months of birth, and clinically diagnosed with uterine fibroids by hysterectomy or ultrasound. Seventy-five percent of the studies evaluated were among African American women in the United States.

STUDY APPRAISAL AND SYNTHESIS METHOD

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology was used to evaluate the studies within this systematic review.

RESULTS

Based on the data across the four studies, there appears to be a low risk of association between phytoestrogen exposure during early-life and the risk of uterine fibroid development. One study, however, did observe an association between fibroid size and early-life phytoestrogen exposure.

LIMITATIONS

Two primary limitations across the epidemiological studies in this review are recall bias and exposure misclassification. Early-life exposures are difficult to obtain in the study population due to participants' inability to self-report childhood feeding data and reliance on parents or caregivers.

CONCLUSIONS

Overall, the studies included in this review had many strengths to decrease disease misclassification by excluding menopausal women and by validating primary outcome of uterine fibroids through physician or clinical diagnosis. More studies that prospectively capture infant feeding data are necessary to determine if phytoestrogens in soy infant formula increases the risk for uterine fibroid development in premenopausal women.

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Evaluating Strain Variations in Routes of *Clostridium difficile* Infections (CDI)

Clostridium difficile is an anaerobic spore-forming, gram-positive bacillus that is frequently implicated in antibiotic-associated diarrhea and infection, especially among hospitalized patients. *C. difficile* infection (CDI) has emerged as a global concern as the incidence of disease and mortality around the world appear to be increasing. These strains are resistant to different antibiotics rendering treatment ineffective. For those who already have comorbidities, CDI infections present a greater risk of adverse health outcomes and mortality. The presentation of CDI shows different strain type involvements depending on location. Numerous studies have assessed the strain variation and risk factors for these unfavorable outcomes, but systematic reviews published have been limited in scope, restricted to certain locations, or lacking in quality. A systematic review was completed to evaluate which of the following exposure-to-development routes was most prevalent for CDI along with determining which strains appear as drivers for the different routes of infections. Most common route is hospital-acquired and hospital-onset while most common strain types are RT027, RT001, and RT017. Given the varying case definitions and outcome measurements, these studies are limited in fully measuring the association of CDI to exposure in either community or hospital settings. In addition, sampling from hospital settings presents specific biases (e.g. Berkson's bias, survivorship bias) that can affect the true associations measured. This review has found some differences in strains that manifest in community or hospital settings. Exposure-to-development routes still are not fully understood, and more focus should be placed on understanding how *C. difficile* is transmitted and develops into CDI.

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AI/AN Children with Asthma or Respiratory-Related Illness and Exposure to Household Air Pollution in North America: A Systematic Review

The impact of household air quality on asthma or respiratory disease development remains unclear. Asthma is the most common chronic disease in children and acute lower respiratory infections (ALRI) are a leading cause of morbidity and mortality in children globally. AI/AN children are a population identified as living with a high prevalence of asthma, an estimated 13.3%, compared to children in different racial groups within the United States. This study examined all relevant human data evaluating a link between household air pollution exposure and development of asthma or respiratory-related illnesses (RRI). The examination of relevant data meant to evaluate household air pollution exposure and disease development among a Native or Indigenous population for a possible association. The study identified and reviewed relevant epidemiologic study articles from 1950 to 2016 using a database search algorithm. Each study was reviewed by quality and bias assessment criteria and pertinent data extracted. 11 articles were identified, reviewed, and analyzed. There is evidence in epidemiologic studies that increased exposure to household air pollutants is associated with asthma and RRI. However, study design and exposure measurements within the studies fitting inclusion criteria were highly varied and most used small samples of convenience; therefore, this study could not adequately determine an association between household air pollution and asthma among the AI/AN population. The research did determine a deficiency of community-based participatory research practices within the study populations, as well as evidence-based exposure assessments. Additional studies are needed to examine the effects of household air pollution within this population. In addition to rural locations, urban environments must be assessed for AI/AN asthma risk factors. Conducting high quality, community-based participatory research practices must be utilized when working with AI/AN communities; this is imperative to produce replicable data necessary to enhance the health of this marginalized population.

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Pesticide Mixtures and Risks of Human Sperm Aberrations

BACKGROUND

Endocrine-disrupting chemicals (EDCs) such as organophosphate (OP) and pyrethroid (PYR) pesticides, affect human reproductive health. Investigating “real-life” environmentally relevant concentrations and mixtures of EDCs is important to identify potential interactions between highly correlated environmental exposures and reproductive health outcomes.

OBJECTIVES

This study investigated the effects of combined environmental exposures to OP and PYR pesticides and their association with the frequency of sperm chromosomal abnormalities (disomy) among adult men. We evaluated the hypothesis that pesticide mixtures, specifically OP and PYR interactions, alter associations of sperm chromosomal abnormalities.

METHODS

One hundred fifty-nine men originating from a parent study of couples seeking infertility evaluation were evaluated. Fluorescence *in situ* hybridization was used for chromosomes X, Y, and 18 to determine disomy in sperm nuclei. Urine was analyzed for concentrations of PYR metabolite [3-phenoxybenzoic acid (3PBA)] using high-performance liquid chromatography. Gas chromatography coupled with mass spectrometry was used to analyze urinary concentrations of dialkyl phosphate (DAP) metabolites of OPs. Poisson regression models were used to calculate incidence rate ratios for each disomy type by exposure quartile of OP and PYR pesticides, controlling for potential confounders. Interactions between each DAP metabolite and 3PBA and associations with each disomy outcome were examined.

RESULTS

Significant interactions were found between DAP metabolites and 3PBA for all disomy outcomes. Most of the associations showed increased disomy rates, higher than the values previously reported for each individual chemical class, by levels of specific DAP metabolites and 3PBA exposure. Increase in disomy rates occurred mainly between the second and third exposure quartiles and without substantial additional increases between the third and fourth exposure quartile, producing non-linear dose responses. Nonmonotonic patterns were observed in depicted graphs (displaying bell-shaped profiles). Significant inverse and positive parameter estimates were seen across all DAP metabolites by 3PBA quartiles.

CONCLUSIONS

This study demonstrates the methodological problems posed when evaluating environmental chemical mixtures, particularly when the health outcome is a count that is best suited for non-logistic modeling, such as Poisson regression. Consistent interactions were observed between OP and PYR pesticides, which strengthened the associations seen beyond the main effects of each individual exposure. Methods specific to investigating interactions in Poisson models are needed to determine an optimized approach for evaluating pesticide mixtures (with different EDC modes of action) and their effects on count based outcomes.

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The Effect of Anatase Titanium Dioxide Nanoparticles via Intranasal Instillation on Oxidative Stress in Mice Brain: A Systematic Review

BACKGROUND

With a wide range of applications, titanium dioxide nanoparticles (TiO₂ NPs) have become one of the top five most commonly used nanomaterial worldwide. TiO₂ NPs occur in three crystalline polymorphs. Anatase TiO₂ NPs has a higher surface area and gives rise to a more superior photocatalytic performance, leading to its high use. However, this property results in the formation of highly reactive radicals, producing more adverse biological effects than its other counterparts. A growing number of studies have documented that TiO₂ NPs can cross the blood brain barrier, leading to accumulation in the brain, yet little research has been done examining the impact on oxidative stress in the brain after TiO₂ NPs exposure.

OBJECTIVE

This systematic review sought to identify relevant studies evaluating the relationship between exposure to anatase TiO₂ via intranasal instillation and oxidative stress in mice brain, summarize the exposure data for each neurotoxic endpoint, and identify a dose-effect relationship.

METHODS

Compendex, Inspec, Inspec Archive, GEOBASE, Knovel, PubMed, Cochrane, Scopus, and the reference lists of included studies were searched for all related studies in English.

RESULTS

Four studies were identified that investigated the effect of oxidative stress in mice brain after exposure to anatase TiO₂ NPs. The biomarkers used to measure oxidative stress in the brain include O₂•⁻, H₂O₂, MDA, carbonyl content, 8-OHdG, GSH-Px and GSH activities, GST, CAT activities, and SOD. MDA was the only biomarker consistently used in all four studies. Increased exposure to TiO₂ NPs was significantly associated with an increase in oxidative stress.

CONCLUSION

Each of the four studies used different biomarkers to measure oxidative stress, making comparison between the studies' findings challenging. However, based on our findings, we concluded that there is "sufficient" evidence that mice exposure to anatase TiO₂ NPs via intranasal instillation leads to oxidative stress in the brain.

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Climate Change, Natural Disasters, and Suicide: A Systematic Review

BACKGROUND

Natural disasters are projected to increase due to climate change. Mental health is not a well-researched area in public health, particularly as it relates to environmental health and in the aftermath of natural disasters. The suicide rate is approximately 13 per 100,000 people in the US, nationally. This already high suicide rate warrants researching this area mental health. Understanding the relation between natural disasters and suicide rates might help alleviate human suffering and potentially save lives in the future, in post-disaster settings. This research will further the knowledge of the association between natural disasters and suicide and provide foundation and reasoning for funding such research, as well as investment in mental health services.

OBJECTIVES

The objective of this systematic literature review is to explore the relation between natural disasters and suicide rates among the affected population in the aftermath of major natural disasters.

METHODS

This research was produced thorough a systematic literature review following PRISMA methodology. Four digital databases, PubMed, Scopus, Cochrane, PsycINFO, were utilized to conduct a thorough, systematic literature review. After applying the predetermined inclusion and exclusion criteria and reviewing the literature in detail, seven studies were included in the final literature review.

RESULTS

Most of the studies (n=5) included in this review found a positive correlation between suicide rates and natural disasters. The suicide rates varied for different natural disasters and some studies found an increase of up to 40% after certain natural disasters such as recurring floods. Natural disasters found to be most associated with increased suicide rates included heatwaves, flooding, and droughts. Other studies exploring tsunamis and hurricanes found no significant increase in suicide rates.

LIMITATIONS

With only seven articles, it limits confidence in a strong association between disasters and suicide rates. Another major limitation is the inclusion of English-Language-Only articles.

CONCLUSION

This literature review found some evidence of an association between natural disasters and suicide. Further research with better study designs is recommended to understand and prepare for increasing natural disasters as a result of climate change and their impact on mental health and suicide. We also recommend funding allocation for mental health services in emergency preparedness plans.

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A Systematic Review of the Impact Access to Green Spaces has on Rates of Depression in Urban Dwelling Adults

BACKGROUND

Understanding how the built environment impacts our health is crucial to urban planning and development. Urban environments are ideal settings for studying the impact of green space on chronic, non-communicable disease and disorders, yet a majority of research has focused more broadly mental and physical health.

OBJECTIVES

The aim of this review is to examine a specific mental health indicator, depression, and how rates within urban dwelling adults are impacted by the presence of and access to green space within the built environment.

METHODS

Systematic review of 8 peer-reviewed studies published between 2002 and 2016.

RESULTS

All studies were cross-sectional, and despite heterogeneity in study design, the overall findings indicate that access and exposure to green space mitigate rates of depression in adults.

CONCLUSIONS

Evidence of an inverse association between green space access and exposure and rates of depression suggests that urban planning and development, as well as public health practitioners and professionals should factor in green space as part of the built environment to remediate depression rates. Further studies are needed to assess the direct biological mechanisms associated with depression and green space, as well as how measures of frequency, duration, intensity, and proximity to green space impact depression outcomes.

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Extreme Heat Exposure and Adverse Birth Outcomes

Global and regional increases in temperature and climate-related events as a result of climate change promise to adversely affect the health of vulnerable populations. While not traditionally included in groups impacted by extreme temperature exposures, pregnant women and their fetuses are susceptible health consequences from these exposures. There is a relative dearth of information on climate change processes that affect pregnancy outcomes and neonatal health. This systematic review aims to identify recent literature that investigates increasing heat and extreme temperatures on pregnancy outcomes in order to create a comprehensive understanding of how immediate effects will be sustained in the next generation. Following the PRISMA guide, articles that focus on temperature exposures and adverse health effects in pregnant women were systematically selected from PubMed, Cochrane Reviews, and through hand selection. Studies were selected based on their adherence to these search criteria, and were evaluated based on the strength of their findings and the risk of bias present in each study. In synthesizing the research, there is evidence that temperature extremes do adversely impact birth outcomes. Studies measuring the effects of abnormal heat patterns found changes in birth weight, length of gestation, birth length and neonatal stress in both unusually hot temperature exposures and cold temperatures. Furthermore, in some instances, these results varied with socioeconomic status. Previous literature has already demonstrated the role of warmer climates on decreased birth weight; these results appear in temperate, cold, and hot climates, indicating that relative tolerance to temperature swings may play a role in pregnancy outcomes. The studies included in this review indicate that not only is there a need for further research on the ways that climate change, and heat in particular, may affect neonatal outcomes, but that uniform standards for assessing the effects of heat on maternal fetal health also must be established.

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Association of Obesity, Race and Semen Parameters among Washington, DC-Area Men

PURPOSE

A decades-long decline in semen quality in developed countries has partly coincided with an upsurge in obesity. Evidence suggests that obesity plays a role in male reproductive health outcomes, though studies examining Body Mass Index (BMI) and semen parameters are mixed. In addition, few have examined men of color. This investigation is examining the association between obesity, race and semen parameters while accounting for several demographic and lifestyle variables. It is analyzing an ethnically-diverse cohort of men attending the Medical Faculty Associates (MFA) physician health clinic in Northwest Washington, DC.

METHODS

Participants were recruited from adult medicine, endocrinology, and fertility clinics. Semen samples from 139 men were analyzed. Sperm concentration, motility and morphology were evaluated continuously and categorically according to WHO-abnormal lower reference limits. Categorical BMI and race were each evaluated as a primary predictor. Lifestyle variables including age, abstinence time, medications, drinking and smoking history were evaluated as potential confounders. Kruskal-Wallis, Chi-Square, and Fisher-Exact tests were used to compare semen parameters and descriptive characteristics among groups. Multiple linear and logistic regression models were evaluated.

RESULTS

The mean age of the sample was 41 and 81.8 percent of the sample was overweight or obese. Minority men made up half of the sample (50.3 percent). Descriptive data revealed some differences in semen parameters by BMI, race, and certain lifestyle characteristics. Black men were more likely to have been obese, made a partner pregnant, and non-drinkers compared to the rest of the population, and were less likely to have earned a college degree. Black men had reduced mean sperm concentration, motility and normal morphology compared to the rest of the population, while Hispanic men had elevated normal sperm morphology. Nearly two-thirds (65.9 percent) of the population had abnormal sperm morphology as defined by WHO lower-reference limits.

CONCLUSION

Results showed some differences in semen parameters by race but not by BMI among this sample, the majority of whom were overweight or obese. Given how few studies have evaluated fertility among men of color, future reproductive health studies should examine the sperm health of minority men and further examine whether overweight or obesity influences fertility.

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FISHing with Rat Sperm; The Effect of Glyphosate Toxicity on Sex Chromosome Aneuploidy in Rats

BACKGROUND

Glyphosate (N-(Phosphonomethyl-glycine)) is one of the most frequently used chemicals in herbicides worldwide; and is ubiquitous in the environment and food supply. Recent studies have identified glyphosate as a potential endocrine disrupting chemical (EDC). EDCs have been associated with a decrease in testicular function, including increases in aneuploidy—an abnormal number of chromosomes—in sperm cells. The presence of aneuploidy in sperm cells can contribute to early embryo loss as well as children with Klinefelter and Turner syndromes. This study investigates the impact of glyphosate in its chemical form and in the form of the commercial herbicide Roundup®, on testicular function.

METHODS

Triple-probe fluorescence in situ hybridization (FISH) is used to identify sex chromosome disomy (XX, YY, XY) in sperm cells. The FISH method being developed for this study is based on three peer-reviewed studies using rat sperm FISH to ascertain aneuploidy, and our current lab protocol for human sperm FISH. For methods development we used 14 samples of epididymal sperm from 8 non-study rats extracted in differing volumes of sodium citrate buffer. Our protocol includes removal and separation of the sperm tail for enhanced imaging, swelling of the nucleus and denaturation of the DNA to provide ideal conditions for hybridization of custom-made probes for chromosomes X, Y and an autosomal control. The probes are enumerated using an adaptation of the human sperm procedure for imaging and nuclei are scored semi-automatically using a Leica DMI8 inverted fluorescent microscope and specialized analysis software. To investigate the effects of glyphosate, we collected 54 epididymal sperm samples from rats in three groups; (I) no treatment, (II) treatment with glyphosate, (III) treatment with Roundup®. Animals in treatment groups were dosed through drinking water at the acceptable daily intake for humans in the USA, 1.75mg per kilogram of body weight per day.

CONCLUSIONS

Preliminary data on aneuploidy frequencies, specifically XX, XY, YY, and total disomy, and comparisons between dosed and non-dosed animals will be described and observations about chemical impacts on sperm abnormalities will be provided.

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Reactive Toxicity of Three Haloacetamide Drinking Water Disinfection Byproducts

Haloacetamides (HAMs) are toxic electrophiles formed as a byproduct of drinking water disinfection. Predicted SN2 reactivity correlates with genotoxicity for three monohalogenated acetamides (monoHAMs) iodoacetamide (IAA), bromoacetamide (BAA), and chloroacetamide (CAA). To further investigate the relationship between chemical structure (halogen species), reactivity, and toxicity for the monoHAMs abiotic (in chemico) reactivity and in vitro toxicity or stress response endpoints were measured. Additionally computational (in silico) estimates of electrophilic softness/reactivity were evaluated as predictors of the in chemico and in vitro endpoints. In chemico reactivity, was measured as depletion of free thiol, using N-acetylcysteine as a standard nucleophile. The rank order of thiol/thiolate reactivity was IAM > BAM >> CAM; CAM did not have a significant effect after the 30 min reaction. Antioxidant response element (ARE) signaling activity and nuclear Rad51 accumulation were assayed as in vitro measurements of oxidative/electrophilic stress and genotoxicity, respectively. Each of the HAMs significantly induced nuclear Rad51 accumulation and ARE activation compared to a negative control. The rank order of effect was IAM > BAM > CAM for Rad51, and BAM \approx IAM > CAM for ARE signaling activity.

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Organophosphate Pesticide Exposures and Diabetes Mellitus Among U.S. Adults: Findings from the National Health and Nutrition Examination Survey, 2007-2008

BACKGROUND

Organophosphates are the most widely used pesticides in agricultural and residential settings worldwide. Many organophosphate residential uses have been phased out due to the implementation of the Food Quality Protection Act (FQPA) of 1996, but some OPs are still used in the U.S. to control insects on food crops, making them the most commonly used pesticides for indoor pest control. Several toxicology studies have demonstrated positive associations between organophosphate exposures and increases in blood glucose and the development of diabetes. Very few studies have evaluated these associations among humans.

OBJECTIVES

Our aim was to investigate the associations between organophosphate pesticide urinary metabolites and diabetes mellitus in a representative sample of the U.S. adult population ≥ 20 years of age.

METHODS

We investigated adult participants in NHANES 2007-2008 (unweighted $n=5,707$), and investigated associations between six creatinine-adjusted organophosphate urinary metabolites (dimethylphosphate (DMP), diethylphosphate (DEP), dimethylthiophosphate (DMTP), diethylthiophosphate (DETP), dimethyldithiophosphate (DMDTP), and diethyldithiophosphate (DEDTP)) levels and life-time diabetes status. We conducted univariate analyses and multivariable logistic regressions to estimate the adjusted odds of diabetes in relation to organophosphate metabolites above the limit of detection (LOD). All analyses accounted for NHANES' complex survey design. Age, gender, income to poverty ratio, race/ethnicity, education, body mass index, and waist circumference were evaluated as potential confounders.

RESULTS

The mean age was 46.8 and more than 75% of participants were non-Hispanic Whites (12.5% non-Hispanic Black, 5.3% Mexican American/Hispanic, and 6.6% other races). Seventy two percent of participants were over weight or obese. DMTP was detected (more than LOD) in 74% of participants, while other organophosphate metabolites were not detected in the majority of participants (DMP: 38.7%; DEP: 31%; DETP: 40%; DMDTP: 21%; and DEDTP $< 1\% \geq \text{LOD}$). About 8.5% had ever been diagnosed with diabetes and more than 38% had a positive family history of diabetes. Results from multivariate models examining organophosphate metabolites and diabetes will be presented.

CONCLUSIONS

This is the first study of this size among the U.S. adult population investigating the relationship between organophosphates and diabetes. Given the widespread use of organophosphates and the growing burden of diabetes, further studies are required to evaluate these associations.

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MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH

Occupational Exposure to Cleaning Products and Asthma Risk in Healthcare Workers and Professional Cleaners: A Systematic Review

BACKGROUND

Work-related asthma (WRA) includes work-exacerbated asthma (pre-existing asthma condition that is made worse due to workplace exposures) and occupational asthma (asthma that can be directly attributed to workplace exposures). One possible cause of WRA is exposure to chemical products that irritate the respiratory system. Some cleaning products and disinfectants in particular, are potential respiratory irritants of concern for healthcare practitioners and cleaning professionals.

OBJECTIVE

This systematic review examines the state of the evidence on the potential association between occupational exposure to cleaning products and the risk of WRA for healthcare practitioners and professional cleaners, compared to those with low or no exposure to cleaning products.

METHODS

I conducted my literature search using three public health databases: PubMed (63 papers), SCOPUS (69 papers), and the Cochrane Library (1 paper). After removing study duplicates, I screened 101 papers for original epidemiological research that investigated the possible link between exposure to cleaning products and asthma within the two populations of interest, and subsequently included 13 papers in my review. Of these, 5 studied healthcare workers and 8 studied professional cleaners. I assessed the quality of each study based on: 1) strengths and limitations of the study design, 2) the strengths of the specific methodology and analysis employed in the study, and 3) the risks of bias in the data.

RESULTS

Overall, the evidence supports a positive association between occupational exposure to cleaning products and risk for asthma symptoms for both healthcare practitioners and professional cleaners. Four of five studies for healthcare workers and seven of eight studies for cleaners found significant associations between occupational exposure to cleaning products and WRA symptoms. However, limitations of this study include data availability restrictions, as the majority of studies included in this review were conducted using self-reported information that are subject to recall bias.

CONCLUSIONS

Based on the general agreement between studies that there is a positive association between the exposure to cleaning products and WRA symptoms, awareness should be raised for at-risk populations in order to promote personal risk mitigation activities. Employers should consider program-wide intervention for employees, such as product substitution or the use of personal protective equipment to reduce risk of respiratory exposure to known irritants. Since much of the current epidemiological data on exposure to cleaning products is dependent on self-reported data that is susceptible to recall bias, future research is needed to develop better-validated measurements to investigate this issue.

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Prenatal EDC Exposures and Biomarkers of the Chronic Stress Response

BACKGROUND

Humans are widely exposed to endocrine disrupting chemicals (EDCs) through consumer products, foods, and cosmetics. EDCs may interact with the glucocorticoid receptor; however associations between EDCs and the chronic stress response have not been well studied in humans. Chronic stress, which can manifest itself through inflammation, can contribute to adverse health outcomes during pregnancy including poor birth outcomes.

OBJECTIVE

We investigated associations between prenatal exposures to persistent EDCs and biomarkers of the inflammatory response in women during pregnancy and the postpartum period.

METHODOLOGY

We used data from a cohort recruited from the San Francisco Bay area. The majority of the study participants were non-white, low-income pregnant women that are overweight or obese. Blood samples were collected during early pregnancy and at 3 and 9 months postpartum. Serum concentrations of polybrominated diphenyl ether (PBDE) analytes, polychlorinated biphenyl (PCB) and organochlorine pesticide analytes, and perfluorochemicals (PFCs) were measured during early pregnancy. Serum concentrations of interleukin 6 (IL-6), interleukin 10 (IL-10), tumor necrosis factor (TNF), and corticotropin-releasing hormone (CRH) were measured at all three time points. Multivariable linear regression models were used to investigate the cross-sectional relationship between EDC exposure and inflammation biomarker levels. Longitudinal associations were examined with mixed models using IL-6, IL-10, TNF, and CRH measurements from all three time points.

RESULTS

In the cross-sectional analyses, we observed positive associations between PBDE-47, PBDE-99, and PBDE-100 concentrations and IL-6 and TNF during early pregnancy ($p < 0.05$). Similar statistically significant positive relationships were observed between levels of 6-OH-BDE-47 and PFOA and IL-6 during early pregnancy, and between PFOS and TNF during 9 months postpartum. Negative associations were observed between PFHxS and CRH during early pregnancy, and between oxychlorane and TNF during 9 months postpartum. In the longitudinal analyses, positive relationships were observed between 6-OH-BDE-47, PFOS, and PFOA levels and IL-6 and TNF ($p < 0.05$). Similar statistically significant positive associations were also observed between PBDE-47 and PBDE-99 and TNF. A negative association was observed between PFHxS and CRH in the longitudinal analyses. No statistically significant results were observed in the mixed models for IL-10.

CONCLUSIONS

These findings suggest that exposure to specific EDCs is associated with increased inflammation among pregnant women during early pregnancy and the postpartum period. This study is one of the first to investigate the relationship between exposure to EDCs and biomarkers of chronic stress. Our findings may shed insight on mechanisms of EDC toxicity.

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The Efficacy of Household Water Treatment (HHWT) in Reducing Water-Borne Disease in Complex Emergency Settings

Of the 1.8 billion deaths caused by diarrheal disease worldwide, contaminated water is the leading cause. A 40 percent increase in morbidity and mortality has been shown in emergency relief camps attributable to diarrheal disease. Therefore, access to clean water is an essential first step during complex emergency relief to reduce the risk of disease and death. Household water treatment (HHWT) has been proven effective in developmental settings, but the impact of HHWT in emergency settings lacks conclusive evidence. The purpose of this review is to evaluate the quantity and quality of evidence related to HHWT interventions in complex emergencies and to uncover any gaps in the literature. A systematic literature review was performed through electronic database searches using specific inclusion and exclusion criteria to measure water-borne disease outcomes against HHWT interventions. Of interest were articles published online, in English, after 1995, with quantitative or qualitative outcomes directly related to both the health status and intervention type. A total of 524 studies were identified, and 7 studies were included in this review after meeting the strict inclusion criteria. All of the studies used HHWT methods, two of them measured experimental technology, four of the studies accounted for natural disasters, and one study accounted for forced resettlement. Three cross-sectional studies, two experimental studies, one case study, and one unblinded randomized control trial were included. It was found that HHWT methods are more effective after the acute phase of emergencies, while large scale treatment methods are more effective in the acute phase. Household chlorination is the method showing the highest and only corroborated success rate. The evidence surrounding the association of HHWT interventions and a reduction of water-borne disease in complex emergencies is limited and a gap in the literature has been identified. Future research should focus on standardizing research methods in emergencies, testing experimental technology, and measuring disease status rather than using proxy measures. Overall, there is a need for better program design, implementation, and evaluation of HHWT in emergency settings.

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The Role of Health in the Perception of Climate Risk: Panel Cohort Study

BACKGROUND

Public and political consensus does not exist involving the primary role of humans in climate change. *Years of Living Dangerously (Years)* aired its second season in the fall of 2016 on National Geographic to educate the public on climate change. This project is a national investigation of the impact of viewing the series on knowledge, attitudes, and behaviors.

METHODS

200 individuals were recruited from Amazon Mechanical Turk (nationally representative crowd-sourcing internet marketplace). Participants completed baseline surveys, watched the weekly *Years* episodes as they aired, completed weekly surveys, and a follow-up survey at 10-weeks. Eligibility criteria involved being over 18 and access to view the series through home cable programming. Data was analyzed through SAS.

RESULTS

A national sample of N=197 completed the baseline survey. 49.24% female, 49% married/cohabitating, 46% college graduates, and 49% Democrat, 20% Republican, and 24% Independents. At baseline, 84% believe that "problems associated with climate change will keep getting worse in the years to come" (agree or strongly agree).

Approximately, 53% never or very rarely have watched a documentary on climate change, global warming or similar topics. There also was statistically significant differences by political affiliation in the belief that the US can take "specific steps to reduce global climate change" ($\chi^2 = 45.07, p < .01$) and that citizens overall ($\chi^2 = 31.33, p < .01$) and they themselves ($\chi^2 = 27.09, p = .01$) could have a personal "significant impact on reducing the effects of global climate change".

At the final 8-weeks *Years* series, n = 160 completed the follow-up at 10-weeks baseline. Demographic characteristics remained consistent (74% were between the ages of 25-44). When asked if they learned a lot; 97.71% of Democrats, 81.25% of Republicans, and 83.33% of Independents strongly agree or agree. When asked if the series made them "realize that my actions matter when it comes to climate change"; 80.24% of Democrats, 50% of Republicans, and 60% of Independents strongly agree or agree.

CONCLUSIONS

This sample was in general, educated, politically diverse. Racial diversity was lacking. Political affiliation appears to come with, philosophical differences for some, differences in the perception of global, national, citizen, and individual roles and responsibilities. While, some differences do exist regarding those representing each political affiliation, the belief of impact and perception of knowledge remains statistically significant throughout all affiliations.

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Toxic Metals in Private Drinking Well Water and Urinary Tract Outcomes in North Carolina

We investigated the association between levels of inorganic arsenic, cadmium, lead and manganese in private well water, incidence of bladder and kidney cancer and end stage renal disease [ESRD] prevalence in 100 counties in North Carolina, a state that has among the highest proportion of well water consumption in the country.

Between 1998-2010, samples from private wells across counties were used to determine levels of inorganic arsenic, cadmium, lead and manganese (n=63,836, n=22,915, n=70,675 and n=65,535 measurements, respectively) and geocoded. Bladder and kidney cancer incidence for each county between 1990 and 2011 were obtained from the North Carolina Department of Health and Human Services. Prevalent cases of ESRD overall and subtypes were obtained from the US Renal Data System administrative data for all counties from 1991-2011. Counties with fewer than 11 cases or fewer than 10 well measurements for any metal were excluded from the analysis. County-level data on potential confounders were obtained from US Census Bureau data (2010) and the Behavioral Risk Factor Surveillance Study (2003, 2005). For each analyte, county-level mean concentration was calculated and divided into tertiles. We then used Poisson regression to estimate incidence rate ratio (IRR) for cancer outcomes and prevalence ratio (PR) for ESRD, 95% confidence interval (CI) between exposures and urinary tract outcomes, adjusting for age, gender, race, education, physical activity, smoking, diabetes, hypertension and residential well water supply using counties as the unit of analysis.

Altogether, there were 24,989 kidney cancer and 34,270 bladder cancer cases and 2,76,091 ESRD cases. Elevated IRRs for kidney cancer were observed for both the 2nd tertile (0.60-0.98 ppb: IRR=1.07 (95% CI 1.03, 1.11)) and 3rd tertiles (0.99-11.44 ppb: IRR=1.06 (95% CI 1.01, 1.10)) of inorganic arsenic. For arsenic and ESRD, the 3rd tertile 0.99-11.44 ppb, vs. the 1st tertile (0.50-0.59 ppb), the prevalence risk was observed to be 1.05 (95% CI, 1.04, 1.07) for ESRD overall, and elevated for subtypes: 1.06 (95% CI: 1.03, 1.08) for diabetic nephropathy, 1.46 (95% CI: 1.42, 1.50) for hypertensive nephropathy, and 1.17 (95% CI: 1.13, 1.22) for glomerulonephritis. A dose response was observed for kidney and bladder cancer incidence in manganese exposure but not for ESRD and ESRD subtypes. Higher levels of cadmium and lead moderately increased the incidence risk of bladder cancer only.

The conclusions are limited by the ecological approach, but the consistency of the associations suggests that the influence of metals, especially inorganic arsenic in private well water, on urinary tract outcomes deserves additional investigation.

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Agricultural Pesticide Exposure and Congenital Abnormalities (CA) in Mexico: A Systematic Review

BACKGROUND

Pesticides have been used in Mexico for different purposes including agricultural and malarial control. Exposure to pesticides has been associated with congenital abnormalities (CA). CA are a public health concern in Mexico and can adversely affect the health of infants, be a financial strain on families (especially those of low socio-economic status) and health systems. Fetuses are highly vulnerable to the effects of environmental toxins and newborns of those engaged in occupations using agricultural pesticides or those living near areas treated with pesticides are susceptible to CA. A growing number of studies have evaluated different factors that could play a role in the etiology of various CA associated with pesticide exposure.

OBJECTIVE

This systematic review intended to identify literature that addressed the relationship between parental exposure to agricultural pesticides via agricultural work or agricultural areas and CA among infants of Mexican parents. The systematic review sought to communicate the findings of the association and to identify the strengths and limitations of the identified literature to make recommendations for further research.

METHODS

Articles were identified using PubMed with secondary searches of Scopus, PubMed Central, ProQuest Environmental Science, Academic Search Complete, Popline and hand search of references of the identified articles.

RESULTS

Seven studies were identified that investigated the association between agricultural pesticide exposure and CA in Mexico. Six of the studies observed a positive association between pesticide exposure of parent(s) and CA; one of the studies found no association. Five of the studies investigated exposure to specific pesticide(s) and two investigated general pesticide exposure. Five of the studies relied solely on self-reporting for ascertainment of exposure and/or outcome. Two of the studies used more objective methods, such as biomarkers and clinical diagnosis for both the exposure and outcome of interest. Five of the studies investigated specific CA while two of the studies investigated CA generally.

CONCLUSION

The studies conducted to date were limited in the number that explicitly investigated the association between pesticide exposure among Mexican farmworkers and specific CA among their newborns. The current literature reviewed provided evidence to support the positive association between pesticide exposure and CA while demonstrating a need for improved exposure and outcome ascertainment. The strengths and weaknesses of the prior study designs and recommendations for how associations between pesticides and congenital abnormalities in Mexico can be investigated more rigorously will be presented.

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Evaluation of Exposure Assessment Methods Used to Quantify Occupational Exposure to Carbon Nanomaterials: A Systematic Review

OBJECTIVE

This systematic review sought to examine exposure assessment methods used to quantify occupational exposure to carbon nanomaterials (CNM).

BACKGROUND

As Engineered Nanomaterials (ENM) use in research, manufacturing, and production increases, occupational exposure to ENM particulate matter (PM) is also increasing.. Currently ENMs are being used in industries such as medicine, electronics, information technology, energy, homeland security, food safety, and environmental science among others. Many traditional occupational exposure assessment methods and sampling equipment may not be well suited to assess emissions and exposures on the nano scale. There is also concern that ENM emissions may not be well controlled via traditional engineering controls and personal protective equipment (PPE). To continue to grow the field while protecting worker health, it is imperative to develop appropriate exposure assessment approaches and methodologies that will allow the quantification of ENM exposure.

METHODS

Compendex, Inspec, Inspec Archive, GEOBASE, Knovel, and reference lists of included studies were searched. To be included, studies were required to be published in English, empirical in design, and focus on exposure assessment methods specific to CNMs.

RESULTS TO DATE

5 studies were identified using the before mentioned search strategy. The studies found that mobile aerosol direct reading alone might not characterize exposures well enough to be relied upon without the use of other equipment. Multiple exposure assessment techniques were used in conjunction to quantitatively assess CNM exposure. Multiwalled carbon nanomaterials (MWCNM) surface exposures were identified and quantified using assessment tools that are low cost and readily available.

CONCLUSIONS

With the proper techniques and equipment, occupational exposure to CNMs can be assessed and methods for control can be developed. There should be an effort to quantitatively and systematically assesses worker exposure to CNMs.

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Household Chemicals and Prostate Health: Serum Prostate Specific Antigen Levels and Urinary Benzophenone-3, Bisphenol A, and Triclosan Levels in Males: NHANES 2005-2010

BACKGROUND

Exposure to environmental phenols (e.g., bisphenol A, benzophenone-3, and triclosan) is widespread in the population. Many of these chemicals have been shown to have adverse effects on reproductive organs and hormones, both in vitro and in vivo.

OBJECTIVE

This study aimed to (1) provide descriptive information about prostate specific antigen levels and (2) examine the association of bisphenol A (BPA), benzophenone-3 (BP-3), and triclosan (TCS) with serum prostate specific antigen (PSA) levels in male participants (ages 40+ years) in the National Health and Nutrition Examination Survey (NHANES) 2005-2010.

METHODS

Geometric and weighted means, chi-square tests, and logistic regressions were used to provide descriptive information about PSA distribution in these male participants. Multivariable logistic regression was used to estimate associations between serum PSA level risk classification for prostate cancer (high and low) and levels of log-transformed and creatinine adjusted urinary BPA, BP-3, and TCS, in male participants.

(PRELIMINARY) RESULTS

BP-3 was associated with significantly higher likelihood of higher prostate specific antigen levels and prostatic cancer in males.

(PRELIMINARY) CONCLUSIONS

To the researcher's knowledge, this is the first study to produce a report on the distribution of PSA in the USA from NHANES. It also is novel in its report of an association of BP-3 with serum PSA in males. However, because of the limitations inherent to the cross-sectional study design, further studies are needed to confirm and elucidate on our findings.

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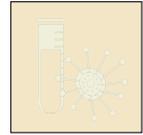
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Challenges in conducting research on sexual violence and HIV and methods to overcome them

BACKGROUND

Studies have implicated sexual violence as a potential correlate of HIV acquisition in women. Characterizing how violence affects the female immune system may provide insight into the biological mechanisms of HIV transmission and ultimately improve global HIV prevention strategies. Little research has been done in this domain, and the obstacles to investigation can be daunting. We describe methodological challenges encountered and solutions explored while implementing a study of dysregulation of immune biomarkers in pre- and postmenopausal women following sexual assault.

METHODS

We compared immune biomarkers indicative of HIV susceptibility between women who had experienced forced vaginal penetration during the preceding 12 weeks (cases) and women who had never experienced forced or coerced vaginal penetration (controls). Participants provided blood, cervicovaginal lavage and cervical swab samples for biomarker analysis at one or five visits, depending on study arm. In addition, some participants completed a computer self-administered interview at each visit.

RESULTS

From July 2014 to June 2016, we enrolled 24 cases (21 pre-menopausal and 3 postmenopausal) and 30 controls (25 pre-menopausal and 5 post-menopausal). Challenges included accessing and defining sexual assault survivors, ensuring participant well-being during research engagement, reducing selection and information bias, collecting and processing biological samples, and adjusting for confounders such as reproductive tract infections and emotional and physical abuse. Use of sensitive, mature, and highly trained research staff in conjunction with well-articulated community and medical partnerships were key methods to overcoming challenges while promoting the safety and welfare of vulnerable study participants.

CONCLUSIONS

Research into the relationships between sexual assault, immune biomarkers and HIV is possible though not without challenges. Moreover, many survivors of sexual assault welcome the chance to help other women at risk for violence. This field of research would benefit from the development of multi-site consortia, which would allow for the combined accrual of larger study populations to clarify the individual and interacting effects of various causal factors.

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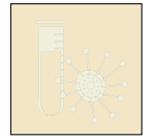
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Sex-Differences and Interactions in Head Injuries and Concussions among Collegiate Soccer Players: NCAA ISP, 2004-2009

INTRODUCTION

Some of the highest rates of head injuries and concussion among all contact/collision sports are observed in soccer; yet, the multifactorial determinants of head injuries among players remain relatively undefined. We extend previous analyses and examine sex-differences in the rate and the severity (concussion and lost days of participation) of head injuries among collegiate soccer players between 2004 and 2009.

METHODS

Data were analyzed from the National Collegiate Athletic Association (NCAA) Injury Surveillance Program (ISP). Multivariable logistic regression and negative binomial regression modeling tested the relation between sex and head injury outcomes, while controlling for contact, setting, and competition level, as well as their joint effects.

RESULTS

Between 2004 and 2009, the sex-specific rate of soccer-related head injuries was 0.87 per 1000 AEs in women and 0.71 per 1000 AEs in men (RR = 1.23, 95% CI = [1.08, 1.41]). The rate of head injuries due to player-to-player contact was comparable between women and men (RR=0.95, 95% CI=[0.81, 1.11]); however, the rate of injury due to contact with apparatus (ball/goal) was nearly 2 ½ -fold higher (RR=2.46, 95% CI = [1.76, 3.44]) and the rate due to contact with a playing surface was over two-fold higher (RR=2.29, 95% CI = [1.34, 3.91]) in women than in men. We also observed a significant joint effect between sex and contact in our regression models.

CONCLUSIONS

Among female players, head contact with a ball, a goal post, or the playing surface may be especially deleterious compared with head contact with another player.

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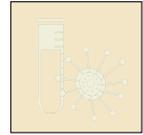
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Role of IL-21 in CD8 T cell response against *E.cuniculi* infection

Microsporidia are a group of obligate intracellular opportunistic parasites that induce a wide-range of pathology in immunocompromised individuals, including HIV-AIDS patients, organ transplant recipients, cancer patients and the elderly. Among the many species of microsporidia, at least eight can infect humans, but the pathogen is often underdiagnosed due to its small size and the need to be identified by specialized staining techniques. *Encephalitozoon cuniculi* is a microsporidia with one of the widest host ranges among mammals and has the ability to disseminate into multiple tissues. Due to the fact that it can be cultured in the laboratory, a majority of experimental studies have been conducted with *E.cuniculi*.

In a mouse model of *E.cuniculi* infection, robust CD8 T cell response manifested by strong polyfunctional characteristics (both IFN γ and cytolytic activity) is critical for host protection. Interestingly, the parasite does not induce a high inflammatory environment, and the CD8 T cell response elicited after oral/natural infection is independent of IL-2 and primarily driven by IL-21. Although importance of IL-21 is associated with B cell responses, this cytokine has also been reported to play a critical role in maintaining a robust CD8 T cell memory. We observed that in the absence of IL-21 signaling (IL-21R KO), effector CD8 T cell response to *E.cuniculi* infection was reduced both in terms of number and polyfunctionality. T follicular helper cells (TFH) are considered to be the major source of IL-21 and this CD4 T cell subset is critical for the formation of germinal centers, which is dependent on signaling lymphocytic activation molecule (SLAM)-associated protein (SAP) expression.

SAP knock out animals were used to study the role of this CD4 T cell subset in programming of effector CD8 T cell response against *E.cuniculi*. Intracellular staining analysis showed that TFH (ICOS^{hi}PD1^{hi} CD4 T cells) are the main producers of IL-21 during early infection. As compared to wild type animals, SAP^{-/-} mice exhibited lower IL-21 production at day 5-post infection. Interestingly, although the knock out mice exhibited increased short-lived effector CD8 T cell response (SLEC; KLRG1+CD127⁻) in terms of numbers, their polyfunctionality (IFN γ production and significantly impaired cytotoxicity) was reduced. Moreover, activation status of SAP deficient SLECs (based on CD43 staining), in comparison to cells from wild type mice was also decreased. These findings strongly suggest that early IL-21 production by TFH may be critical for optimal effector CD8 T cell immunity against *E.cuniculi* infection.

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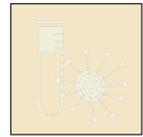
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Predictors of Post-Concussive Symptoms 12-months post-deployment in soldiers with and without mTBI: A Prospective Cohort Study

BACKGROUND

While it is believed that symptoms related to mild TBIs will improve within a few days or weeks in most cases, some may continue to experience troubling residual symptoms that have hidden costs such as disinhibited behavior and altered mood states. Traumatic Brain Injury research on OEF/OIF service members and veterans is advancing our understanding of mTBI, although the prognosis of post-concussive symptoms in these combat veterans remains uncertain.

METHODS

For this longitudinal analysis, we obtained data on returning soldiers who were screened for mTBI shortly after returning from deployment. TBI screening questions were based on DoD/ DVA, American Congress of Rehabilitation Medicine (ACRM) and Centers for Disease Control and Injury Prevention (CDC) criteria which require alteration in mental status following an injury event. Soldiers screening positive for mTBI (cases) were oversampled. Participants were evaluated at baseline, approximately 3 months (T1), approximately 6 months (T2), and approximately 12 months (T3) post-deployment. The roles of socio-demographic factors, military related factors, number of previous deployments, and TBI status at baseline on the trajectory of symptoms were evaluated. For the present analysis, the primary outcome measure was the endorsement of one or more severe/very severe symptom at T3, as assessed using the Neurobehavioral Symptom Inventory (NSI).

RESULTS

A total of 1567 soldiers participated in baseline interviews, of whom 631 (226 cases; 405 controls) completed 12-month interviews. TBI cases were twice as likely to report severe/very severe symptoms compared to non-TBI controls at twelve month (54.9% vs. 27.4%, $p < 0.001$). The most commonly reported symptoms (cases vs. controls) were sleep problems (33% vs. 15%), forgetfulness (27% vs. 10%), irritability (23% vs. 8%), headaches (17% vs. 9%), problems with concentration (16% vs. 6%), and fatigue (19% vs. 7%). TBI cases had more than doubled odds of 12-month NSI symptoms ($aOR = 2.39$, $p < 0.001$) after adjusting for demographic and military factors. Controlling for TBI, individuals who served in a combat position (combat MOS) were 1.5 times more likely to experience severe/very severe symptoms ($aOR = 1.5$, $p < 0.05$). Higher education ($aOR = 0.42$, $p < 0.05$) and officer ranks ($aOR = 0.60$, $p < 0.05$) were protective factors.

CONCLUSION

Findings indicate that among recently deployed service members, the majority of those who had sustained an mTBI during deployment reported clinically relevant NSI symptoms at 12-months. Symptoms were also reported by a large minority of those without mTBI.

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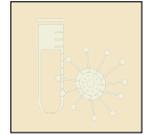
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Assessment of the Effectiveness and Durability of Weight Loss after Sleeve Gastrectomy and Gastric Bypass by Age Group

BACKGROUND

The CDC reports that rates of obesity across all age groups in the US range from 33% to 43%, however optimal treatment options may well be age-dependent. Effective treatment options such as metabolic surgeries (Bariatric Surgery) are often offered to patients to induce weight loss. Bariatric surgeries especially Laparoscopic Sleeve Gastrectomy (LVSG) and Roux-en-Y Gastric Bypass (RYGB) have been gaining more popularity compared to Gastric Banding (LAGB) as procedures for the treatment of obesity. However, the results of the three procedures have rarely been compared longitudinally in terms of effectiveness and durability by age groups, in large samples.

OBJECTIVE

The aim of the study was to compare age-stratified weight loss and maintenance for those who underwent LVSG, LAGB, and RYGB at 12, 24 and 36 months postoperatively.

METHODS

A convenience sample of 6,761 individuals, that underwent bariatric surgery at a community hospital in Baltimore, Maryland between 2001 and 2016, was studied to examine 12, 24 and 36-month, post-surgical trends in weight loss and maintenance using a mixed linear model [PROC MIXED]. Weight data were derived from follow-up patient visits and were not self-reported.

RESULTS

Between 61% and 62% of patients undergoing LAGB (N=1798), RYGB (N=3356), and LVSG (N=1607) were between 35-54 years of age, had mean baseline body mass indices between 43.9 and 48.4, and were more likely to be female (82%) and white (61%). Patients receiving RYGB had significantly higher BMIs on the day of surgery and significantly longer post-surgical hospital stays. Compared to baseline weight values the RYGB procedure induced weight loss similarly to LVSG at 12, 24 and 36 months for patients age 44 or less as evidenced by the overlapping confidence intervals. Patients age 45 or greater who had the RYGB procedure seemed to receive greater surgical benefit when compared to LVSG at 12 and 24 months and possibly at 36, although the sample size is relatively small. LAGB performed consistently and significantly worse for weight loss and maintenance across all age groups and at post-operative follow-up time points.

CONCLUSIONS/IMPLICATIONS

On average, after 12, 24 and 36 months of follow up, Roux-en-Y gastric bypass (RYGB) did not induce more significant weight loss than the LVSG procedure as has been previously reported. However, our data suggest that the RYGB may be more beneficial than LVSG for patients older than 44 years. A future study with enhanced follow-up data on more elderly subjects may demonstrate the superiority of the RYGB in this group. Trends of weight maintenance by procedure type and age group must also be examined at more extended time intervals to elucidate optimal age- and procedure-dependent efficacies.

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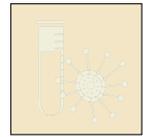
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MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH

Persistent Organic Pollutants and Mortality in the United States

BACKGROUND/OBJECTIVES

Persistent organic pollutants (POPs) are environmentally and biologically persistent chemicals that include polybrominated diphenyl ethers (PBDEs), per- and polyfluoroalkyl Substances (PFASs), polychlorinated biphenyls (PCBs), and organochlorine (OC) pesticides. Currently, there is limited data on the association between exposure to POPs and the risk of mortality in the general US population. The objective of this study was to determine if higher exposure to POPs are associated with greater risk of all-cause, cancer, heart/cerebrovascular disease, or other-cause mortality in persons aged 60 years and older.

METHODS

The analyses included participants aged 60 years and older from the 1999-2006 National Health and Nutrition Examination Survey (NHANES). A total of 483 subjects were included for analyses of PBDEs, 1428 for OC pesticides, 1043 for PFASs, and 461 for PCBs. Exposures to POPs were estimated using biomarkers measured in serum. Mortality status through December 31, 2011 was obtained from public-use, linked mortality files. We used adjusted Cox proportional hazard models to quantify the associations between POPs and all-cause and cause-specific mortality.

RESULTS

Serum measurements of PBDEs, PFASs, PCBs, and most OC pesticides were not clearly associated with increased all-cause, cancer, or heart/cerebrovascular disease mortality in the US elderly population in adjusted models. Beta-hexachlorocyclohexane was associated with an increased risk of all-cause mortality [HR=1.18, 95% CI=1.01, 1.38]. Oxychlorane [HR=1.15 95% CI 1.06, 1.25], p,p'-DDE [HR=1.12, 95% CI=1.02, 1.23], Trans-nonachlor [HR=1.11, 95% CI=1.04, 1.18], and Beta-hexachlorocyclohexane [HR=1.25, 95% CI=1.03, 1.52] were associated with increased risk of other-cause mortality. The associations were robust to adjustment.

CONCLUSION

Our study found higher exposure to four OC pesticides is associated with increased non-cancer, non-CVD mortality in adults 60 years or older in the US. The finding of adverse associations between OC pesticides and other-cause mortality will require confirmation in an independent dataset.

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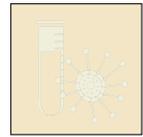
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MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH

Polytobacco Use Among Metropolitan and Non-Metropolitan Adolescents: A Latent Class Analysis

SIGNIFICANCE

In recent years, the number of tobacco products on the market has increased, as well as the number of youth reporting the use of more than one tobacco product (i.e., polytobacco use). Studies conducted in the past have shown differences in polytobacco use between demographic groups, such as sex and age. However, no studies have examined polytobacco use comparing metropolitan and non-metropolitan adolescents.

METHODS

Data from the 2014 Florida Youth Tobacco Survey were analyzed to assess patterns of tobacco product use by metropolitan and non-metropolitan youth. Participants who were in high school (grades 9-12) and aged 14-17 were included in the analysis (n=28,045). Rural-urban continuum codes used to classify residence.

RESULTS

Overall, 12% of participants reported polytobacco use in the past 30 days (n=3,300). Polytobacco use was more commonly reported among youth living in non-metropolitan than metropolitan areas (14.1% versus 10.3%; Chi-square=35.31, $p<0.01$). Latent class analysis was used to examine polytobacco use separately among metropolitan and non-metropolitan youth, controlling for sex, age and race/ethnicity. Past 30 day use of seven tobacco products were examined: (1) cigarettes, (2) chewing tobacco, snuff, or dip, (3) cigars, cigarillos, or little cigars, (4) bidis, kreteks, or tobacco in a pipe, (5) hookah, (6) snus, and (7) e-cigarettes. A five factor solution was identified as the best solution for both groups, but class structure and distribution across five classes differed by metropolitan status. For metropolitan youth, the main products that defined each class were (1) combustibles (35%), (2) smokeless tobacco (21.5%), (3) cigarette & e-cigarette (16.3%), (4) all products (13.8%), and (5) hookah and e-cigarettes (13.3%). In contrast, the main products defining the five classes for non-metropolitan youth were (1) cigars and hookah (31.6%), (2) hookah and e-cigarettes (28.3%), (3) cigarettes and e-cigarettes (16.7%), (4) all products (16.2%), and (5) cigarettes and cigars (7.2%).

CONCLUSIONS

Polytobacco use is more prevalent among non-metropolitan youth than metropolitan youth, and product use patterns vary among these two groups. Understanding how tobacco products are used together will be critical for the development of interventions designed to reduce polytobacco use. The present findings suggest that interventions to address polytobacco use among youth may need to be tailored to the different polytobacco use patterns by metropolitan status.

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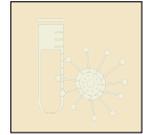
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Impact of Chronic Sexual Abuse and HIV on Genital Tract Biomarker Expression in Women

BACKGROUND

Sexual violence is associated with increased risk for HIV acquisition/transmission in women. Chronic exposure to sexual violence can result in genital tract trauma and psychosocial stress subsequently affecting immune functions. We hypothesized that women with chronic sexual abuse and depression would have dysregulated genital tract immune mediators that can affect HIV risk.

METHODS

Using the Women's Interagency HIV Study (WIHS) repository, we identified 4 groups of HIV+ and HIV- women (8-10/group) representing chronic sexual abuse exposure and depression (CES-D score > 16): 1) no history of sexual abuse at baseline or depression (Control); 2) no history of sexual abuse at baseline but current depression (Depression); 3) chronic sexual abuse but no depression (Abuse); 4) chronic sexual abuse with current depression (Abuse+Depression). Cytokines (IL-6, IL-8, IL-1 α , IL-1 β , TNF- α , TGF- β), chemokines (MIP-3 α , IP-10, MCP-1) and antimicrobials (Secretory leukocyte protease inhibitor (SLPI), Elafin, and Human beta defensin 2 (HBD-2)) were analyzed in cervical vaginal lavage (CVL) samples using ELISA. Linear regression was used to model levels of biomarkers with both depression and abuse as predictors. Models were run separately for HIV+ and HIV- women, with CD4 counts and viral load as covariates for HIV+ group.

RESULTS

In HIV- women reporting Abuse+Depression we found significantly higher levels of IP-10 compared to Control and Depression groups. Abuse+Depression group also had significantly higher levels of IL-1 α but significantly lower levels of TGF- β , compared to Depression group. In HIV+ women, significantly lower levels of MIP-3 α were found in the Abuse+Depression group compared to Controls whereas MCP-1 levels were highest in the Abuse group. When comparing by HIV status, HIV+ women reporting depression had significantly higher levels of IP-10 compared to HIV- women reporting depression. MCP-1 levels were significantly higher in HIV+ Abuse group compared to HIV- Abuse group. However, for MIP-3 α , levels were significantly lower in HIV+ Abuse+Depression compared to HIV- Abuse+Depression. In HIV- women, there was evidence of an interaction between abuse and depression for IL-1 α and IP-10.

CONCLUSIONS

Our data suggests genital immune biomarkers are affected by chronic sexual abuse and HIV status. Further studies are needed to understand biological mechanisms of HIV acquisition/transmission in these women.

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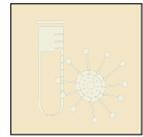
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Cardiovascular Risk Factors among Persons Receiving Housing Rental Assistance in the U.S., 2006-2012

BACKGROUND

High blood pressure, obesity, and diabetes are among the major risk factors that lead to cardiovascular disease (CVD), the leading cause of death in the U.S. There is little available information about how the prevalence of CVD risk factors differs among low-income persons receiving housing rental assistance compared to those unassisted, and whether housing assistance positively impacts health outcomes.

METHODS

The National Center for Health Statistics and the U.S. Department of Housing and Urban Development linked administrative data with health survey data from the National Health Interview Survey. This study sought to analyze select cardiometabolic CVD risk factors, including hypertension, diabetes, and obesity among a national sample of HUD assisted low-income renting adults 2006-2012 (n=2,834) compared to unassisted low-income renting adults (n=7,166).

RESULTS

HUD assisted low-income renting adults have 25% greater odds (AOR=1.25 [95% CI 1.034, 1.522]) of having ever been told by a healthcare provider they have diabetes, 10% greater odds (AOR=1.10 [95% CI 0.943, 1.272]) of being told they have hypertension, and 27% greater odds (AOR=1.27 [95% CI 1.101, 1.462]) of being obese (BMI \geq 30) than the unassisted adults, controlling for sociodemographic characteristics.

CONCLUSIONS

HUD assisted low-income renting adults have greater odds of having ever been told by a doctor they have the selected CVD risk factors, offering insight into the chronic health condition of households receiving HUD assistance and suggesting further research on the uniqueness of individuals who receive HUD assistance.

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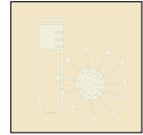
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Impact of Sexual Violence on Chemokines in the Female Genital Tract: Risk of HIV acquisition

Sexual violence is a known risk factor in HIV acquisition and transmission, and may cause dysregulation of genital immune microenvironment. IP-10, MCP-1 and MIP-3 α are chemokines that act as chemo-attractants for macrophages and T-cells. Since macrophages and T-cells are targets for HIV, increase in these chemokines may lead to an increased risk of HIV infection in women experiencing sexual violence.

Cases were defined as women who had experienced non-consensual vaginal intercourse in the last 3 months (n=42) and controls, defined as women who had no history of sexual violence, were recruited from the local Washington DC community (n=63). Cervical-vaginal lavage (CVL) samples were collected by washing the cervical-vaginal tract with 10 mL of sterile saline. Premenopausal women were asked to return 4 more times over 8 weeks to collect information about their menstrual cycle. Post-menopausal women were asked to return as well to match premenopausal women. Samples were analyzed by standard Enzyme Linked Immunosorbent Assay (ELISA) (R&D Systems) for three chemokines, MCP-1, IP-10, and MIP-3 α according to manufacturer's protocol. Data was analyzed using GraphPad Prism (version 5.04) and SAS version 9.4. Multiple visits were treated as distinct records for analysis.

We observed MIP-3 α to have significantly lower levels ($p < 0.0001$) in Cases compared to Controls. In addition, MIP-3 α levels were also affected by menopausal status showing significantly lower values for both premenopausal Cases ($p = 0.0004$) and post-menopausal Cases ($p = 0.0147$) relative to their respective Control groups. The results from MCP-1 was different, showing a significantly ($p = 0.0196$) lower concentration in Cases compared to Controls. Stratifying by menopausal status, we found significantly lower levels of MCP-1 in post-menopausal Cases ($p = 0.0297$). We also found that MCP-1 levels were decreased among pre-menopausal Cases but these results were not statistically significant. Analysis of IP-10 levels in CVL revealed no statistically significant differences in between Cases and Controls or between premenopausal and postmenopausal status.

Our results indicate that sexual violence may cause immunological changes in the genital tract microenvironment in a manner that might enhance risk of HIV infection. All three chemokines that we analyzed function to attract T-cells and macrophages to an area of localized inflammation caused by damage to tissues or infection. Additionally, menopausal status might alter the immune environment further and therefore should be considered in studies involving women's health and HIV.

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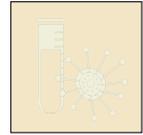
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MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH
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Preliminary Analysis of Risk Behaviors and Risk Reduction Strategies among Newly Diagnosed and Viremic Persons Living with HIV (PLWH) in Washington, DC

BACKGROUND

While high risk behaviors among PLWH contribute to onward transmission of HIV, it is well-documented that knowing one's HIV status can lead to risk reduction behaviors including disclosure, reducing the number of sexual partners, sero-sorting, and consistent condom use. Washington, DC has a high HIV prevalence of 2%, thus understanding the sexual risk behaviors of PLWH may help inform future interventions to interrupt transmission.

OBJECTIVE

To describe the sexual risk behaviors and risk reduction strategies of recently diagnosed PLWH in DC compared to those chronically infected but with detectable virus.

METHODS

The DC Cohort is a longitudinal observational cohort study of PLWH receiving care at 14 clinical sites in DC. As part of a Molecular Epidemiology sub-study, Cohort participants who were either diagnosed in the 12 months prior to their enrollment or viremic (>1500 copies/mL) as of their most recent viral load test were eligible. This analysis focused on data from the sub-study cross-sectional behavioral survey. Univariate analyses using chi-square and Wilcoxon rank sum tests were conducted to describe participants and examine differences between recently diagnosed and viremic participants.

RESULTS

Of the 91 participants enrolled to date, 33% (N=30) were recently diagnosed; 67% (N=61) were viremic. Viremic participants were diagnosed a median of 15 years, were more likely to be older (51 vs. 34 years), heterosexual (62% vs. 27%), Black (92% vs. 60%), and have acquired HIV through heterosexual contact (46% vs. 17%); ($p<.05$ for all). Overall, 63% of participants were sexually active in the past 12 months (mean number of partners: 6). Over half (54%) had disclosed to their most recent partner, 24% of whom were also HIV+, and 25% of whom were reportedly taking pre-exposure prophylaxis (PrEP). More recently diagnosed participants had unprotected sex during their last sexual encounter (47% vs. 23%, $p=0.02$) and more recently diagnosed MSM used condoms inconsistently during anal sex with their most recent partner (91% vs. 50%, $p=0.05$) compared to viremic participants. More viremic participants reported always using condoms with each sexual partner (53% vs. 30%, $p=.04$), and refraining from anal sex (33% vs. 20%, $p=.01$) as risk reduction strategies compared to recently diagnosed participants.

CONCLUSIONS

Despite a relatively high number of sexual partners, modest disclosure rates, and inconsistent condom use, differences in risk behaviors and risk reduction strategies between recently diagnosed and viremic participants were observed. Primary and secondary prevention interventions focused on consistent condom use and PrEP should be emphasized.

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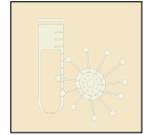
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EPIDEMIOLOGY AND BIostatISTICS



MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH

Make Big Data Alive: Interactive Data Visualization in Metabolomics Research

Metabolomics research has rapidly evolved in recent years. In this data-intensive field, effective and simple data visualization tools empower researchers to present the big data in a meaningful way that people can quickly understand and use. Compared with traditional static graphics and tables, interactive visualization takes the concept a step further by allowing self-service faceting, probing and drill down.

We developed several interactive data visualization applications for metabolomics research using Shiny by RStudio coupled with R packages ggvis and plotly. The applications present information including quality control and regression analysis of more than 3000 metabolites in thousands of different models. Results are conveyed both in data tables and statistical graphs. Data tables contain complete information and are downloadable. In statistical graphs, users are allowed to view pointwise values using mouse-over controls, to drill down for detail through zooming, to compare and contrast the models and to display subsets of results by filtering on p-values, treatment groups, model adjustments, metabolites classes or even selecting an individual metabolite. The application can be published on websites to allow public or secure (authenticated) access and share with others. The above features of these Shiny applications enable a self-service, meaningful and flexible way to review and communicate data.

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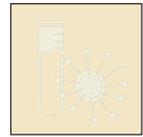
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The Economic Burden of Malaria Cases Imported from Hispaniola to other Non-Endemic Countries in the Western Hemisphere (2007- 2013)

BACKGROUND / OBJECTIVES

Hispaniola is the only island endemic for malaria in the Caribbean region. Widening income disparity and natural disasters have hindered malaria control. Routine travel between Hispaniola and other non-endemic countries in the western hemisphere could pose a risk for the re-introduction of malaria in non-endemic countries. Given the paucity of information on the cost of imported cases to non-endemic countries in the Americas, this study sought to estimate the cost and evaluate the economic burden of malaria cases imported from Hispaniola to non-endemic countries in Americas.

METHODS

Epidemiologic data on imported malaria cases came from reports from the US Centers for Disease Control and Prevention, Public Health Agency of Canada, the Canadian Malaria Network, the World Health Organization and the Pan American Health Organization. Calculation of costs per disability adjusted life-year (DALY), were based upon the WHO burden of disease estimates of DALY loss due to malaria in non-endemic countries in Americas, and the costs of diagnosis and treatment of malaria.

RESULTS

During 2007-2013, the estimated number of malaria cases, imported from Hispaniola, to non-endemic countries in North America ranged between 30 and 192. Disease management costs varied between \$100,018 and \$1,229,320; the Cost/DALY range was \$121,377 to \$1,079,557. Between 2011 and 2013, 24 cases from Haiti reported in non-endemic Caribbean Islands; they cost \$53,076, with no loss of DALY reported.

CONCLUSION

Understanding the economic and human impact of malaria on endemic countries as well as on their non-endemic neighbors helps strengthen the case for worldwide malaria elimination.

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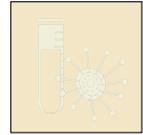
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Genitourinary Paraganglioma: Demographic, Pathologic, and Clinical Characteristics in the Surveillance, Epidemiology, and End Results (SEER) Database (2000-2012)

BACKGROUND

Extra-adrenal paragangliomas (PGL) are infrequent, benign, neuroendocrine tumors arising from chromaffin cells of the autonomic nervous system. Most PGLs are sporadic but up to 32% are associated with inherited syndromes such as neurofibromatosis type 1, von Hippel-Lindau disease, and familial PGL. While most PGL develop above the umbilicus, they have been reported in the genitourinary (GU) tract. Due to the paucity of literature on the rates of GU PGL, the objective of our study is to describe the demographic, pathologic, and clinical characteristics of GU PGL, and compare them to non-GU sites of PGL using the Surveillance, Epidemiology, and End Results (SEER) database.

METHODS

The SEER 18 database was utilized to identify all cases of PGL from 2000-2012. Demographic, pathologic, and clinical characteristics were described using chi-square and t-test for categorical and continuous variables, respectively. The Kaplan-Meier method was used to compare overall survival between GU and non-GU PGL. Statistical significance was defined as $p < 0.05$. All analyses were performed using excel and SAS/Stat version 9.4.

RESULTS

299 cases of PGL were retrieved from SEER. 20 (6.7%) of the total PGL arose from the GU tract. The mean age at diagnosis was higher in non-GU than GU PGL (50.4 ± 17.2 vs 40.8 ± 15.6 , $p = 0.026$). 83.3% of GU PGLs developed in the bladder, followed by the kidneys/renal pelvis (16.7%), and spermatic cord (2%). Non-GU PGL developed most frequently within the endocrine system (43%). PGL, overall, was more common in men than women, and it was more common in whites than all other races. While 50% of GU PGL was organ confined, only 5.7% of non-GU PGL was localized at diagnosis. All cases of PGL were treated with surgery. There were 2 (10%) cause-specific deaths in the GU PGL groups from 2000-2012. 5-year overall survival was 93.3% for GU PGL versus 65.5% in non-GU PGL ($p = 0.062$).

CONCLUSIONS

Genitourinary PGL remains rare, with low incidence (6.7% of all PGL cases) in the US population between 2000 and 2012. Also, it had better 5-year overall survival compared to PGL developing outside of the GU tract. The bladder represents the most common site of involvement and surgery is the mainstay of treatment for GU PGL. Clearer prognostic factors are needed to better elucidate PGL management in the future; thus, pooled studies from various institutions with detailed clinical information are needed to delineate these prognostic factors.

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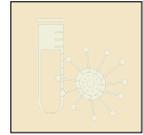
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Understanding Fetal Immune Responses to Congenital Porcine Reproductive and Respiratory Syndrome Virus Infection

Porcine Reproductive and Respiratory Syndrome (PRRS) is one of the most economically significant diseases in the global swine industry, causing approximately \$600 million annually in productivity losses in the United States alone. While this virus can cause a respiratory infection, it can also cross through the maternal endometrium and fetal placenta during late gestation and cause congenital infections and fetal death. Studying the extent to which the disease affects growing fetuses has been difficult because it is variable between gilts (a young female pig who has not had a litter) and between fetuses in her litter. Few studies have previously explored the immune pathways that alter fetal PRRS resistance/ susceptibility. We used a model where 3rd trimester pregnant gilts were euthanized at 2, 5, 8, 12, or 14 days post infection (DPI) with PRRS virus (PRRSV). Samples from the fetal thymus and placenta, and maternal endometrium were collected and viral loads measured (U Saskatchewan) to determine when the virus crosses the placental barrier and the level of PRRSV infection in each tissue. Fetal RNA was extracted with a Qiagen RNA Isolation kit, and gene expression was determined using a 230-gene swine immune NanoString array to evaluate differential expression (DE) of genes and biomarkers previously predicted to alter PRRS resistance and susceptibility. Biomarkers included measures of innate immunity, interferon signaling, B and T cell receptors, cell division, apoptosis, tissue remodeling and epithelial integrity, based on pathways identified using Ingenuity Pathway Analysis. Neighboring fetuses from PRRSV infected gilts from the same DPI but with different infection statuses and viral levels will be compared to determine DE genes between fetuses, litters and across DPI. Data should reveal immunological pathways that contribute to fetal susceptibility or resistance. Understanding these mechanisms will benefit future research dedicated to exploring targeted approaches to halt the congenital spread of this disease.

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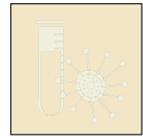
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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Ranking States on Adolescent Coverage with Cancer-Preventing Vaccines: The influence of Imprecision

PURPOSE

Identifying the “best” and “worst” states for coverage with cancer-preventing vaccines (hepatitis B [HepB] and human papillomavirus [HPV]) may guide public health officials in developing programs, such as promotion campaigns. However, acknowledging the imprecision around performance ranks is important for avoiding over-interpretation.

METHODS

Data on coverage of HepB and HPV vaccines among 13- to 17-year-old adolescents came from 2011-2015 National Immunization Survey-Teen (n=103,729 from 50 states and Washington D.C.). We calculated coverage, 95% confidence intervals (CI's), and ranks for vaccination coverage in each state, and generated simultaneous CI's around ranks through a Monte Carlo method with 100,000 simulations.

RESULTS

Across years, HepB vaccination coverage was 92% (95% CI=92-93%; states' range: 84-97%). HPV vaccination coverage was 57% (95% CI=57-58%; range: 42-78%) for girls and 31% (95% CI=30-32%; range: 19-59%) for boys. States with the highest and lowest ranks generally had narrow CI's; for example, Rhode Island was ranked 1st (95% CI=1-1) and Kansas was 51st (95% CI=49-51) for girls' HPV vaccination. However, states with intermediate ranks had wider and more imprecise CI's; for example, New York was 27th for girls' HPV vaccination coverage, but its CI included ranks 18-35.

CONCLUSIONS

Coverage varied considerably by vaccination and by state. States' ranks of coverage of cancer-preventing vaccines were imprecise, especially for states in the middle of the range; thus, performance rankings presented without measures of imprecision could be over-interpreted. However, ranks can still highlight especially high- and low-performing states to target for further research and vaccination promotion programming.

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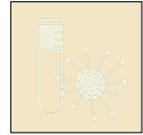
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EPIDEMIOLOGY AND BIostatISTICS



MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH

Designing a Targeted NGS Approach for Detecting Drug Resistant Mutations (DRMs) in HCV.

Hepatitis C virus (HCV) primarily affects the liver, if left untreated it can result in liver cancer or cirrhosis. HCV is a major public health concern and one of the few notifiable diseases in which mortality rate is still on the rise, especially in adults 50 years and older. A large percentage of infected individuals are unaware of their status. According to the Centers for Disease Control and Prevention there were over 30,500 new cases of HCV in the US in 2014, and an estimated 2.7-3.9 million individuals who are chronically infected.

Since 2011, treating HCV infections has become more effective with the introduction of a class of drugs called Direct Acting Antivirals (DAAs). DAAs target four specific nonstructural (NS) proteins: NS3/4A protease inhibitor (PIs), NS5A inhibitor, NS5B nucleoside polymerase inhibitor and non-nucleoside polymerase inhibitors. Currently the Food and Drug Administration has 10 approved DAAs for managing HCV. However, ~10-15% of individuals infected with HCV genotype 1, who have no history of exposure to NS5A inhibitors, are found to have detectable levels of HCV NS5A resistance-associated variants.

To address this concern and our desire to assess HCV DRMs, we designed HCV-specific PCR primer sets targeting 25 DRMs in 3 gene regions: NS3/4A (836 bp; 8 DRMs), NS5A (1032 bp; 5 DRMs) and NS5B (1460 bp; 12 DRMs). These primer sets recognize both HCV 1a and 1b subtypes, is the most prevalent genotype here in the US.

Ten de-identified HCV positive plasma samples (7; HCV 1a and 3; HCV 1b genotype) were used as controls in developing our targeted Next Generation Sequencing (NGS) approach. The viral load of these samples ranged from 3,067,577-12,502,372 copies/mL (mean; 5,823,201). After RNA extraction and cDNA synthesis, the 3 different HCV-specific primer sets were used to amplify NS3/4A, NS5A or NS5B regions. The sizes of the PCR amplicons were confirmed by gel electrophoresis, and concentrations determined using Qubit technology. DNA libraries were prepared using Nextera XT library preparation kit and the pooled libraries sequenced using MiSeq V2 chemistry (150x2). Data analysis on *fastq* files was carried out using CLCbio genomics workbench. Reference genomes were HCV 1a; EU256002 and HCV 1b; EU482883. Basic variant DRM analysis was completed for the 10 samples.

In conclusion, the results of this study illustrate our success in designing a targeted NGS approach for HCV sequencing across 3 regions encompassing 29 DRMs that will be useful tool for HCV molecular surveillance studies.

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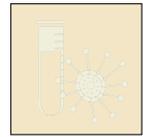
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CHILDREN'S NATIONAL MEDICAL CENTER

Clinical and Demographic Factors Associated with Emergency Medical Services Arrival to a Pediatric Emergency Department

OBJECTIVE

To examine demographic and clinical factors associated with emergency medical services (EMS) use in a pediatric emergency department (PED).

METHODS

We performed a retrospective cross-sectional review of encounters with patients aged 0-21 years during calendar years 2014-2015 in an urban academic PED with two campuses, a tertiary-care site and an urban satellite community site. Encounters with patients arriving by interfacility or police transport were excluded. Acuity was classified by Emergency Severity Index (ESI). Chi-square and logistic regression were used to analyze associations between demographic and clinical factors and EMS arrival.

RESULTS

There were 220,792 eligible encounters over a 2 year period, with 15,605 encounters arriving by EMS (7.1%). In bivariable analysis, patients arriving by EMS were more likely to have encounters involving seizure (OR 10.19; 95%CI 9.55-10.87), poisoning (OR 6.22; 5.51-7.03), psychiatric concerns (OR 2.05; 1.87-2.27) and injury (OR 1.86; 1.79-1.92). In multivariable analysis of demographic factors, EMS arrival was associated with gender (aOR 0.85; 95%CI 0.80-0.89 for females) and older age (aOR 0.75; 0.69-0.82 for infants, aOR 0.64; 0.60-0.68 for ages 1-4, and aOR 0.72; 0.67-0.77 for ages 5-11 compared with ages 12-21). The odds of EMS arrival for Hispanic patients was lower (aOR 0.59; 0.55-0.64) and for non-Hispanic white patients was greater (aOR 2.0; 1.86-2.19) than the odds EMS arrival for non-Hispanic black patients. These demographic associations were not significant in analysis of the highest acuity patients.

Patients with public insurance had decreased odds of EMS arrival (OR 0.80; 0.77-0.83) but no significant difference after adjusting for acuity. Subgroup analysis showed patients living within the surrounding city limits with public insurance had increased odds of EMS arrival (aOR 1.30; 1.18-1.43) after adjusting for acuity. Patients arriving by EMS had increased odds of admission (OR 3.33; 3.18-3.45) and this remained true in the subgroup of lowest acuity patients, ESI levels 4-5 (aOR 2.44; 2.07-2.92).

CONCLUSION

Pediatric encounters for seizure, ingestion, psychiatric concerns, and injury are more likely to utilize EMS. Odds of EMS arrival to PED varies with age, gender, and race. Associations between public insurance and EMS use may vary with proximity to the hospital or jurisdiction.

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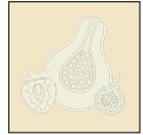
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EXERCISE AND NUTRITION SCIENCES



SCHOOL OF NURSING

A Retrospective Analysis of Surgeon Estimated Time and Actual Operative Time to Develop an Efficient Operating Room Scheduling System

PROBLEM

Surgical departments account for sizable budgets in hospitals. To ensure efficiency, optimal processes need to be maintained. The current practice for posting a surgical case is using surgeon estimated times (SETs), which only includes the reporting points of component 2 (C2) "incision" to "dressing."

OBJECTIVE

To analyze if there was a significant difference in minutes between actual operative times (AOT) and SET in patients undergoing outpatient general laparoscopic and inpatient orthopedic total joint surgery.

METHODS

The facility is a level one trauma teaching center, with 371 beds, and a yearly surgical volume of 17,000 cases. This retrospective study used random sampling to compare and analyze the difference between AOT and SET, as well as actual operating room time (AORT): component one (C1) - "patient in OR to before incision" and component 3 (C3) - "after dressing to patient out of OR." With a statistical power level of 0.8%, an alpha of 0.05%, a sample size of 120 surgical patients from each category was included.

RESULTS

In hypotheses testing for outpatient general laparoscopic and inpatient orthopedic total joint patients, the results indicated that SET time (mean=105.8, \pm 31.6; mean=147, \pm 36.4) in minutes was significantly greater than the AOT times (mean=75.5, \pm 30.6; $p=0.001$; mean=111.5, \pm 23.4; $p=0.0001$) in minutes, respectively.

CONCLUSIONS

The results uncovered a significant variance between AOT and SET suggested over booking; whereas in AORT and SET, results suggested under booking. An interdisciplinary team will be assembled to develop an efficient scheduling system.

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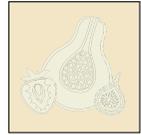
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MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH

The Joint Effects of Sedentary Time and Physical Activity on Mobility Disability Risk in Older People: NIH-AARP Diet and Health Study

PURPOSE

To determine the level of physical activity necessary to minimize the deleterious effects of large amounts of sitting on risk of mobility loss in an aging cohort.

METHODS

We analyzed prospective data from 134,269 participants (age 50-71 years) in the NIH-AARP Diet and Health Study between 1995-1996 and 2004-2005, who reported no major chronic diseases and rated their health as fair or better at baseline. Total sitting time (h/day), TV viewing time (h/d) and light- and moderate-to-vigorous-intensity physical activity level (h/week) were self-reported at baseline, and mobility status at follow-up was defined by perceived walking speed. Multivariable logistic regression modeling determined the independent and joint effects of sedentary time and total physical activity on risk of mobility disability (unable to walk or walks at easy speed).

RESULTS

At follow-up, 38,798 participants (29%) were defined as having a mobility disability. After adjustment for light- and moderate-to-vigorous intensity physical activity, as well as for important covariables, the independent impact of total sedentary time was almost negligible, whereas disability risk increased in a dose-response manner with increasing category of TV time ($p < 0.001$), sitting 6 or fewer h/day was not related to excess risk of mobility disability, and those in the most active group who reported the highest level of sitting time (≥ 7 h/day) still had a significantly lower risk (OR=1.11; 95%CI=1.02, 1.20) compared with those reporting the lowest level of sitting (< 3 h/day) in the least active group (≤ 3 h/week; OR=2.07; 95%CI=1.92-2.23). In contrast, increased TV time was significantly related to increased mobility disability within all levels of reported physical activity—and this risk was accelerated in the least active participants.

CONCLUSION

Reductions in sedentary time, combined with increases in physical activity may be necessary to maintain health and function in older age—particularly among those who are the least active.

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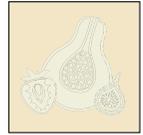
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EXERCISE AND NUTRITION SCIENCES



SCHOOL OF MEDICINE AND HEALTH SCIENCES

Nutrition in Medical Education: Where Do We Stand and What Needs to be Explored?

INTRODUCTION

Dietary interventions and nutrition care improve patient outcomes and reduce healthcare costs. Despite status as a necessary topic in medical school education, many U.S. medical schools do not adequately prepare future physicians for everyday nutritional challenges in clinical practice. There is immense research behind the necessity of nutrition education but little concerning the methods of implementing this change. The purpose of this work was to review the current innovations of nutrition curriculum in the literature and discuss future directions for our medical school.

METHOD

A systematic search of scientific literature databases was performed to examine existing literature about the current state of nutrition curriculum and identify current methods of improving nutrition curriculum. A database search of the undergraduate GW SMHS curricula helped us map where nutrition is currently taught and look into ways to expand and integrate it.

RESULTS

Shortcomings in sufficient nutrition education result from lack of proficient faculty, low funding, and lack of established core curricula with guidelines and protocols. Additionally, international medical schools have recognized their deficiency in nutrition education compared to U.S. standards. U.S. institutions making headway in new nutrition education programs include The University of North Carolina, Chapel Hill, Boston University School of Medicine, Southern Illinois School of Medicine, University of Nevada School of Medicine, Northwestern University Feinberg School of Medicine, University of Colorado School of Medicine, Mercer University School of Medicine, and various institutions introducing “culinary medicine.” Successful nutrition integration should be spread longitudinally across all years with an emphasis on active-learning techniques over rote memorization. Creativity, chief support, an established taskforce, trained faculty, and evaluation methods are essential tools to enhance medical curriculum. Looking at GW SMHS curricula, nutrition is concentrated in the Pre-Clinical years with very little emphasis in the Clinical years, a common trend across most medical schools. Medical students may be more confident incorporating nutrition into patient care if nutrition were spread proportionally across all years to combine basic foundations with clinical application.

CONCLUSION

Expanding nutrition curriculum at The George Washington University School of Medicine could involve utilizing the Nutrition in Medicine project developed by The University of North Carolina, Chapel Hill or bringing in internationally renowned chef José Andrés to expand on his previous culinary courses and incorporate nutrition fundamentals into the medical curriculum. Future directions need to evaluate existing programs, current initiatives, and their effectiveness in order to be able to improve programs across the continuum.

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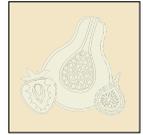
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EXERCISE AND NUTRITION SCIENCES



SCHOOL OF MEDICINE AND HEALTH SCIENCES

Perceptions and Consumption of Sugar-Sweetened Beverages among Medical Students at the George Washington University

OBJECTIVE

Consumption of sugar-sweetened beverages (SSB) is associated with a variety of negative health outcomes, including diabetes and obesity. Healthcare providers have the opportunity to educate patients regarding their dietary habits, including reducing sugar consumption, for the prevention and management of chronic disease. Because nutritional coursework is not standardized across medical school curriculums, students likely have varying beliefs regarding the role of SSB in a healthy diet, as well as health outcomes associated with their consumption. Furthermore, there may exist a discrepancy between students' beliefs about SSB and their actual consumption practices. The purpose of this study was to survey medical students at the George Washington University (GWU) in order to gain insight into perceptions of SSB within the medical community and how this may relate to their own SSB consumption.

METHODS

All procedures were approved by the Institutional Review Board at GWU prior to beginning data collection. Two-hundred and forty GWU medical students were recruited via email and completed a five-part questionnaire, which was developed in order to assess various aspects of SSB consumption. These included (1) types, frequency, and volume of SSB consumed, (2) preferred location to purchase SSB, (3) motivation for consuming SSB, (4) habits regarding SSB consumption, and (5) beliefs surrounding SSB consumption and associated health outcomes.

RESULTS

Of 240 students, over half (58%) reported drinking at least one SSB per week. Fifty-nine percent indicated that they "strongly agreed" with the statement that "SSB consumption is associated with diabetes," while 3% of respondents indicated that they were "uncertain" with regards to this statement. Thirty-five percent indicated utilizing campus vending machines to purchase SSB, compared to 53% who indicated purchasing SSB from campus eateries, and 63% who indicated drinking SSB when free at on-campus events. Thirty-eight percent of respondents expressed interest in seeing a decrease in SSB offered in campus vending machines.

CONCLUSIONS

Although SSB consumption is prevalent among GWU medical students, over one-third of participants expressed support for decreasing access to sugary drinks on campus. This calls attention to an apparent 'disconnect' between awareness of the adverse health consequences associated with SSB intake and individual behavior change, even in this health literate population. Further research will aim to understand the driving factors underlying SSB consumption among medical students in order to identify effective strategies for reducing their consumption.

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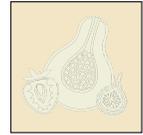
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EXERCISE AND NUTRITION SCIENCES



MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH

Statistical modeling of musculoskeletal ultrasound images reveals correlates of age-related muscle performance

BACKGROUND

Musculoskeletal ultrasound (MUS) is an inexpensive method to assess age-related changes in muscle tissue composition. Statistical modeling of MUS image data is relatively unexplored and may reveal correlates of muscle function and quality. The primary objective of this study was to determine how well several statistical models fit MUS image data. The secondary objective was to assess the association between model parameters and muscle performance in young and older adults.

METHODS

Seventeen young (age = 24 yrs. \pm 2) and seventeen older (age = 65 yrs. \pm 7) adults enrolled in the study. Ultrasound scans of the rectus femoris muscle were obtained using B-mode MUS with a 13-6 MHz linear array transducer. For each scan, grayscale data were extracted from a region encompassing the muscle, and parameters for the normal, Poisson, and negative binomial distributions were estimated. Theoretical data were generated from parameter estimates, and R^2 values were computed to assess agreement between grayscale and theoretical data. A one-way ANOVA was used to test for differences between each statistical model and F-tests were performed to compare goodness-of-fit. Muscle performance was measured with a hand dynamometer, and correlation analysis was conducted to determine the association between hand grip strength and parameter estimates.

RESULTS

Mean R^2 values were similar between the negative binomial ($R^2 = 0.93 \pm 0.06$) and normal ($R^2 = 0.84 \pm 0.10$) distributions ($p = 0.141$) and both demonstrated good agreement with grayscale data. The Poisson distribution had poor agreement ($R^2 = -0.34 \pm 0.60$) was dissimilar to the other models ($p < 0.001$), and was excluded from further analysis. Fit between grayscale and theoretical data was statistically better using the negative binomial distribution compared to the normal distribution for all ultrasound scans (mean $F_{253,253} : 2.70 \pm 1.10$, $p < 0.0001$). Hand grip strength was strongly associated with negative binomial dispersion parameter estimates in older ($R^2 = 0.80$), but not young ($R^2 = 0.17$), adults. Mean grayscale values were moderately associated with hand grip strength in both young ($R^2 = 0.39$) and older ($R^2 = 0.39$) adults.

CONCLUSIONS

MUS data are best modeled by the negative binomial distribution, and dispersion parameter estimates could be used to assess loss of muscle quality with age. Future work is needed to determine whether dispersion parameter estimates are associated with measures of muscle quality attained using other imaging modalities and to explore if our findings generalize to other muscle groups.

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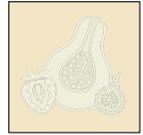
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MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH

Prevalence of Low-calorie Sweetener Intake in South Asian Adults

The consumption of low-calorie sweeteners (LCS), commonly found in diet beverages, reduced-sugar foods, and tabletop packets, has increased rapidly over the past decades in the general United States (US) population, and has been found to be associated with increased cardiometabolic risk. However, no data exist regarding the prevalence of LCS consumption among South Asians, one of the fastest growing ethnic groups in the US. We therefore conducted a cross-sectional analysis to determine the prevalence of LCS use in a community-based cohort of South Asians living in the US (the Mediators of Atherosclerosis in South Asians Living in America study). Consumption of LCS, specifically diet soda and LCS packets, was assessed using a culturally appropriate and validated food-frequency questionnaire. Chi-squared and ANOVA tests were used to evaluate differences in LCS consumption with socio-demographics, health characteristics, and metabolic risk. A total of 892 South Asians (47% women) were included for the analysis with mean age 55.3 (SD=9.4) y. Twenty-two percent of South Asians reported consumption of LCS at least three servings per week, with higher consumption among older individuals ($p=0.049$), men (26% vs. 18%, $p=0.003$), participants with a longer length of residence in the US ($p=0.048$), and among those who spent more time in TV viewing ($p<0.001$). Higher prevalence of LCS consumption was also seen among participants with obesity (prevalence: 32% vs. 21%, $p=0.006$), those who had at least one chronic disease condition (prevalence: 28% vs. 16%, $p<0.001$), diabetes (47% vs. 17%, $p<0.001$), hypertension (29% vs. 17%, $p<0.001$) and in those with coronary artery calcification (Agatston score greater than 0; prevalence: 28% vs. 18%, $p=0.001$). Additionally, LCS consumption was associated with higher visceral ($p=0.001$) and subcutaneous fat ($p=0.011$), and waist circumference ($p<0.001$). Our findings emphasize the need to investigate potential metabolic effects of LCS use in already-metabolically vulnerable South Asian individuals.

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MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH

An Investigation of Relative Age Effect in Youth Football

BACKGROUND

Youth sport programs typically group children based on an annual birthdate cut-off (e.g., U8, U9, U10). However, research indicates this results in relative age effect (RAE), the overrepresentation of children born early in the selective year and underrepresentation of children born later (Barnsley et al., 1985), which inadvertently advantages older and more biologically mature children (Hancock et al., 2013). Sports in which physical size contributes to success often have a more pronounced RAE from youth to professional levels; however, studies of American football at the professional level have not observed RAE. This absence is speculated to be a product of youth football policies that use additional factors, such as weight and skill level, coupled with age to group children (Wattie et al., 2015). Interestingly though, RAE has not yet been studied in youth football. Therefore, the purpose of this study was to determine the extent to which RAE is promoted or diminished when grouping children by various developmental factors (i.e., age, weight, and skill level).

METHOD

Data was acquired from a mid-Atlantic youth football registration database that used a standardized weight matrix to organize children of various ages and grouped them into teams based on their skill assessment. A purposive sample (N = 1,265) of 8-13 year old boys was extracted and classified into quartiles based upon birth month for data analysis. Multiple chi-square goodness of fit tests were run using expected values of live birth from the CDC.

RESULTS

The mean age of the sample was 11.0 years. Chi-square goodness of fit tests indicated significant differences ($p < .001$) of departures from expected frequencies when independently categorized by age only (AO), weight only (WO), and skill level only (SO). However, there were fewer significant departures when categorized by age + weight + skill level (AWS).

DISCUSSION

The findings from this study provide youth sport programs with needed data to for considering alternative organizing practices were grouping children together. Specifically our study indicates using a singular developmental criterion to group children together (e.g., by age, promotes RAE, whereas a more robust developmental approach appears to alleviate RAE. (e.g., age + weight + skill level). This is significant because the absence of RAE provides children with the opportunity to develop sport-specific skills in a fairer environment among their peers with more developmentally appropriate instruction (Wattie et al., 2008), which promotes more positive sport-based, physical activity experiences for them.

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EXERCISE AND NUTRITION SCIENCES



SCHOOL OF MEDICINE AND HEALTH SCIENCES

Effect of Aerobic Exercise on Fat Derived Mesenchymal Stromal Cells (MSCs)

The effect of aerobic exercise has been studied extensively using various inflammatory biomarkers. Previously, we have shown endothelial progenitor cells (EPCs) can act as a strong cellular biomarker of endothelial function following aerobic exercise as an intervention. In this study, we are examining the effect of aerobic exercise on adipocyte derived MSCs as a cellular surrogate of fat metabolism.

METHODS

In an on-going study overweight and obese subjects (n=8) were enrolled in a 12 week exercise intervention study. The biweekly exercise sessions were supervised by a trained exercise physiologist and consisted of a 1 hour sessions that included warm-up and cool-down and 30 min of combined aerobic and resistance training at an exercise intensity of 50-80% of heart rate reserve. The patients were also encouraged to be physically active during the rest of the week. Subcutaneous abdominal fat biopsies were obtained and fat derived stromal cells were cultured in vitro for 2-3 weeks. MSCs were analyzed for mRNA gene expression (qRT-PCR) and cellular oxygen consumption rate (OCR), pre and post 12 week exercise.

RESULTS

With the intervention, gene expression analysis showed glucose transporter, GLUT1 (p= 0.04), COX4 (p= 0.01), antioxidants SOD3 and GPX3 (p values= 0.04, 0.03, respectively) upregulated significantly with a trend of improvement in other antioxidant such as Catalase (p values= 0.07) and reduced expression of inflammatory gene COX2 (p value= 0.1), pre vs post exercise. Oxygen consumption rate of MSCs between pre and post exercise group, however did not showed any significant difference at this stage of the project.

CONCLUSION

Preliminary outcome analysis of this on-going study indicates that aerobic exercise modifies gene expression of MSCs. Exercise appears to augment certain mRNA expressions such as, cellular glucose transporters and cellular anti-oxidants with a trend of reduced inflammatory marker gene. Though, no significant difference was observed between oxygen consumption rates, significant upregulation of COX4 gene indicates better mitochondrial function with intervention.

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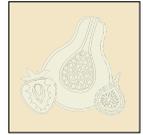
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EXERCISE AND NUTRITION SCIENCES



MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH

Effects of Exercise on Complications of Gestational Diabetes Mellitus (GDM) During Pregnancy

BACKGROUND

GDM is defined as carbohydrate intolerance that first occurs or is first recognized during pregnancy. According to a study conducted by the Centers for Disease Control and Prevention (CDC) in 2010, GDM affects as many as 9.2% of pregnancies in the United States.¹ Effects of GDM include macrosomia, which leads to large-for gestational-age (LGA) fetuses. Complications for the mother include preeclampsia, increased risk of cesarean delivery, and development of type 2 diabetes. In addition, pregnancies complicated by GDM may result in long-term complications for the child, such as increased risk for glucose intolerance, diabetes, and obesity. The purpose of this systematic review is to determine whether physical activity is effective in preventing/reducing complications associated with GDM.

METHODS

Keywords related to GDM, physical activity, and pregnancy outcomes were used to search PubMed, Cochrane, CINAHL, and Scopus. Search terms included birth weight, Caesarian sections, gestational diabetes, aerobic activity, and several others. Studies were excluded for the following reasons: not a randomized trial; study participants did not have a diagnosis of GDM; or the study did not have an exercise intervention. Any form of physical activity was included, regardless of the type.

RESULTS

The initial search generated 808 references. A study was excluded if it did not meet the inclusion criteria, was not a completed study, and if it involved a combined diet and exercise intervention where effects of the exercise component could not be independently assessed. Therefore, of the 808 articles identified, only five were ultimately included in the review. Taken together, no differences in rate of caesarian deliveries or infant birth weight were observed between the control and experimental groups.

DISCUSSION

The current literature review did not demonstrate differences in mode of delivery or infant birth weight in women with GDM who were randomized to exercise interventions compared to women with GDM who were assigned to the control. It is unclear if this lack of an effect is due to the studies starting at a gestational age between 24-34 weeks, rather than earlier in pregnancy. Despite the lack of effects of exercise on infant birth weight and rate of Caesarian delivery, it is important to evaluate effects of exercise during pregnancy on other neonatal and obstetric outcomes in this population.

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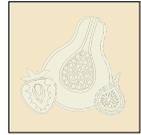
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MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH

The association between musculoskeletal ultrasound measures and knee arthritis status in older Veterans

BACKGROUND

Radiography is routinely used to assess knee osteoarthritis (OA), a degenerative condition involving articular cartilage and skeletal muscle. However, OA radiographic features do not consistently agree with patient-reported quality of life and other imaging modalities may offer better clinical utility. Diagnostic musculoskeletal ultrasound (MUS) can characterize muscle tissue structure and composition in knee OA. However, less is known about the association between MUS findings and patient symptomology. The purpose of this study is to determine whether quantitative MUS measures of skeletal muscle morphology and morphometry are associated with clinical markers of knee OA.

METHODS

Male Veterans with knee OA ($n=36$; age= 62.2 ± 5.7 yr; BMI= 31.2 ± 6.5) participated in the study. Self-reported symptoms and physical function were evaluated using the Knee injury and Osteoarthritis Outcome Score (KOOS). Knee OA asymmetry was determined by the Kellgren-Lawrence grade and self-reported pain. B-mode quantitative MUS with a 13-6 MHz linear array transducer were used to obtain tissue echogenicity and muscle thickness values. The primary scanning site was the rectus femoris of the participants more and less involved leg. Additional sites included the trapezius, deltoid, pectoralis major, and brachioradialis. Echogenicity was used as proxy measure of muscle tissue composition, and muscle thickness values were used as a proxy measure of muscle mass.

RESULTS

Lower echogenicity ($\Delta = -3.04$ grayscale levels, $t=2.70$, $p=.01$) and greater muscle thickness ($\Delta = .17$ cm, $t=2.21$, $p=.03$) of the rectus femoris were identified in the less involved limb. Additionally, the summed MUS muscle thickness values were associated with the Symptom and Sports/Recreation KOOS subscales ($r=.37-.39$, $p=.02-.03$). When considering individual muscle morphometry in the analyses, the muscle thickness of the deltoid was the only measure associated with all 5 KOOS subscales ($r=.36-.45$, $p=.01-.04$).

CONCLUSIONS

MUS-based measures of muscle morphology and morphometry identified knee OA asymmetries in older adult Veterans. Key upper extremity muscle groups and proxy estimates of lean body mass should not be overlooked as factors that affect the KOOS score. Future work should explore the role of lean body mass in the management of knee OA, and determine if changes in rectus femoris echogenicity and muscle thickness are associated with disease status.

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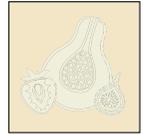
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EXERCISE AND NUTRITION SCIENCES



SCHOOL OF MEDICINE AND HEALTH SCIENCES

Iron, Performance, and Bone Health in Female Athletes

Iron deficiency (ID) and iron deficiency anemia (IDA) are common problems for female athletes. ID has been linked to problems including impaired aerobic adaptation and reduced endurance, while iron supplementation has been shown to improve fatigue resistance, energetic efficiency, perceived fatigue, and mood disturbance. What is less well understood, however, is the interaction between ID and bone health, and its implications for athletic performance. Here, we review what is known about ideal ferritin levels for female athletes and link ID and IDA to Relative Energy Deficiency in Sport (RED-S). We will discuss the relationship between iron and bone health, relating the impact of anemia on fibroblast growth factor 23 (FGF23) and discussing the possible effects of anemia on hematopoietic stem cell lineage differentiation. Finally, we explore unanswered questions and needs for further research regarding the impact of iron deficiency on bone health and performance.

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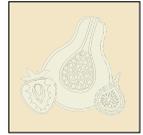
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MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH

How Sweet It Is: The Many Reasons for Low-calorie Sweetener Consumption by Young Adults

BACKGROUND

Over 40% of adults and 25% of children report consuming low-calorie sweeteners (LCS) daily. Despite their widespread use and non-caloric nature, whether LCS are beneficial for weight management is unclear. Epidemiologic studies demonstrate that LCS promote weight gain, yet human intervention studies suggest that replacement of added sugars with LCS may be beneficial, particularly in the context of behavioral support. The purpose of this study was to elucidate reasons why individuals consume LCS to gain insight into the contextual factors associated with LCS consumption, which may dictate the extent to which they are ultimately helpful or harmful for metabolic health.

METHODS

Sixty-eight college students (18 to 35 years of age) reporting habitual LCS consumption participated in the study. Each participant identified their reasons for LCS use through a secure web link and responded to the focus prompt "I consume low-calorie sweeteners and/or products labeled "diet," "sugar-free" or "no sugar added" because" Each participant was asked to report as many reasons for their LCS use as possible. Once saturation was reached in brainstorming, idea synthesis, a form of qualitative content analysis, was conducted by the research team to sort and group statements based on their collective meaning.

RESULTS

A list of 195 statements was generated during brainstorming. Idea synthesis resulted in 38 independent reasons that represented the full saturation of ideas from the original statement list. Reasons for LCS consumption included 13 discrete themes: taste (10), calorie/weight management (8), finances (3), performance (3), overall health (2), sugar reduction (2), access (2), dietary patterns (2), "addiction" (2), weather (1), habit (1), family influence (1), and social influence (1).

DISCUSSION

The current body of literature investigating LCS effects within the context of intensive weight loss interventions captures only one of many contexts in which LCS are consumed. Our findings demonstrate that LCS are consumed for numerous reasons, spanning palatability, cost, habit, peer and family influences, and craving, in addition to weight management. These results will aid in the design of subsequent studies to investigate LCS health effects in a manner that best reflects 'real-life' consumption. Furthermore, these findings may explain seemingly discrepant conclusions of epidemiologic and rodent studies compared to human intervention trials. Future investigations should also aim to quantify the extent to which the 38 reasons identified for consumption are true of the broader population of individuals who regularly consume LCS.

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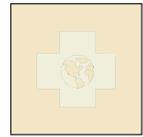
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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Needs Assessment of Pediatric Radiological Equipment and Cross-Cultural Investigation into Parental Empowerment in Pediatric Radiology Program Development in the Kingdom of Bhutan

BACKGROUND

Bhutan is a magnificent mountainous country hugged by India to the east and west and by China to the North and South. This peaceful nestled country faces challenges in combating non-communicable diseases due to the lack of radiological equipment necessary for early diagnosis. Prior to implementation of these medical devices, it is imperative to investigate the cultural attitudes, beliefs, and infrastructure, to ensure successful integration. Bhutan is beginning to implement a pediatric radiology program for the nation with the assistance of ABAH Foundation and RAD-AID International, both of whom partnered with graduate students at George Washington University School of Medicine and Health Sciences. The initial stage of investigation focused on cultural consensus among parents and caregivers of children who have come to the hospital for CT scan at Children's National Medical Center in Washington, DC and at the Jigme Dorji Wangchuck National Referral Hospital in Thimphu, Bhutan. The investigation collected information on fundamental and culture specific concerns of mothers over the safety and well being of their children during radiologic examination.

METHODS

This project consisted of two parts; the first to gather administrative, health services, and epidemiological information of public record within Bhutan, prior to the initiation of a pediatric radiology program, and the second to learn about parental cultural beliefs in relation to pediatric radiology services. A total of 50 families were interviewed in Bhutan using a standard open format interview technique to generate items and phrases from parents for use in future anthropological investigation into "what matters" to Bhutanese caregivers during the medical imaging process. Bhutanese medical professionals and health officials collaborated in the efforts to provide further information on logistical and technical information on how to successfully integrate further medical imaging services. This was implemented with the effort of the Radiological Readiness Assessment completed by the Director General of Medical Services of the Ministry of Health and the Chief of Medical Staff of the Eastern Referral Regional Hospital in Bhutan.

RESULTS

Early investigative studies highlighted the need for further investigation into the cultural education and exploration of misconceptions in the use of radiological services in children. In addition, limitations in trained staff to perform and interpret radiological studies is limited which places a need on both the financial and logistical barriers to successfully implement further imaging machines.

CONCLUSION

There will be ongoing investigations into cultural consensus among parents and caregivers of children who have come to the hospital for CT scans at the Jigme Dorji Wangchuck National Referral in Thimphu, Bhutan, at the Eastern Referral Hospital in Mongar, Bhutan, and in the south in Gelephu, Bhutan. This project is being done under the signed Terms of Reference with the Ministry of Health of Bhutan between ABAH Foundation and the Royal Government attached as Enclosure. ABAH Foundation is arranging and partially supporting the travel and project.

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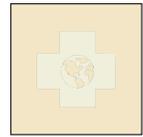
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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Supporting Village Health Teams in Mukono District, Uganda

According to recent WHO estimates, Sub-Saharan Africa is facing a severe shortage of healthcare workers which would need to be expanded by over 140% to meet the needs of each country. OmniMed is a non-profit organization seeking to address this health worker shortage and has trained over 1400 Village Health Team Members, called VHTs, in basic preventative health methods in Mukono District, Uganda. This study involved collaborating with employees of OmniMed to improve work satisfaction of VHTs and therefore to improve long-term retention of VHTs. Through interviews with VHTs at quarterly meetings, several factors were identified which negatively affected the work satisfaction of VHTs including: poor attendance at quarterly meetings due to lack of transportation and monetary resources; VHTs lack personal identification and do not currently have clearly defined roles at the local health centers; three full-time staff members were solely responsible for training and communicating with VHT's in parishes around the Mukono District without any local representation. The plan to improve VHT retention and satisfaction is three-fold. First, a tiered leadership system was developed in which VHT leaders were elected for each parish and would work directly with OmniMed employees. Second, VHTs will be better integrated into local health centers when a health assistant, who is an employee of the Ministry of Health, is hired and will work with local health centers to designate specific tasks to be completed by VHTs within the health centers. The health assistant will also educate the local health care staff about the role of the VHTs. Third, providing reimbursement for transportation and identification badges to VHTs will be a priority with the aim of facilitating attendance at quarterly meetings. OmniMed was working on implementing these structural changes as of Summer 2015 with plans to conduct a randomized control trial to determine how these changes affected VHT work satisfaction and retention.

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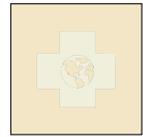
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MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH

Combatting Maternal Mortality: Analyzing the Three Delay Model to Provide Maternal Care in Remote Regions

The world has made significant strides in reducing maternal mortality globally, but it remains a debilitating problem in the most remote regions, which have little access to safe and adequate medical facilities and cannot be easily reached via roads. This study focused on the Three Delay model, which outlines the factors that result in maternal mortalities given that most occur because of delays in receiving proper treatment during a pregnancy (i.e. delays in deciding to seek medical assistance, reaching the nearest medical facility, and receiving appropriate and timely treatment). This study attempts to widen the research on (1) the biggest challenges to lowering maternal mortality in remote regions, (2) initiatives countries are taking to improve the situation and if they've been successful, and lastly (3) innovative technology to improve access to maternal health care in these regions. Data was collected by reviewing secondary sources and interviewing academics, local non-profit leaders, and members of UN organizations, including the Director-General of the World Health Organization. The countries of focus were Nigeria, India, and Bangladesh. This study found that the biggest challenges for the average woman in these countries to carry out a successful pregnancy were lack of healthcare personnel, shortage of well-functioning equipment, and unreliable sources of electricity and water. These countries have created programs to train midwives to respond to complications, provide transportation in the most unreachable areas, and communicate with doctors in other parts of the country through the use of telemedicine. There is still much work to be done—but through new innovations and initiatives by governments with the goal of women's empowerment, easily avoidable complications no longer need to lead to fatalities, and millions of children can know their mothers.

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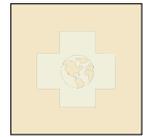
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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Examining Cultural Differences Between the United States and Thailand in OBGYN Healthcare and the Effects on STD and Teenage Pregnancy Rates

The cause of increasing rates of Sexually Transmitted Diseases (STD's) as well as an increasing prevalence of teenage pregnancy in Thailand is clearly multi-factorial, however, culture is arguably one of the largest of these factors. Khon Kaen, Thailand is the fourth most populous city in Thailand, and is a home to one of the top medical university hospitals in the country, Srinagarind Hospital. This hospital is the primary healthcare facility within a 500 mile range, and serves thousands of people per day. The aim of this study was to examine the differences in Obstetrician and Gynecologic healthcare within both inpatient and outpatient settings between the United States and Thailand, to determine if there are any cultural contrasts which may contribute to these increasing rates. Observation took place over 8 weeks in 2015 and focused on health education, the role of the provider, and adequacy of the healthcare facility itself. Results showed there is a more severe stigmatization of STD infection and teenage sex in general in Thailand compared to the U.S., causing a major lack of education regarding consequences of unsafe sex, as well as a delay in screening under national guidelines. The analysis will serve the hospital primarily as a tool for understanding the provider's role in unsafe sex and high rates of sex at early age, and will help in working towards reducing these rates within the Khon Kaen community.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Stakeholders' Perceptions of a Hospital Based Emergency Medicine Education & Training Program: A System Change

BACKGROUND

Emergency Medicine (EM) is a new and developing specialty around the world. In India, one model for capacity building has been the development of partnerships between US academic institutions and private healthcare institutions for implementing post-graduate education and training in EM. Initiated in 2007, programs have grown both in number and scope and have continued to attract new students and partner institutions. This study was undertaken to better understand the impact of EM training programs on hospital systems.

METHODS

A mixed-methods evaluation was undertaken at 5 program sites across India in the summer of 2016. Two researchers conducted onsite semi-structured interviews with key program stakeholders. Participants included hospital administrators, program directors, hospital consultants, and ancillary staff at each hospital. Interviews were recorded, transcribed and then analyzed using a rapid assessment process. Participants also completed a brief survey. Written surveys were analyzed with univariate analysis.

RESULTS

A total of 109 stakeholders were interviewed. Positive impacts were reported among all stakeholders, particularly among administrators, consultants, ancillary staff, and supervising physicians in the ED. 80% of hospital administrators and 90% of direct ED supervisors report improved quality of care particularly among critically ill patients. Some respondents, including 89% of administrators, attributed increased patient volumes at least in part due to the educational program. Of respondents, non-ED consultants were less likely to report improvement in quality during off-service rotations, but 92% reported improved patient care in the hospital related to the program. Positive impacts extended beyond the hospital with many examples of community outreach, layperson education, and improved hospital reputation.

DISCUSSION

Evaluation of a changing system of emergency care has proven challenging to study. These data reflect substantial impacts to a hospital and the surrounding system after development of an EM training program, extending beyond the hospital itself to community outreach programs and a wide variety of education and training programs. Further investigation may prove helpful in quantifying the reported improvement in quality and scope of impact.

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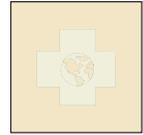
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SCHOOL OF NURSING

Because it Belongs to the Baby: Practice and Cultural Beliefs on Umbilical Cord Management in Haiti

Studies show that waiting to clamp and cut the umbilical cord at birth is associated with multiple benefits for the infant. Early cord clamping (clamping as soon as the baby is born) has been shown to double the risk of infant anemia. Delayed cord clamping (DCC) provides as much as a 60% increase in iron rich red blood cells. For preterm newborns, DCC decreases the incidence of necrotizing enterocolitis, intracranial hemorrhage and the need for blood transfusion. Research conducted in low resource settings has demonstrated magnified benefits with delayed clamping when the mother herself is anemic.

Iron deficiency anemia in the first year of life is a significant health issue, because adequate iron stores are essential for growth and brain myelination. Infant anemia has been associated with long term neurocognitive deficits for as much as 25 years into adulthood, even when treated. DCC is an effective preventative strategy to support normal newborn development.

In Haiti, 63% of infants between 6 and 11 months are anemic. In addition, over 60% of women are anemic and maternal anemia is a significant risk factor for infant anemia. The maternity care system in Haiti is complex. Only 36% of births in Haiti occur in an institution. Skilled attendants are present at just 15% of rural births and 47% of urban births. A wide variety of care providers assist at births including traditional birth attendants (matrons), nurses (infirmière), direct entry midwives (auxiliaire sage femme), nurse-midwives (infirmière-sage femme), and a small number of physicians. Little is known about umbilical cord care and the perspectives of birth attendants in Haiti. Given the high incidence of maternal and infant anemia and the potential for long-term deficit effects, a better understanding is warranted.

Student and faculty researchers from the GW School of Nursing conducted a descriptive mixed methods study of Haitian maternity care providers regarding their umbilical cord practices and cultural beliefs. Semi-structured interviews were conducted with a convenience sample of fifty matrons, nurses, infirmières, auxiliaire sage femmes, infirmière-sage femmes, and physicians. The study was approved by the GW IRB.

Many care providers in Haiti knew about DCC. Although some believed that the baby would "bleed out" into the mother if the cord was not cut immediately, others adhered to traditional "ways of knowing" that had been passed down from previous generations. According to the latter providers, delayed clamping is important as it provides needed blood to the infant.

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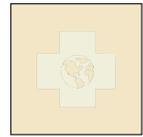
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MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH

Victims or Heroes? How Did Journalists Frame the Ebola Crisis in Liberia?

The Ebola Virus Disease epidemic in West Africa in 2014 with over 11,000 deaths made headlines worldwide, causing fear and posing a challenge to traditional media, entrusted with the task of reporting about the spread of the disease. Individuals and communities rely on media to obtain health information, including decisions related to disease prevention and behavior to protect their health. Therefore, frames used by the media to report about health emergencies impact public perceptions. Mass media framing during crises has been associated with emotional and behavioral responses that are consistent with the thematic depiction of unfolding events. Moreover, message frames can influence the weight assigned to specific viewpoints and alter the importance given to particular concerns, potentially leading to enhancement of selective information in the public's consciousness and heightened awareness.

This study assessed the types of message frames used by media in Liberia in the midst of the epidemic. The methodology is based on a quantitative content analysis of 745 news articles from three major Liberian newspapers and 182 audio files from seven local radio stations and programs from January 2014 through December 2015. A theory-driven codebook based on risk communication frameworks was developed and intercoder reliability scores of $K \geq .85$ attained by all six members of the coding team.

Results show an emphasis on particular frames by channel. The four main journalistic frames of radio messaging were behavioral steps (47.8%), anti-stigmatizing (10.8%), victim (9%), and blame directed toward the Liberian government (4.8%). In newspaper articles, "hero frame" was the most frequently used (38.8%), followed by disaster frame (20.7%), behavioral steps to address the crisis (10.9%), victim frame (9%), and blame (8%). Achieving a better understanding of frames utilized in Ebola-related communication as the crisis was unfolding provides the opportunity to identify and evaluate the presence (or lack thereof) of risk communication best practices. This in turn has the potential to inform future risk-communication efforts to address health emergencies.

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Health System Determinants of Maternal Mortality in Tanzania: An analysis of regional disparities in health system capacity and its impact on maternal mortality in Tanzania

INTRODUCTION

The Government of Tanzania has made a commitment to reduce the maternal mortality ratio (MMR) in Tanzania from 410 deaths per 100,000 live births in 2015, to 292 by 2020. This target is based on raising the percentage of facility-assisted deliveries and improving access to and quality of emergency obstetric care at the dispensary and health center level (MOHSW, 2015). Census data from 2012 show great regional disparity in MMR with the highest and lowest regions differing by a factor of 5. This cross-sectional study investigates whether regional health systems capacity contributes to the variability in regional MMR.

METHODS

The study uses regression analysis to correlate regional health system usage and quality factors identified in the Service Provision Assessment (SPA) and Demographic and Health Survey (DHS), both from 2015, with sub-national maternal mortality data collected in Tanzania's thirty administrative regions during the 2012 Household and Population Census. Health system factors included quality variables for dispensary and health center readiness to deliver basic emergency obstetric care (BEmOC), which were created based on fifty-six factors taken from the SPA. Socio-economic and variables related to service access barriers from the DHS were included to isolate the partial contribution of health system factors to variability in regional MMR.

RESULTS

Facility-assisted Delivery was the health system factor most highly correlated with MMR, but not with a linear relationship. In fact, the direction of the correlation only becomes negative after facility-assisted delivery reaches 65% coverage. ($p=0.001$) the factor most significantly correlated to higher levels of coverage of facility-assisted delivery was contraceptive prevalence (mCPR) ($p=0.000$). Dispensary readiness was also a contributor to facility-assisted delivery ($p=0.001$), even when controlling for maternal education.

CONCLUSIONS

Facility-assisted delivery is a critical path to achieving targeted reductions in MMR; however, drivers of increased facility-assisted delivery are not only the readiness of facilities to provide quality BEmOC, but reducing the burden on facilities and physical risk factors for women by increasing the use of modern contraception. While the findings from this study support the strategic priorities of Tanzania's One Plan II, an impact on MMR cannot be expected until all regions of the country achieve a 65% level of facility-assisted delivery. This will likely require regionally specific strategic plans to increase mCPR and dispensary readiness.

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Predictors of Measles and Rubella Serostatus in Mother-Infant Pairs in Rural Nepal

BACKGROUND

Measles and rubella cause serious infections in young infants, including congenital rubella syndrome, pneumonia and disseminated disease. Measles-rubella (MR) vaccine has been recommended as a universal childhood vaccine in low-income countries, including Nepal. National measles coverage in Nepal began in the 1980s, with rubella added in 2013; childhood immunization with MMR (measles-mumps-rubella) in the USA has been ongoing since 1971. We aim to define and compare the seroprevalence of measles and rubella antibody in pregnant women and infants in two populations, and evaluate factors associated with negative serostatus.

METHODS

Measles and rubella immunoglobulin G (IgG) levels were measured in pregnant women participating in a placebo-controlled influenza vaccine study in southern Nepal and pregnant women in Seattle, WA. In both cohorts, paired maternal-cord blood samples were collected at delivery (286 pairs from Nepal [March 2012-December 2013] and 45 pairs from Seattle [December 2014-September 2015]). Sera was qualitatively tested for measles and rubella IgG (Zeus, Branchburg, NJ). Comparisons of proportions with protective antibody levels were performed using t-tests and Fisher's exact tests.

FINDINGS

Pregnant women in Nepal were younger than Seattle women (23 vs. 33 years; $P < 0.001$), had greater numbers of children in the household (2.3 vs. 0.40; $P < 0.001$), and lower birthweight infants (2855 vs. 3630 grams; $P < 0.001$) born at an earlier gestational age (39.3 vs. 40.1 weeks; $P < 2500$ grams).

INTERPRETATION

High rates of immunity to measles and rubella were observed in both populations, despite the only recent introduction of rubella vaccination in Nepal. These results suggest that as MR vaccination progresses in Nepal, further surveillance may be required to ensure continued high levels of immunity from vaccination.

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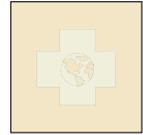
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MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH

A Comparative Study on the Impact of World Vision’s Water, Sanitation and Hygiene Programming in Southern Africa Region, Malawi, Mozambique, and Zambia: Analyses using Lives Saved Tool

BACKGROUND

According to the World Health Organization, diarrheal disease is the second top killer of children under five years of age (U5), claiming around 760,000 young children’s lives every year, and 88% of diarrheal disease is attributed to unsafe water supply, inadequate sanitation and hygiene. The humanitarian aid organization, World Vision, launched community-based water, sanitation and hygiene (WASH) project in 76 Area Development Programs (ADPs) for 506,019 target U5 population across Southern Africa Region (SAR): Malawi, Mozambique and Zambia in 2010.

OBJECTIVE

This study estimated the retrospective health impact of the project between 2010 and 2014 to measure how effectively WASH interventions were implemented.

METHODS

Computer-based modeling software, Lives Saved Tool (LiST) was utilized for quantitative analysis. The effectiveness and scaled up coverage of five WASH interventions—improved water source, home water connection, improved sanitation, hand washing with soap, and hygienic disposal of children’s stools—were calculated by conducting ADP field visits and analyzing SAR’s quantitative data.

RESULTS

The significant impact demonstrated that the combined effect of interventions have prevented 989,745 diarrheal cases; this translated to the prevention of 1.96 cases of diarrhea for every U5 and 13% prevention rate for diarrhea. It contributed a 209% mean increase in percentage of U5 lives saved and 15.5% mean decrease in U5 mortality rates. The total number of U5 lives saved from diarrhea was 550.

CONCLUSIONS

These results suggest that the project is achieving the organization’s ultimate goal, “Every child deserves clean water,” and LiST acted as an effective tool for conducting the quantitative impact assessment of the project at subnational level. To reach the universal coverage by 2020 to prevent all 3 cases of diarrhea per child each year, programming activities must include promotion and facilitation of household-level water connection and regular availability of soap or equivalent, WASH-related health interventions must be fully incorporated into programming, and the existing community-level water treatment sensitization meetings should be leveraged as a forum to bring together additional sector representatives for raising awareness about integrated WASH programming.

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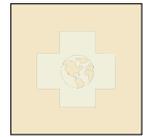
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SCHOOL OF MEDICINE AND HEALTH SCIENCES

“Brain Drain” and Medical Workforce Retention within Ethiopia, Addis Ababa

According to studies published in the Sub-Saharan African Medical School Study one in eight physicians trained in Sub-Saharan African region is lost to more developed nations and shortage of physicians in these regions are predicated to increase rapidly. This medical migration is known as “brain drain.” This project consist of a qualitative research to investigate the concept of “Brain Drain” in Ethiopia, Addis Ababa and understand incentives that encourage physicians’ retention within the country. This project helps understand the main reason why medical students choose to leave their school and move abroad and the single most important thing that could change to encourage retention among students. Similarly, the project highlights main reason why faculty members and physicians migrate to a foreign country and determine the most important factor that will motivate them to stay and work at the hospital. Moreover, different perspectives of the administration of the hospital and medical school on the challenges of retaining their faculty members, physicians, and students are discussed. The purpose of this project is to be able to determine the main common ground and overlapping theme that should be address in order to ultimately reduce brain drain and encourage retention of physicians. Out of the 52 physicians surveyed and interviewed. 30 people answered better salary as being the number one reason or incentives for them to practice medicine within Ethiopia, 22 people answered housing and transportation opportunities as the second reason and incentives, 14 people answered scholarship and post graduate medical opportunities as the third reason/incentive and 7 said better infrastructures as the fourth reason. On the other hand, out of the 60 students being surveyed the number one reason or incentives for them to practice medicine within Ethiopia is better salary with 22 responses, followed by housing and transportation opportunities as the second incentive with 7 responses, and research support as the third reason with 6 responses.

The conclusive result of my project shows that the most important incentive in retaining physicians is better salary. A better alternative to incentivize retention that most individuals across different group agreed on was the availability of housing and transportation opportunities. Most physicians don’t own a house or a car, which are among the basic necessities. Every group I surveyed and interviewed agreed that the government should set up a system in which physicians are able to afford getting these basic necessities with their low salaries.

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The Effects of Solar Disinfection on Childhood Diarrhea Rates in Sub-Saharan Africa: A Review

BACKGROUND

Solar disinfection (SODIS) provides a cheap, quick, and effective way to disinfect water in low and middle income countries (LMIC). Lack of access to clean drinking water makes the residents of these nations, in particular children, highly susceptible to contracting and potentially dying from diarrheal disease. According to the World Health Organization (WHO), diarrheal disease is the second leading cause of death in children under 5 years old and kills close to 800,000 children yearly. Death due to diarrheal disease is preventable. If implemented and used properly, SODIS can reduce the incidence of diarrheal disease and subsequent death in many low and middle income countries.

METHODS

A systematic review was conducted following PRISMA guidelines. Searches were conducted via Pubmed, SCOPUS, OVID, and Engineering Village databases. Searches were limited to papers published between 1996 and 2016, and were reviewed by the author to provide an analysis of content. A total of 141 publications were initially retrieved, 11 full text reviews of publications were completed, 6 publications were included in the systematic literature review.

RESULTS

SODIS is an effective way of disinfecting water. All of the studies included in the systematic review found that when SODIS was implemented, incidence of diarrhea decreased significantly. Results also showed that SODIS can be effectively used during a cholera outbreak to prevent disease spread and death due to diarrheal dehydration.

CONCLUSIONS

All of the literature included in the review showed that SODIS is an adequate intervention and can be used in lower and middle income countries in order to reduce diarrheal disease transmission and diarrhea associated deaths.

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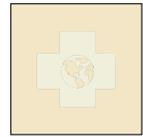
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Compounded Trauma: Gender-Based Violence in the Wake of Natural Disaster

In the aftermath of the 2005 hurricane season, news stories primarily ran around the destruction of the storms and on the seemingly state of anarchy among the affected areas. Rumors of rampant rape and sexual assault circulated through the conversation as well. How true were these rumors? And how much of the new incidence of violence against women (and gender-based violence) was directly due to the hurricane? Is there an increased incidence of sexual violence or domestic violence specifically following a natural disaster, as opposed to a violent event? That gender-based violence can be expected to increase during and after complex emergencies is widely accepted by the humanitarian and public health communities. But the relationship between specific natural disasters and gender-base violence is less well understood. Feminist social science scholars began writing on this topic in the late 1980s and early 1990s, but since then the focus of women’s studies in disaster settings has focused on mental health outcomes (PTSD and depression). While mental health outcomes might be closely related to incidence of gender-based violence, these studies do not produce data that can be directly applied to the question of a relationship between the nature of the disaster and the incidence of gender-based violence. Many of the existing literature reviews on this topic include studies on populations of refugees from violent crises, which could confound the impact of the event on the incidence of gender-based violence.

This systematic review of existing literature sought to answer these questions by employing the PRISMA method and evaluating peer-reviewed sources published since 1990. Articles sought had to be focused on refugee or internally-displaced women that were victims of a natural disaster event, and the article itself had to focus specifically on some aspect or type of gender-based violence, not exclusively mental health outcomes. The resulting articles did not present a unified answer, but did reveal some key gaps in the knowledge and weaknesses of the existing research. The greatest risk factors to women and girls in disaster situations include existing social-gender inequality, loss of resources, and loss of the support system. Given the expected increase in natural disaster events with the progression of climate change (Barnett and Adger, 2007), it is imperative that the risks to vulnerable populations are well understood. Without this knowledge, attempts to protect women and girls will be reactive and insufficient.

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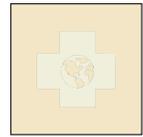
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MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH

Parental Migration and Early Childhood Development in Rural China

BACKGROUND

In rural China, over 61 million children age 0-17 (28% of all rural children) are left behind by at least one parent seeking employment elsewhere. Little empirical evidence exists regarding how parental migration in the first few years of children's life affects early child development, and whether the effect is dependent on the family social economic status (SES) when a child was born. This study aims to address this gap.

METHODS

The data used in the analyses are derived from three waves of the China Family Panel Studies (CFPS), collected in 2010, 2012 and 2014. A number of early childhood development outcomes are assessed: height, childhood illness, pre-primary school enrollment, social behavioral development and intermediate outcomes including cognitive stimulation and breastfeeding duration. Capitalizing on the longitudinal nature of the CFPS, we address the complexity and dynamic processes of family migration strategies by distinguishing various types of migration, taking into account of timing, intensity and cumulative of exposure to parental migration. An interaction term between initial SES and various independent variables was used to test differential impact.

RESULTS

By age 5, over 52% of rural children experienced being left-behind by at least one parent. Compared to children never experienced parental migration, outmigration of mother is associated with 0.17 lower probability of being breastfed for at least 6 months ($p < 0.05$). Experience being left-behind by both parents is negatively associated with linear growth ($p < 0.1$), and longer exposure is more detrimental. Experienced parental migration during age 0-1 is associated with higher likelihood of being ill in the preceding 4 weeks ($p < 0.1$). For ECD outcomes of preschool enrollment, social behavior score and early cognitive stimulation, we found significant interaction between initial family SES and ever experienced both parent migration; and between initial family SES and cumulative exposure to both parent migration for childhood illness, early cognitive stimulation and preschool enrollment.

CONCLUSION

Overall, children experienced parental migration exhibit few significant differences on ECD outcomes relative to children constantly living with both parents. For children from the poorest families migration of both parents increases the chance of their children to get pre-primary school education, it has not, however, benefited their physical or social behavioral development. Contrary to the hope of most migrants, labor migration confers little significant advantage to their left-behind children.

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HEALTH POLICY AND MANAGEMENT



MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH

Promotion of New Diabetes Products in the District of Columbia

BACKGROUND

Growth in pharmaceutical expenditures for diabetes outpaced growth in diabetes prevalence. Prescribers accepting gifts and meals from pharmaceutical companies have been linked with higher prescription rates and costs. Pharmaceutical marketing to these prescribers and patients often promotes newer, more expensive drugs, such as the GLP-1 analogues and SGL-2 inhibitors. These two drug classes are more expensive but no more effective than metformin, the recommended first-line treatment for diabetes, and the oldest and cheapest available treatment. We investigated how cost of diabetes treatment was affected by marketing practices in the District of Columbia.

METHODS

The AccessRx program in DC requires pharmaceutical companies to report gifts given to healthcare providers, drug advertising expenses, and the salaries for staff engaged in promotional activities (“detailing expenses”). We combined data from AccessRx and the federal Open Payments system to estimate promotional payments. We used Medicaid drug utilization data to examine spending for diabetes treatment.

RESULTS

In 2014, DC Medicaid spent more than \$17.1 million on pharmaceutical treatments for diabetes. We estimated that ten companies spent \$3.8 million in detailing expenses to market diabetes drugs in 2014. SGLT-2 inhibitors and GLP-1 analogues had the highest estimated detailing expenses, each totaling more than \$1.2 million. From 2014 to 2015, DC Medicaid spending for Victoza (liraglutide), a GLP-1 analogue, increased 51% (from \$183,873 to \$362,230) and Invokana (canaglifozin), a SGLT-2 inhibitor, increased 213% (from \$8,933 to \$27,958).

CONCLUSIONS

Pharmaceutical promotion drives unnecessary use of newer, more expensive medications. The District of Columbia should provide education on rational prescribing for diabetes treatment (including diet and exercise).

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MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH

Evaluating the Patient-Centered Quality of Cancer Survivorship Care Models

OBJECTIVE

The growing population of cancer survivors (15.5 million in the US) face myriad physical and psychosocial health issues even after treatment has ended. Because of this, cancer is increasingly viewed as a chronic condition that requires systematic and coordinated care. Cancer centers have begun providing survivorship care; however, efforts are varied and scattered given the lack of evidence-based guidance on how care should be organized to most effectively provide high quality, patient-centered care. This study aims to evaluate the impact of three emerging models of cancer survivorship care on a newly developed patient-centered measure of quality care.

METHODS

We conducted a comparative effectiveness research (CER) study with 32 high-performing survivorship programs distributed across three models of survivorship care to examine the quality of care provided to survivors of breast, prostate and colorectal cancer. A total of 991 cancer survivors across the 32 institutions were recruited and followed for six months. We collected self-reported data on the quality of care provided during survivorship services using the Patient-Prioritized Measure of High Quality Survivorship Care (PPM) containing 46 individual metrics categorized into nine domains of care. GLM and Pearson chi-square tests of independence were conducted to determine whether and which models had statistically significantly different scores across the domains and individual metrics.

RESULTS

The emerging models of survivorship care identified are: 1) Specialized consultative model, 2) Specialized longitudinal model, and 3) Oncology-Embedded model. Preliminary quality results from patients' first survivorship visit suggest that the embedded model performs lower than the specialized models in eight of the nine PPM domains ($p < 0.05$), including: care coordination, patient-provider engagement, and provision of a full spectrum of survivorship-related services and resources. Between the two specialized models, differences in mean domain scores is significant for just one domain (with model 2 performing better in providing a medical home, $p < 0.05$); however, differences are significant for several of the individual metrics. For example, clinicians in model 2 are more likely to review patients' medications, which is a metric contained within the care coordination domain.

CONCLUSIONS

It appears that certain models of survivorship care are better at providing specific aspects of patient-centered quality of care, suggesting cancer centers should consider their patients' needs before committing to a particular model of care. The next step of this research is to examine whether differences in the quality and patient-centeredness of care is associated with differences in quality of life and patient self-efficacy outcomes.

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HEALTH POLICY AND MANAGEMENT



SCHOOL OF MEDICINE AND HEALTH SCIENCES

A Medical Student Foray into the Depths of Public Health: An Exploratory Investigation Toward a Community Dashboard Characterizing the Experiences of Frailty in Order to Guide Improvement

While it is known that there are many shortcomings in the care of the elderly, their rate and impact on the community and the elderly themselves is not well understood. In exploring the possibilities for using existing data and available informants, a dashboard could be created that would enable a geographic community to understand the experience of living with disabilities in old age, to prioritize problems, and to test improvements.

The methods included a literature review to understand what and how easily information could be accessed, gathered, and presented. In regards to literature on data collection, CMS claims data, MDS, OASIS, and death certificate follow back interviews were examined. In addition, other databases and dashboards were explored to better understand methods and aims. Interviews were then pilot-tested with caregivers of frail elders, both alive and deceased.

It was ultimately concluded that by using existing data from utilization and other required data sets, a geographic community could construct a useful dashboard to prioritize and monitor improvements in elder care. The biases, which would be fairly stable across time for any one community, could be estimated. The costs could be mitigated with inexpensive access and off-the-shelf analytic packages. Most importantly, by marrying the breadth of information from large data sources with the depth of caregiver interviews, a platform could be created that motivates communities to undergo a very necessary elder care reform.

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HEALTH POLICY AND MANAGEMENT



MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH

State Policies on the Administration and Uptake of the Human Papilloma Virus Vaccine

BACKGROUND

Human Papillomavirus (HPV) is the most common sexually transmitted infection in the United States, with a prevalence of roughly 79 million Americans currently infected and approximately 14 million new infections each year. Although there is a highly effective vaccination on the market for HPV, the prevalence of the infection and its associated morbidities and cancers are extremely high. The unique political landscape in each individual state can directly affect the uptake rates of the HPV vaccine. All 50 states and Washington D.C. were studied to understand if certain combinations of policies correlate to higher uptake rates.

RESEARCH OBJECTIVE

There are five state policies that were considered when analyzing the uptake rates of the vaccination. These policies of interest were if pharmacists were able to administer the HPV vaccine, if the state has expanded Medicaid, if the HPV vaccine is required for school entry, if there are non-medical reasons for exemption, and if children or adolescents are required to receive comprehensive sex education in school. After collecting this information on relevant state policies, the results of a qualitative comparative analysis (QCA) will describe the combinations of policies that correlate to the states with the highest uptake rates of the HPV vaccine.

METHODS

The information on these five policies was collected online through state legislatures websites and relevant national associations. A database was assembled, with a tab for each of the policies, containing each of the 50 states and Washington D.C and the information pertinent to the HPV vaccine uptake. The population of interest was the male and female adolescent residents of each state.

CONCLUSIONS/IMPLICATIONS FOR POLICY OR PRACTICE

From this initial research, it is interesting to see the politics involved in affecting a healthier society. It is widely agreed that the vaccine is beneficial, but different political landscapes in each state affect its uptake. Five states including Georgia, North Carolina, Illinois, Tennessee and Montana, have increased their rate significantly in the past few years by implementing a combination of both political and social initiatives. The QCA will determine if the combinations of certain policies directly impact the vaccination rates within states, and hopefully can inform policy makers on the implications of different political options within their state.

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HEALTH POLICY AND MANAGEMENT



SCHOOL OF MEDICINE AND HEALTH SCIENCES

A Conceptual Model for Episodes of Acute, Unscheduled Care

We engaged in a 1-year process to develop a conceptual model representing an episode of acute, unscheduled care. Acute, unscheduled care includes acute illnesses (eg, nausea and vomiting), injuries, or exacerbations of chronic conditions (eg, worsening dyspnea in congestive heart failure) and is delivered in emergency departments, urgent care centers, and physicians' offices, as well as through telemedicine. We began with a literature search to define an acute episode of care and to identify existing conceptual models used in health care. In accordance with this information, we then drafted a preliminary conceptual model and collected stakeholder feedback, using online focus groups and concept mapping. Two technical expert panels reviewed the draft model, examined the stakeholder feedback, and discussed ways the model could be improved. After integrating the experts' comments, we solicited public comment on the model and made final revisions. The final conceptual model includes social and individual determinants of health that influence the incidence of acute illness and injury, factors that affect care-seeking decisions, specific delivery settings where acute care is provided, and outcomes and costs associated with the acute care system. We end with recommendations for how researchers, policymakers, payers, patients, and providers can use the model to identify and prioritize ways to improve acute care delivery.

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MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH

Examining the Medicaid IMD Exclusion and its Implication in Mental Health Outcomes

Recent political unrest regarding the Medicaid Institutions for Mental Disease (IMD) Exclusion has resurrected the provision among both policymakers and stakeholders as a gap in coverage for many Americans. This study sought to find connections between access to inpatient and community-based mental health services and patient outcomes. Data from the Substance Abuse and Mental Health Service Agency Uniform Reporting System was analyzed to identify significant findings among state spending on inpatient mental health services, state spending on ambulatory and community services, rates of Serious Mental Illness among adults aged 21-64, and rates of homelessness. It was found that states spending more on both inpatient and ambulatory and community mental health services have higher rates of SMI/1000 adults aged 21-64, and there is no significant relationship between state spending on both inpatient and ambulatory and community mental health services and rates of homelessness. This signals that simply increasing funding among existing programs or eliminating the Medicaid IMD Exclusion may not be a complete solution for improving mental health outcomes for adults aged 21-64 with SMI.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Impact of Expanded Medicaid Coverage on Hospital Length of Stay Following Injury

INTRODUCTION

Despite implementation of the Affordable Care Act (ACA) in 2010, 32 states—including The District of Columbia (DC) and Maryland (MD)—expanded their Medicaid insurance coverage, while nineteen states, including Virginia (VA), did not expand their coverage. The region served by the trauma center at George Washington University Hospital (GWUH) represents three unique payer systems with liberal, moderate, and no Medicaid expansion (DC, MD, and VA, respectively). Trauma centers are required to treat all patients regardless of insurance status, yet patients may have different hospital length of stay (LOS) depending on their access to care post-discharge. The purpose of this study is to identify if expanded Medicaid eligibility in DC and MD correlates with a shorter LOS for trauma patients.

METHODS

A retrospective study of trauma registry patients admitted to the GWUH, a Level 1 adult urban trauma center, during a 38-month period (January 1, 2013 to March 6, 2016) was performed. Patients encompassed those on non-commercial insurance, including Medicare and Medicaid, as well as those who are uninsured. Patients with commercial insurance or whose payer information was not identified were excluded. Additionally, patients who were pronounced dead on arrival or who died during their hospitalization were excluded. Primary outcome measures were comparison of type of insurance and LOS by state of residence among DC, MD and VA.

RESULTS

During the study period, 4883 patients were admitted to the trauma service with 2728 patients enrolled per our inclusion criteria. Medicaid patients from DC had a significantly shorter average LOS (2.64 days) than patients from MD (3.53 days, $p = 0.003$) or VA (4.56 days, $p = 0.02$). This difference persisted after controlling for Abbreviated Injury Score (AIS) for both head and pelvis, Injury Severity Score (ISS), gender, age, and penetrating mechanism of injury in our multivariate linear regression model.

CONCLUSION

The District of Columbia and MD, states that participated in Medicaid expansion, are associated with shorter hospital LOS for trauma patients than the non-expansion state of VA. However, as the result of the differing Medicaid coverage eligibility requirements in DC and MD, discrepancy also exists in LOS between these states. It is expected that Medicaid expansion is associated with shorter hospital LOS for trauma patients due to increased access to rehabilitation facilities and home health services. Future work investigating the discharge destination of Medicaid patients under the ACA is needed.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Medical Students as Health Coaches to Decrease the Cardiovascular Burden of Diseases

This study investigates 1) the potential impact of coaching by medical students for patients with uncontrolled hypertension and 2) the value of the coaching to the medical students' professional development. Previous studies have demonstrated that coaching in health care settings improves a variety of medical conditions. These studies utilized a small group diverse group of coaches; health professional students and medical assistants. However, no study conducted has utilized a relatively large number of medical students as coaches or has directly studied the impact of medical students as coaches. This study will involve 22 medical students each assigned to a patient. Both quantitative and qualitative metrics will be utilized to evaluate impact of coaching and disease severity. One coaching supervisor will train first year medical students participants of the George Washington University using an established coaching curriculum. A research coordinator will then assign a health coach to each patient and the two will interact using an established protocol over a six-month period. This study has the potential to mitigate cardiovascular disease particularly hypertension by helping high-risk patients better control their disease burden. This research has the potential profound impact since more students are enrolled in medical school than ever.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Continuous Positive Airway Pressure Improves Arterial Stiffness and Endothelial Progenitor Cells (CD34+ cells)

OVERVIEW

Obstructive sleep apnea (OSA) is a common condition characterized by intermittent breathing pauses during sleep. OSA is an independent risk factor for cardiovascular disorders (CVDs) with endothelial dysfunction playing a role in its pathogenesis. OSA patients are known to have endothelial damage due to oxidative stress and decreased ability to repair via endothelial progenitor cells (EPCs). Arterial stiffness (AS) is a known indicator of endothelial health, and hence cardiovascular risk. Continuous positive airway pressure (CPAP) is the gold standard when it comes to treating patients with OSA, and has shown to decrease cardiovascular risk in OSA patients. We studied the effect of CPAP on the EPCs and arterial stiffness in OSA patients.

METHODS

8 patients diagnosed with OSA, but without prior CPAP treatment, were recruited. Pulse Wave Velocity (PWV), a measure of AS, and EPC number and function were assessed at baseline (prior to starting CPAP treatment) and post-12 week CPAP treatment. The Wilcoxon Signed Rank Test was used to test changes in measurements per day of CPAP > 4hr (median of 48 days).

RESULTS

Arterial stiffness, measured by PWV, was improved with CPAP treatment ($p = 0.008$). Although no statistically significant change was noted in EPC colony forming units, the percent of CD34+ cells (relative to total mononuclear cells) increased after treatment ($p = 0.05$). Additionally, in targeted gene expression analysis, a trend towards increased gene expression was noted for eNOS (endothelial nitric oxide synthase) and CXCR4 (a receptor for SDF1A, a known chemotactic factor for EPCs).

CONCLUSIONS

An improvement in arterial stiffness, along with an increase in CD34+ cell numbers most likely explains the cardiovascular risk reduction post CPAP therapy. While a larger cohort is needed to elucidate the specific molecular mechanisms involved in this process, this pilot study serves to introduce potential key players.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES
CHILDREN'S NATIONAL MEDICAL CENTER

Lightning Can Strike Twice: Cobalamin C Deficiency and Down Syndrome in the Same Patient

BACKGROUND

Cobalamin C deficiency (Methylmalonic acidemia with homocystinuria, CblC) is an autosomal recessively inherited disorder with a prevalence of about 1:60,000-100,000 in the United States, Down syndrome is a more common with a incidence of 1:800 in the United States. Rarely, do we see a child with two separate unrelated disorders.

CASE PRESENTATION

Here, we present a young girl with Down syndrome (confirmed Trisomy 21) who was found to have an elevation in methylmalonic acid during a hypoglycemic event. She was eventually was diagnosed with Cobalamin C deficiency. Genetic testing identified two variants within MMACHC gene. The first mutation is a pathogenic variant (c.440G>C,p.G147A) which is considered a missense alteration and the other mutation is of uncertain clinical significant (c.395G>C,p.R132P) which is predicted to be pathogenic. The patient responds well to cobalamin (B12) and has been developing appropriately given her diagnoses.

DISCUSSION

Children with Down syndrome do not typically have elevations in methylmalonic acid and hypoglycemia and as a result, further evaluations were done to explore possible B12 deficiency and abnormalities in B12 metabolism. In this case, these further evaluations produced a second treatable diagnosis. In summation, it is important to pursue additional testing if an individual's diagnosis does not match their phenotype.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Anatomical Knowledge Retention in Changing Curricula

Traditionally anatomy is one of the first subjects taught in medical school. Practicing physicians have commented on medical students' poor anatomical knowledge in surgically oriented clerkships. Literature also shows that correlating clinical and anatomical sciences throughout early medical education may improve anatomical knowledge retention. With major medical school curricular changes happening across the nation, more quantitative data confirming this correlation is needed.

The medical curriculum at the George Washington University School of Medicine recently underwent reorganization, transforming an earlier discipline-based curriculum to that of an integrated system-based one. In order to determine whether reorganization has an effect on anatomical knowledge retention, comparisons of anatomical knowledge between classes in the different curricula were made. Students from the last class of the discipline-based curriculum and students from the first class of the new, integrated curriculum completed the same 27-question test before beginning their general surgery and obstetrics and gynecology (OB/Gyn) rotations. Scores for specific anatomy categories related to general surgery and OB/Gyn were then analyzed and compared between classes.

Comparing the scores from the 2013 and 2016 cohorts, there was an overall decrease in retention from 65.69% to 63.64%. Item analysis per topic revealed a mean decrease in surgical anatomy and OB/Gyn anatomy retention of 2.53% and 1.58%, respectively. There was a 21.6% increase in inguinal canal anatomy retention and a 17.33% increase in appendix related questions. There was also a 12.02% decrease in fallopian tube anatomy retention.

In conclusion, when comparing the 2013 to the 2016 data there were overall decreases in retention for the anatomy as it relates to general surgery and OB/Gyn; however improvements were noted for specific topic areas. These results suggest that the change in retention is apparent and multifactorial. The differences between surgical anatomy retention and OB/Gyn anatomy retention scores may be related to the way the subject matter was organized and presented, or how the anatomic foundational knowledge was integrated with its clinical relevance. Although integrative learning has been associated with better retention, more studies will have to be conducted to validate this statement. Finally, analyzing the subject matter, curriculum structure, clinical focus, and objectives should be evaluated moving forward.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Characteristics of anti-MDA5 autoantibody-associated Juvenile Dermatomyositis (JDM) in North America

BACKGROUND/PURPOSE

Anti-MDA5 Abs have been reported to associate with clinically amyopathic and classic adult and juvenile dermatomyositis (JDM), and in particular with severe progressive interstitial lung disease (ILD) and poor prognosis in Japanese pts. The aim of this study was to examine frequency and characteristics of anti-MDA5 autoantibody-associated JDM in North America.

METHODS

Demographic, clinical, laboratory and outcome features of anti-MDA5+ JDM and JCTM/DM pts meeting probable or definite Bohan and Peter criteria were assessed and compared to 60 MSA/MAA negative (Ab-) JDM pts from a US registry of juvenile myositis. Myositis Abs were tested by standard immunoprecipitation (IP) and MDA-5 tested by reverse IP-immunoblot. Differences were evaluated by Fisher's exact and Mann-Whitney tests. Significant univariable results were examined in multivariable logistic regression.

RESULTS

Anti-MDA5 Abs were identified in 37 (7.9%) pts out of cohort of 467 JDM and JCTM/DM pts. MDA5+ had lower serum CK (median 182 vs. 746 U/L, $p < 0.0001$) compared to Ab-. MDA5+ more frequently had arthralgia (86% vs. 47%, $p = 0.0001$), arthritis (86% vs. 42%, $p < 0.0001$), periungual capillary changes (84% vs. 63%, $p = 0.02$), abnormal PFTs (32% vs. 11%, $p = 0.038$), dyspnea at exertion (43% vs. 15%, $p = 0.004$), ILD (24% vs. 1.7%, $p = 0.0007$), weight loss (81% vs. 29%, $p < 0.0001$), and adenopathy (40% vs. 15%, $p = 0.008$) compared to Ab- pts. The median skeletal (0.5 vs. 0.0, $p < 0.0001$), pulmonary (0.0 vs. 0.0, $p = 0.018$) and constitutional (0.5 vs. 0.25, $p < 0.0001$) symptom scores at diagnosis were higher in MDA5+ compared to Ab- pts. Race, age, and gender distributions, delay to diagnosis and family history of autoimmune disease did not differ between anti-MDA5+ and Ab- pts. Anti-MDA5+ did not differ in total number or types of medications received, or in time to discontinuation of steroids or other major therapies compared to Ab- pts. Frequencies of complete clinical response and remission were also similar between MDA5+ vs. Ab- pts.

Multivariate analysis revealed weight loss ($p < 0.0001$), arthritis ($p = 0.007$) and lower serum CK level ($p = 0.005$) were significantly associated with anti-MDA5+ vs. Ab- pts. At median follow-up of 2.7 yrs, MDA5+ pts had more often skin rashes (58.3% vs. 33.9%, $p = 0.032$). There were no differences in other outcomes, including disease course, and mortality.

CONCLUSION

JDM pts with anti-MDA5 Abs in a large US myositis registry have frequent arthritis, arthralgia, weight loss, adenopathy, and ILD, but lower serum muscle enzyme levels (CK and aldolase). These pts have comparable outcomes and treatment responses to Ab- pts.

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QuantiFERON-TB Gold Testing in Hidradenitis Suppurativa Patients

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic, recurrent, inflammatory disease of the apocrine sweat glands, characterized by recurrent abscessing inflammation. The disease affects approximately 1-4% of the population and there is currently no known cure. A common treatment for HS is Tumor Necrosis Factor alpha (TNF- α) inhibitors. However, prior to commencing TNF- α inhibitors, screening for mycobacterium Tuberculosis (mTB) is required. Often this is achieved using QuantiFERON-TB Gold testing. QuantiFERON-TB Gold tests use an Interferon-Gamma Release Assay (IGRA) that measure the immune response that leukocytes have when mixed with antigens from the bacteria. In patients who have previously been exposed or who are actively infected with mTB leukocytes will release interferon-gamma. The purpose of this study was to investigate frequency of positive QuantiFERON-TB Gold testing in patients with HS and the characteristics of patients who test positive.

MATERIALS AND METHODS

This research was conducted through the Wound Etiology and Healing Study (WE-HEAL Study), a longitudinal biospecimen and data repository approved by The George Washington University IRB (041408). All subjects gave written informed consent for longitudinal collection of their data while they receive treatment according to standard of care. QuantiFERON-TB Gold testing was considered positive if the patient had a TB Ag minus Nil value greater than or equal to 0.35 IU/ML.

RESULTS

Of the 64 HS patients, 60 were tested for TB. Of the 60 total tested using QuantiFERON-TB Gold, 10% had abnormal results. Follow up testing revealed 50% of these results were false positives and 50% of these patients had confirmed latent TB. The false positive rate was 5.26%, and the true positive rate was 100%. The true positive rate of the QuantiFERON-TB Gold test has been reported to be 92% and the true negative rate equal to 94.74% - 99%. Our results align with the previous literature. There was no significant difference in age or sex between the positive and negative groups, and HS disease activity was not correlated with QuantiFERON-TB Gold results. Positive QuantiFERON-TB Gold testing was more common in the Asian population with HS ($p=0.008$) but this is not unexpected given known geographic risk factors for mTB exposure.

CONCLUSION

In conclusion, QuantiFERON-TB Gold testing in HS patients showed similar specificity and sensitivity as has been reported in the general population. Age and sex were not a predictor of a positive TB test, however, as in patients without HS certain racial groups had higher prevalence of positive results.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Pain Catastrophizing: Can It Predict Functioning?

INTRODUCTION

Pain catastrophizing is a maladaptive cognitive process in response to painful stimuli. This enhanced neural mechanism is thought to worsen the experience of pain and adversely impact functioning. Recent studies suggest that catastrophizing may be a predictor of pain severity and quality of life.

Catastrophizing is quantified using the Pain Catastrophizing Scale (PCS) score, consisting of three subscales, rumination, magnification, and helplessness⁴. The individual components can be evaluated as distinct predictors of functioning and thus modify treatment to target a specific aspect of catastrophizing.

METHODS

With IRB approval, the PCS was randomly administered to 98 patients. An additional questionnaire assessed interference with indices of functioning: activity, mood, walking, relations, sleep, enjoyment of life, and work. Pearson correlations were used to examine inter-item correlations and Cronbach's alpha for overall associations. Indicators of functioning and PCS components were evaluated using general linear regression models, adjusting for age, gender, duration, opioid use, and knowledge of the cause of pain.

RESULTS

Among the 98 observations, 37.76% were male, 57.14% used opioid, 73.47% knew the cause of pain. The Cronbach's alpha is 0.86 for overall functioning. There were no significant associations among baseline variables. Helplessness was a significant predictor of worsening activity, mood, enjoyment, relationships, sleep, and walking, with $p < 0.05$, while rumination predicted ability to work.

CONCLUSIONS

Of the three components of the PCS, helplessness was found to be the only significant predictor of the vast majority of functioning outcomes. Treatment targeting a patient's sense of helplessness may directly improve most aspects of functioning.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Building Referral Services at the Bridge to Care Clinic

The Bridge to Care Clinic was started in March 2015 by the George Washington School of Medicine & Health Sciences student-run free clinic, the GW Healing Clinic, in partnership with the Prince George's County Health Department. It was originally created with the goal of connecting uninsured residents of Prince George's County to the health care system and providing short-term medical management to them with the hope of ultimately transitioning them to a stable medical home for long-term care. Throughout the first year of the clinic, it became clear that many of our patients could not easily be transitioned to a medical home due to their lack of insurance or ability to get insurance and often their undocumented immigration status. The Bridge to Care Clinic found that it could effectively manage patient's primary care needs, but the two largest referrals we needed to make were for imaging studies and for specialty provider consultations. There were several referrals that patients were told they would receive that were not possible to find despite extensive student efforts. While surrounding counties like Washington, DC and Montgomery County have medical safety nets in place to address these challenges, Prince George's County currently does not. The goal of this project was three-fold: (1) to complete a review of existing literature on building a referral system in the student-run free clinic setting, (2) to develop a model to guide the development of a referral network at the Bridge to Care Clinic, and (3) to work to integrate this model into clinic operations. Of the six possible referral network models outlined in the literature review, the Bridge to Care Clinic has the ability to build on the Tin Cup model, which relies on personal relationships and soliciting in order to find specialty services for patients. As a result, the Bridge to Care clinic has been working more closely with other safety net organizations in Prince George's County to understand how they deal with similar challenges in their community and to build long-term partnerships. We have also added further training and discussion in the clinic for our volunteers to help them more appropriately understand the healthcare setting that we are operating in and plan their patient care accordingly. Overall, this research allowed the Bridge to Care Clinic to more appropriately understand its limitations, to find unique solutions to its referral challenges, and to adjust patient care and patient expectations appropriately.

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Analysis of HIV-1 Quasispecies Sequences Generated by High Throughput Sequencing (HTS) Using HIVE

The high level of genetic variability of Human Immunodeficiency Virus type 1 (HIV-1) is caused by the low fidelity of its replication machinery. This leads to evolution of swarm-like viral populations often described as quasispecies. High throughput sequencing (HTS) technology provides higher resolution over Sanger sequencing, enabling detection of low frequency variant genomes. However, quasispecies analysis is still a challenge due to the systematic noise, introduced by HTS technology. This leads to the increase in type I errors (also known as false positives) and the underlying genetic diversity, which can lead to mathematically insolvable type II errors (also known as false negatives). We have developed a pipeline using the tools in the High-performance Integrated Virtual Environment (HIVE), an HTS platform designed for big data analysis and management, to analyze viral populations within each sample and identify their subtype classification and recombination patterns of recombinants. RNA was extracted from 70 plasma samples of chronic HIV-1 infected patients. The 3' half genomes of HIV-1 were amplified using RT-PCR and PCR products were sequenced using Illumina MiSeq. The paired end reads for each sample were assembled using Geneious software and analyzed for presence of HIV-1 quasispecies using HIVE tools. Subtype analysis of 70 samples using Geneious software identified 17 A1s, 4 Bs, 30 Cs, 1 D, 6 CRF02_AG, and 12 unique recombinant forms (URFs). Additionally, we found up to 178 ambiguous bases in the consensus sequences from 41 viral samples (58.6%), suggesting the presence of viral subpopulations. However, Geneious could not determine the major quasispecies populations in each sample. We analyzed the same HTS reads using the HIV-1 quasispecies analysis pipeline and found one predominant population in 11 samples (15.7%), two to ten distinct populations in 45 samples (64.3%), 11-20 in 13 samples (18.16%), and 26 in one sample (1.4%). Interestingly, two equally major viral populations that were not detected by Geneious were identified in five samples (7.1%) by HIVE. The HIV-1 quasispecies analysis pipeline is reliable and more sensitive in its ability to identify distinct viral populations and the recombination patterns not identified by the Geneious software.

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CTLs Eliminate Defective HIV Proviruses Without Impacting Infectious Latent Reservoirs

BACKGROUND

The “shock-and-kill” paradigm of combining latency-reversing agents (LRAs) to “shock” latent HIV reservoirs awake, then “kill” them with immune effectors is currently the predominant strategy in the field of HIV cure research. However, the majority of “shock-and-kill” studies have been performed using primary cell models of HIV latency, which are imperfect representations of natural viral reservoirs found in people living with HIV. Thus, a need remains for a rigorous investigation of the efficacy of this cure strategy in natural reservoirs. Here, we treat *ex vivo* CD4+ T-cells from HIV+ individuals on long-term ARV therapy (>5 years), with LRAs and autologous HIV-specific CTL clones (targeting non-escaped epitopes), and assessed the impact on total and intact-inducible proviruses.

METHOD

HIV-specific CTL clones targeting known HIV epitopes were isolated from ARV-treated subjects by limiting dilution, and killing activities were confirmed by flow cytometric assays. We developed an HIV eradication (HIVE) assay to test the abilities of these CTLs to reduce viral reservoirs in combination with HDACi's, PKC activators, or an IL-15 super agonist with Pam₃CSK₄. In short, resting CD4+ T-cells from HIV+ leukapheresis samples are co-cultured with LRAs + CTLs for 5 days with ARVs, and activation/memory phenotypes are monitored. CD4+ T-cells are isolated after treatment, and total/intact-inducible reservoirs are measured by cell-associated HIV DNA (ddPCR) and by quantitative viral outgrowth assay (QVOA).

RESULTS

Combinations of bryostatin and IL-15SA+Pam₃CSK₄ with HIV-specific CTL generally led to significant decreases in cell-associated HIV DNA, with the greatest effects observed for bryostatin (up to 50% reductions, $p < 0.01$). Critically, these decreases in HIV DNA were not associated with measurable reductions in intact-inducible virus, regardless of the CTL clone or LRA combination used (powered to detect ~50% reductions with 95% confidence). Even when combined with PMA/ionomycin, CTLs were unable to drive reductions in intact-inducible virus. CTLs degranulated (CD107a) in response to autologous activated CD4+ T-cells that had been infected with virus from positive QVOA wells, ruling out a role for immune escape in our observation.

CONCLUSIONS

Recently, it has been demonstrated that some defective proviruses can be expressed as antigens, enabling CTL recognition. Data from our *ex vivo* experiments are consistent with the preferential depletion of defective proviruses by CTLs, leading to reductions in HIV DNA without impacting intact proviruses. Understanding and overcoming the mechanisms limiting CTL against the intact-inducible reservoir may be key to successful CTL-based shock and kill interventions.

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HIV-Specific T Cells Generated from HIV-Naive Adult and Cord Blood Donors Target a Range of Viral Epitopes—Implications for a Cure Strategy after Allogeneic Stem Cell Transplant

Adoptive T cell therapy has been successful in boosting viral-specific immunity post-HSCT, preventing viral rebound of CMV and EBV. However, therapeutic use of T cells to boost HIV-specific T cell immunity in HIV+ patients has met limited success. Despite multiple attempts to eradicate HIV with allogeneic-HSCT, there is only one case of functional HIV cure. We hypothesized that broadly HIV-specific CD8 and CD4 T-cells (dHXTCs) could be expanded from patients on ARVs, as well as HIV-negative adult and cord blood donors (dHXTC), employing a non-MHC-restricted approach for the treatment of HIV+ individuals after autologous or allogeneic HSCT.

We have expanded autologous dHXTCs from HIV+ subjects under NCT02208167. To extend this approach to the allogeneic HSCT setting, we generated dHXTCs from HIV-naive adults (n=9) and cord blood donors (n=11). IFN γ -ELISPOT showed dHXTCs from adult donors were specific against Gag, Nef, and Pol (mean=220 IFN γ SFC/1e5 cells) versus irrelevant antigen actin (mean=6 SFC/10⁵cells)(n=9). Similarly, we are able to produce cord dHXTCs (n=11) that showed specificity to Gag (mean=78 SFC/10⁵cells), Nef (mean=96 SFC/10⁵cells), or Pol (mean=174 SFC/10⁵cells), compared to CTL-only (mean=2 SFC/10⁵cells) in IFN γ -ELISPOT. dHXTCs were polyfunctional producing proinflammatory TNF α , IL2, IL6, IL8, and perforin responses (p<0.05) to HIV stimulation. Importantly, dHXTCs derived from both adult (p=0.0004) and cord blood (p=0.0003) were able to suppress HIV replication compared with nonspecific CD8 T cells when cocultured with autologous CD4 T cells infected with HIV SF162 at an Effector-to-Target ratio of 20:1. Exhaustion marker analysis of cord dHXTC CD3+ cells revealed minimal expression of PD1 (6.8%), TIM3 (3.05%), LAG3 (3.43%), KLRG1 (0.34%), and CD57 (1.08%)(n=6). Comparatively, analysis of adult dHXTC CD3+ cells revealed higher expression of PD1 (10.13%), TIM3 (7.63%), LAG3 (18.28%), KLRG1 (4.54%), and CD57 (2.43%)(n=6). Epitope mapping of both adult and cord dHXTC products revealed that products contained T cells recognizing unique epitopes not typically identified in HIV+ individuals, which may be critical in overcoming viral immune escape post-HSCT.

In summary, HIV-specific T cells can be expanded from HIV+ and HIVneg donors for clinical use. Focusing on donors with HLA types that are associated with well characterized HIV responses (e.g. HLA A02) or associated with delayed progression to AIDS (e.g. HLA B27, B51, B57) may allow us to identify HLA-restricted epitopes critical for the successful development of a potent HIV-specific T cell therapeutic. Hence, the administration of dHXTCs derived from naive donors could offer a unique curative strategy post-allogeneic stem cell transplant.

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IFITM1 Targets HIV-1 Latently Infected Cells for Antibody-Dependent Cytolysis

HIV-1 persistence in latent reservoirs during antiretroviral therapy (ART) is the main obstacle to virus eradication. To date, there is no marker that adequately identifies latently infected CD4+ T cells *in vivo*. Using a well-established *ex vivo* model, we generated latently infected CD4+ T cells and identified interferon-induced transmembrane protein 1 (IFITM1), a transmembrane antiviral factor, as being overexpressed in latently infected cells. By targeting IFITM1, we showed the efficient and specific killing of a latently infected cell line and CD4+ T cells from ART-suppressed patients through antibody-dependent cytotoxicity. We hypothesize that IFITM1 could mark natural reservoirs, identifying an immune target for killing of latently infected cells. These novel insights could be explored to develop clinical therapeutic approaches to effectively eradicate HIV-1.

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DNA-PK Inhibition Potently Represses HIV Transcription and Replication

The regulation of human immunodeficiency virus (HIV) transcription plays a critical role in HIV life cycle. Despite the use of highly effective antiretroviral therapy (HAART), the presence of latent or transcriptionally silent proviruses prevents cure and eradication of HIV infection. These transcriptionally silent proviruses are well protected from both the immune system and HAART regimens. Thus, in order to tackle the problem of latent HIV reservoirs, it is a prerequisite to define all the pathways that regulate HIV transcription.

We have previously reported that DNA-PK facilitates HIV transcription by interacting with the RNA polymerase II (RNAP II) complex recruited at HIV LTR. To extend those studies here we demonstrate the mechanisms of DNA-PK facilitating both HIV transcription and replication by promoting phosphorylation of C-terminal domain (CTD) of RNAP II. The inhibition of DNA-PK via highly specific small molecular inhibitors profoundly restricts both HIV transcription and replication in two different cell lines belonging to myeloid and lymphoid lineages, the main HIV target cell types in humans. We also show that DNA-PK affect Trim28 expression level and its phosphorylation, which suggests DNA-PK also affect HIV integration. To provide further physiological relevance, the results were confirmed in CD4+ primary T cells isolated from peripheral blood mononuclear cells (PBMCs). Treatment of the cells with DNA-PK inhibitors resulted in severe impairment of RNAP II carboxyl-terminal domain (CTD) phosphorylation and establishment of transcriptionally repressive heterochromatin structures at HIV LTR. Our results confirm the important role of DNA-PK in CTD phosphorylation and HIV transcription and replication. Intriguingly, this study sheds light on another important pathway that affects HIV gene expression. These findings provide strong evidence in supporting the use of DNA-PK inhibitors as supplements to HAART regimens in order to further enhance their effectiveness in restricting HIV replication.

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Correlations Between Latent Viral Reservoir Size and HIV-Specific T-Cell Responses in Antiretroviral Treated HIV Patients

BACKGROUND

Antiretroviral therapy (ART) potently suppresses HIV replication but is unable to cure infection. Current strategies aim to improve upon this by eradicating the quiescent, but replication competent, viral reservoirs that persist in these individuals. This can theoretically be achieved by reactivating quiescent virus with latency reversing agents, facilitating clearance by host immune effectors. Baseline characterization of latent viral reservoir parameters and host immune responses are necessary for selecting study participants in these eradication studies and for accurate assessments of end-points. Additionally, there remains a need to determine the relationship between latent viral reservoir sizes, host specific immune responses, and clinical background. Here, we characterize baseline levels of infectious viral reservoirs and cell-associated HIV DNA in CD4+ T-cells from leukapheresis samples. These data will be used both to test for associations between these factors and HIV-specific immune response, and to facilitate future studies on this sample bank.

METHODS

Infectious viral reservoirs were measured using quantitative viral outgrowth assay (QVOA). CD4+ T cells from HIV-infected donors on suppressive ART were activated and plated out in multiple dilutions. Induced virus was expanded in MOLT-4 cells and measured by p24 ELISA to calculate infectious units per million (IUPM). Cell-associated HIV DNA was measured using droplet digital PCR (ddPCR) on DNA from total CD4+ T cells. Lastly, cell-mediated immunity responses were mapped by ELISPOT using HIV peptide pools.

RESULTS

The 19 participants analyzed in this study had IUPMs ranging from 0.02 to 10.46 and a median IUPM of 0.421. Copies of cell-associated HIV DNA ranged anywhere from 23.00 to 1922.84 copies gag/million CD4+ T cells with the median being 444.52 copies gag/million. IUPM and cell-associated DNA were strongly positively correlated using Spearman's rank correlation ($R=0.815$, $p\leq 0.01$, $n=19$). Measurements of HIV-specific T-cell responses in corresponding samples are in process.

CONCLUSION

We observed a strong direct correlation between frequencies of cells harboring HIV DNA (ddPCR) and frequencies of cells harboring replication competent virus (QVOA). This was an unexpected finding as previous studies have reported a lack of such an association. We also observed that only ~1/1,000 provirus-harboring cells were capable of producing infectious virus. QVOA is currently considered to be the most relevant HIV reservoir measure as it assesses only proviruses capable of re-seeing replication, however it is slow, expensive, and cell-number intensive as compared to measuring HIV DNA. Our observation of a strong correlation between these measures is thus of significant interest.

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Ablation of IL-17 Expression Moderates Experimental Autoimmune Myasthenia Gravis Disease Severity

An array of cytokines influences the pathogenesis of early onset myasthenia gravis (MG) and its animal model, experimental autoimmune myasthenia gravis (EAMG). Patients with MG, in particular those with more severe weakness, have elevations of the pro-inflammatory cytokine IL-17 in the blood. We assessed the role of IL-17A in autoimmunity by inducing EAMG in mice with knockout of IL-17 and found a reduction of EAMG severity but not a complete ablation of disease. The IL-17ko mice had no evidence of weakness, low levels of acetylcholine receptor antibodies, and retention of acetylcholine receptor at the neuromuscular junction. Splenic germinal center size was reduced in EAMG IL-17ko mice along with elevations of Foxp3 and BCL-6 gene expression, suggesting a shift away from pro-inflammatory signals. The results emphasize the importance of IL-17 in EAMG development and that IL-17 independent pathways drive the autoimmune reaction.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

RNA Profiling of Whole Blood Reveals Strong Markers of Neutrophil Activation in Lung Infections

BACKGROUND

Peripheral blood is an easily accessible and informative source of changes in the transcriptome due to bacterial and viral infections. Remarkably, the white cell count is a standard, but insensitive and unreliable measure of internal infections. RNA profiling of whole blood was used to identify transcripts which could provide better sensitivity to internal infections.

METHODS

Tempus tubes were collected from 17 patients presenting to the ED with suspicion of lower respiratory infection (LRI), and compared with a similar number of patients with non-infectious complaints, such as hernia. Total RNA was prepared, DNase treated, and further purified using MinElute columns, and quantified by the A260/280 ratio on spectrophotometer. Discovery of differentially expressed was performed on Illumina BeadChip arrays, and then validated and extended using the droplet digital PCR (ddPCR).

RESULTS

A striking elevation of 2-50 fold in a number of neutrophil defensins (i.e. DEFA1) was observed in patients with LRI. Initially, several LRI subjects with normal levels of DEFA1 appeared to be outliers, but closer inspection of their clinical records indicated that the final diagnosis was likely non-infectious, such as asthma, pneumonitis, amiodarone toxicity, or pulmonary embolism. Related studies indicated that the ability to detect DEFA1 and related innate immune markers was highly dependent on the type of blood preservative used, with Tempus tubes yielding ~4-6 fold better levels than Paxgene.

CONCLUSIONS

RNA levels of DEFA1 in whole blood are potentially a highly sensitive measure of neutrophil activation by internal infections, in this case, in the lungs. DEFA1 RNA levels could be quantified as rapidly as a white blood cell count, and provides greater molecular information about activation of the innate immune system by pathogens. Immune transcripts were highly sensitive to the method of collection of the RNA, possibly explaining why prior studies have not detected this strong induction of DEFA1 in lung infection cases.

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Cytokine Production Varies Between Hidradenitis Suppurativa, Chronic Wounds and Normal Keratinocytes in an In-Vitro Wound Closure Model

Hidradenitis suppurativa (HS) is a chronic, recurrent, inflammatory disease of the apocrine glands. This disease affects approximately 1% of the population and there is currently no known cure. In order to develop therapies that target the molecular drivers of this disease, the molecular mechanisms of pathogenesis must be elucidated. Defective keratinocyte function has been implicated in the pathogenesis of HS. The purpose of this study was to compare keratinocyte function in HS, chronic wound (CW), and normal (N) skin samples.

METHODS

Human epidermal keratinocytes were cultured to reach 80% confluence in 6 well plates. A scratch assay was performed using a 1 ml sterile tip of about 100um in diameter. Culture supernatants were collected at 0, 24, 48, 72, and 96 hours after scratch.

Supernatants were analyzed using Luminex immunoassays. A panel of cytokines previously demonstrated to be correlated with HS pathogenesis were measured at each time point.

Apoptosis was assessed by flow cytometry for each group at 96-hour time-point after initial scratch using a FITC-annexinV and Propidium Iodide (PI). Apoptotic cells stained annexinV positive only, whereas necrotic cells stained double positive for annexinV and PI.

Cell viability was measured 96 hours post scratch by fluorescence microscopy with a live/dead vital dye staining method.

RESULTS

Cell viability was similar at 96 hours post scratch in the normal and HS keratinocytes. However, cell viability was significantly lower in chronic wound keratinocytes at 96 hours ($p=0.0138$).

Flow cytometry for AnnexinV and PI demonstrated that CW keratinocytes had a significantly higher rate of apoptosis (annexinV positive) and necrosis (annexinV and PI double positive cells) than normal ($p=0.0075$) and HS ($p=0.028$) keratinocytes.

Significantly higher levels of IL-1 α and VEGF were observed in the normal keratinocyte culture supernatant compared to CW. In contrast IL-22 levels were significantly lower in the HS culture supernatant than both CW and normal keratinocytes ($p=0.0008$). This finding indicates that IL-22 and its downstream pathways merit further investigation as molecules of interest in HS pathogenesis.

CONCLUSION

Using a keratinocyte wound healing model, we were able to show that keratinocytes harvested from HS, CW, and normal skin exhibit distinct behaviors in response to in-vitro wounding. Results indicate that keratinocyte viability and function are associated with, and may be influenced by, specific cytokines and growth factors such as IL-22. Inherent biologic mechanisms at the level of the keratinocyte may contribute to delayed healing in chronic wounds and the pathogenesis of hidradenitis suppurativa.

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From the Study of Chikungunya Arthritis Mechanisms in the Americas (CAMA): A Cross-Sectional Analysis of Chikungunya Arthritis Patients (Median 22-months Post-Infection) demonstrate a Lack of Viral Persistence in Synovial Fluid

BACKGROUND

Chikungunya virus (CHIKV) is a mosquito-borne disease that causes chronic joint pain for months to years in approximately one half of patients infected. The study objective was to determine if CHIKV virus persists in the synovial fluid in patients with chronic arthritis.

METHODS

Design: Cross-sectional

Setting: Atlántico and Bolívar Departments, Colombia.

Sampling: In 2014-2015, 907 patients with a clinical (424) or laboratory (483) confirmed CHIKV infection were evaluated. Sixty-five patients of these patients were randomly selected for screening of which 38 patients were eligible for the chronic arthritis group defined as a clinical or laboratory confirmed diagnosis of CHIKV infection with persistent arthritis including knee pain and swelling for at least three months after CHIKV infection. We also recruited 10 healthy controls without prior CHIKV infection.

Measures: Participants completed a symptom questionnaire. The presence of viral RNA in blood and synovial fluid was assessed by PCR.

RESULTS

Prior chikungunya infection was serologically confirmed in 33/38 (87%) of the cases via IgM (3%) and IgG ELISA (100%). Participants were predominantly women (79%), Afro-Colombian (53%) or White-Colombian (35%) with high school or less level of education (72%). CHIKV arthritis patients were a median 21.7 (IQR 20.7-22.7) months post CHIKV infection. Initial symptoms of CHIKV infection included joint pain (97%), joint swelling (97%), joint stiffness (91%), fever (91%) and rash (88%). The most commonly affected initial joints were knees (87%), elbows (76%), wrists (75%), fingers (56%) and toes (56%). None of the participants were PCR positive for persistent virus in the serum or synovial fluid.

CONCLUSIONS

CAMA was one of the largest observational studies involving CHIKV arthritis patients. Analysis of synovial fluid from all of the CHIKV patients revealed no evidence of CHIKV by PCR. This suggests that a possible mechanism whereby CHIKV causes arthritis is through induction of host autoimmune pathology.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Sarcoidosis with Caseating Granulomas and Little Red Rods

The paradigm that mycobacterial granulomas are caseating and sarcoid granulomas are noncaseating can lead to a quandary when faced with the patient with classic neurosarcoidosis symptoms but mediastinal lymph nodes with caseating granulomas. We present a case of a 47-year-old man who presented with classic neurosarcoidosis symptoms, negative quantiferon gold test, and negative standard mycobacterial culture, but had caseating granulomas and clusters of red rods on acid-fast special stain in his excisional mediastinal lymph node biopsy. With a differential between sarcoidosis and mycobacterial infection, treating for one condition could worsen the other. We review the numerous contradictory test results and their significance based on the literature. Deviations from expected results should be kept in mind, especially due to the very significant treatment differences for infectious versus inflammatory conditions.

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Application of Pharmacokinetics and Pharmacodynamics to Determine Dose Optimization using Beta Lactams in Pediatric Cystic Fibrosis Population

RATIONALE

Cystic Fibrosis (CF) leads to tremendous morbidity and mortality from chronic bacterial infections and acute pulmonary exacerbations (APE). Antibiotic treatment of APEs requires higher dosing and revised dosing strategies in CF patients given the variable absorption, distribution, metabolism, and excretion of the antibiotics in CF patients. Through identification of individual pharmacokinetic (PK) parameters using population PK modeling, the microbiologic efficacy of the drug (pharmacodynamics, PD) can be predicted. For optimal PD of beta lactams, the time above the minimum inhibitory concentration (MIC) must be greater than 40% of the dosing interval for carbapenems, 50% of the dosing interval for penicillins, and 60-70% of the dosing interval for cephalosporins. We sought to determine how many CF patients received an optimal antibiotic dosing with a beta lactam antibiotic regimen for pathogens grown on culture using a population PK modeling with Bayesian feedback approach.

METHODS

Children between the ages of 1-21 years with a known diagnosis of CF at Children's National Health System and hospitalized for intravenous (IV) antibiotics in the three years prior were recruited to participate. Subjects who experienced one or more APEs requiring IV antibiotics during the study were asked to participate for each treatment course. Information collected for each antibiotic included total daily dose, timing of administration, and duration of therapy. MICs for antibiotics were determined by conventional culture techniques. Plasma drug concentrations of IV beta lactam antibiotics during the treatment course were used to model the subjects' antimicrobial exposure.

RESULTS

Twenty patients experienced at least one APE for which they were treated with 31 courses of IV antibiotics. The most common antibiotics used were ceftazidime (65%), tobramycin (61%), meropenem (35%), piperacillin-tazobactam (19%), and vancomycin (16%). The most common combinations of antibiotics were ceftazidime and tobramycin (42%), and meropenem and tobramycin (16%). The patient's dosage of beta lactam antibiotics was deemed optimal or non-optimal based on the time spent above the MIC. 55% of the beta lactam drug regimens achieved optimal dosing, while 45% were suboptimal. Patients receiving ceftazidime were significantly more likely to achieve optimal PD indices ($p=0.0122$).

CONCLUSIONS

Patients receiving ceftazidime were significantly more likely to achieve optimal PD indices, while meropenem and piperacillin/tazobactam were equally likely to be suboptimal. This suggests that CF patients could benefit from therapeutic drug monitoring to improve their beta lactam antibiotic exposure, especially when trying to treat antibiotic resistant organisms.

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Inhibition of IL-13R α 2 Protects Mice from Acute Inflammatory Bowel Disease Pathogenesis

Inflammatory bowel disease (IBD), consisting of Crohn's disease and ulcerative colitis, is a chronic inflammatory disorder of the gastrointestinal tract. IBD pathogenesis has been associated with multiple factors including genetic predispositions, microbial dysbiosis, excessive innate and adaptive immune responses, and breakdowns in barrier function. Patients suffering from IBD are commonly administered anti-TNF α agents for treatment; however, up to 40% of patients are non-responders for unknown reasons. Previous studies identified elevated *IL13RA2* mRNA transcripts in mucosal biopsy samples of patients with active IBD who are non-responders compared to responders, serving as a possible predictive marker for non-responsiveness. IL-13R α 2 is a high affinity "decoy receptor" for IL-13, a cytokine with both anti-inflammatory and wound healing functions. In this study, we hypothesized that TNF α and IL-17 produced during the initiation of IBD induces IL-13R α 2 production that neutralizes the endogenous anti-inflammatory activity of IL-13, promoting IBD pathogenesis. Using an acute dextran sodium sulfate (DSS) model of mouse colitis with a 7-day recovery period, we show that DSS increases the production of both systemic and colonic IL-13R α 2 compared to untreated controls. DSS-induced colitis was less severe in *Il13ra2*^{-/-} mice compared to wild-type controls as decreased shortening of colon length was observed. Additionally, histological analysis of the distal colon revealed less goblet cell depletion, inflammatory cell infiltration, and submucosal inflammation in DSS-administered *Il13ra2*^{-/-} mice compared to DSS-administered wild-type mice. Gene expression, measured by Nanostring, revealed decreased expression of pro-inflammatory genes, such as *Il17ra*, *Ccl5*, *Csf1*, and *Il1r1* in colon tissue of DSS-administered *Il13ra2*^{-/-} mice compared to DSS-administered wild-type mice following 7 days of recovery. Together, these findings suggest that IL-13R α 2 functions as an important regulator of IBD pathogenesis, and the absence of IL-13R α 2 increases endogenous IL-13 bioactivity, which promotes anti-inflammatory responses and recovery from acute IBD.

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Characterizing the Antibody Response to Zika Virus in Colombia

Zika virus (ZIKV) is the latest in the family of flaviviruses, which include West Nile and Dengue, that have expanded their geographical scope in the last several decades. During acute flavivirus infection, the primary antibody response is comprised of IgM antibodies, followed by an IgG response. These responses predominantly target the Envelope (E) virus protein, which shares a high level of genetic similarity between ZIKV and Dengue. The occurrence of the most recent ZIKV outbreak in an area with endemic Dengue infections was a confounding factor in serological diagnosis efforts due to presence of cross-reactive flaviviral antibodies from previous infections. It remains a question how these pre-existing antibodies may have affected immune responses to ZIKV infection. The purpose of this study was to evaluate ZIKV specific antibody responses in a region with endemic Dengue infections. To conduct this study, plasma samples were collected from persons uninfected with ZIKV living in non-endemic Washington, D.C., and from persons living in Colombia, South America, who were either clinically diagnosed with ZIKV infection or not. The presence and strength of antibody responses to the ZIKV E protein were tested by performing indirect ELISAs to measure plasma binding to this protein, and both IgM and IgG titers were measured. We found very low background titers of IgG or IgM in plasma from North America, but detectable IgG titers in uninfected plasma from Colombian individuals. The highest IgG titers against the E protein were measured in ZIKV-infected plasma. For IgM, we detected no background binding in endemic-area plasma that was not ZIKV infected, and only detected one ZIKV-infected individual with an IgM titer. Overall, we observed a difference in pre-existing ZIKV IgG titers between people living in Colombia and in Washington, D.C. as well as very low IgM titers in recently ZIKV-infected individuals from Colombia. These data suggest a difference in baseline immunity for those living in regions with and without endemic Dengue. Presumably, this variation in baseline immunity could lead to an altered primary response to a Zika infection. We will continue to explore this hypothesis by testing more plasma samples using ELISAs and neutralization assays.

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Delayed Onset of IL-17A/F-Mediated Protective Immunity Against Community-Acquired MRSA Skin Infection

The high recurrence rate of *S. aureus* skin and soft tissue (SSTI) caused by community-acquired methicillin-resistant *S. aureus* (CA-MRSA), suggests that long-lasting immunity is not generated in many individuals. If immune-based therapies are to provide an alternative to antibiotics, understanding the key immune responses that promote protection against CA-MRSA is essential. Previous reports in mice found that IL-17A/F production by $\gamma\delta$ T cells mediated early neutrophil recruitment and host defense (within the first 24 hours) against a skin challenge with a methicillin-sensitive *S. aureus* laboratory strain. To elucidate the role of IL-17A/F in host defense against a CA-MRSA SSTI, IL-17A/F-deficient and wt mice were inoculated intradermally with a bioluminescent derivative of a CA-MRSA clinical isolate (USA300 LAC). Remarkably, IL-17A/F-deficient mice did not have an early immune defect, but rather they developed significantly larger lesions and increased bacterial burden compared with wt mice at days 7 and 10 following infection. Using IL-17A/F tdTomato/GFP fluorescent dual reporter mice, IL-17A/F cytokine expression peaked at days 7 and 10, corresponding with the timing of the immune defect in the IL-17A/F-deficient mice. The major IL-17A/F-producing cells in the skin and draining lymph nodes were $\gamma\delta$ T cells. Additionally, TNF α mRNA and protein levels were significantly decreased in the affected skin at day 7 in IL-17A/F-deficient mice compared with wt mice. Taken together, in response to a CA-MRSA SSTI, IL-17A/F (and TNF α) contributed to host defense at later time points during the infectious course than anticipated, suggesting that the delay in the protective immune response might be due to the increased virulence of CA-MRSA isolates.

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Development of an Interleukin-4-Inducing Principle from *Schistosoma Mansoni* Eggs (IPSE)-Specific PCR Assay as a Quantitative Predictor of Schistosomiasis-Associated Morbidity

Schistosomiasis is a neglected tropical disease affecting between 200-500 million people worldwide. The two species causing most human cases of schistosomiasis are *Schistosoma mansoni* and *Schistosoma haematobium*. The gold standard for diagnosis is parasitological detection of parasite eggs in stool using the Kato-Katz method. Counting eggs shed in stool is labor-intensive and inaccurate. Interleukin-4- inducing principle from *Schistosoma mansoni* eggs (IPSE) is the most abundant secreted protein from schistosome eggs. We hypothesized that the mRNA transcripts of the IPSE protein may be found in the liver tissue and stool of experimentally infected animals, and that these transcripts can be specifically targeted as a molecular diagnostic for schistosomiasis in endemic areas. Liver tissue and stool samples were collected from *S. mansoni* infected mice. PCR amplification of IPSE mRNA from liver samples was correlated with positive controls from serial dilutions of a known concentration of pure *S. mansoni* egg RNA. Concentration of sample's RNA was then compared to egg counts from stool samples. Results showed a positive correlation between increasing concentrations of IPSE RNA in infected liver tissue and increasing number of eggs found in stool. Our next steps are to repeat this experiment using *Schistosoma haematobium* infected hamsters, and to further develop the assay as a field diagnostic, correlate IPSE mRNA transcript levels in stool with stool egg counts.

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Restriction Factors Expression Profile in ZIKA virus

INTRODUCTION

Zika virus (ZIKV) has emerged as a severe health threat by virtue of its fast paced global spread and its associated morbidities, including microcephaly and Guillain-Barre syndrome. Restriction factors are potent antiviral host proteins that confer protection against several viral infections. Evaluating the overall anti-ZIKV repertoire in primary cells is critical to identifying host cell-intrinsic defenses against the virus.

RESULTS

We measured the expression of 18 antiviral factors, 14 inflammatory-related genes and 3 developmental associated genes ZIKV exposed peripheral blood mononuclear cell (PBMC), CD4+ T cell and monocyte populations, alongside controls. Expression levels of all genes and confirmation of ZIKV exposure was determined by Real-Time PCR.

Expression of APOBEC3B, IFITM3 and SAMHD1 was increased in PBMCs exposed to ZIKV for 24 hours. We detected an increased expression of CXCL10 (9-fold) and OCT4 gene (13-fold) compared to mock exposed PBMCs. In CD4+ T cells, APOBEC3C was the most up regulated gene (5-fold increase) of the APOBEC family. Among other viral restriction factors, IFITM3 and MX2 showed increased expression in CD4+ T cells (5-fold and 10-fold, respectively). Surprisingly, we detected a 12-fold increase expression for NANOG gene, an embryonic stem cell transcription factor. As opposed to PBMCs, OCT4 gene expression was not modified in CD4+ T cells following ZKV exposure. Limited differential expression was detected in monocytes when compared to corresponding donor PBMCs.

CONCLUSIONS

These results suggest that ZIKV exposure differentially modulates the expression of different antiviral, developmental and inflammatory genes in various immune cell populations. The relevance of these immune responses to the control of ZKV in vivo remains to be elucidated.

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Prevalence of Chronic Joint Pain following Chikungunya Infection from a Colombian Cohort

INTRODUCTION

Chikungunya fever is a viral illness spread by mosquitos. The infection presents with fever, headache, muscle pain, rash, and joint pain. Outbreaks have previously been restricted to Africa, Asia, Europe, and islands in the Indian and Pacific Oceans, causing chronic arthritis lasting months to years in these areas. In 2013, Chikungunya virus was found for the first time in the Americas, on islands in the Caribbean, and has now infected over 800,000 people. The primary objective of this study was to determine the prevalence of chronic arthritis after chikungunya infection in a Latin American cohort and define the clinical characteristics associated with chronic arthritis symptoms.

METHODS

494 Colombian patients with serologically confirmed Chikungunya were included in the study. Patients received a baseline symptom questionnaire and a 20-month telephonic follow-up symptom questionnaire. Comparisons of the reported symptoms were analyzed using chi-square or the Kruskal-Wallis.

RESULTS

The baseline characteristics of the patients include mean age 49 +/- 17 years, 81% female, 94% Mestizo ethnicity, and 76% with high school or less education. Common comorbidities seen in the study sample were hypertension, diabetes, lung disease and depression. 25% of the patients reported current, persistent joint pain at 20-month follow-up. The patients with persistent joint pain in weeks had increased duration of initial joint pain (40.2 ± 37.7) compared to the no persistent joint pain group (11.4 ± 26.3) with $p < 0.0001$. Of the 70 patients that missed work/school, 44 patients had persistent joint pain ($p < 0.001$), and of the 32 patients that had symptoms impact their capacity to continue normal activity, 24 had chronic joint pain ($p < 0.001$). Patients with persistent joint pain had increased disease activity of swollen joint count (0.5 ± 1.0) and tender joint count (3.0 ± 2.3) compared to the no persistent joint pain groups (0.04 ± 0.3 , 0.2 ± 0.8 , respectively) with $p < 0.0001$.

CONCLUSION

Chikungunya caused significant debilitating chronic arthritis in quarter of the patients at 20-months post infection.

FUTURE ANALYSIS

The baseline cytokine profile of cases of chikungunya arthritis in comparison to age and gender matched controls from the same cohort without persistent arthritis will be evaluated to further understand the development chikungunya arthritis and the biomarkers that may predict persistent arthritis.

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Use of Reverse Genetics Tools to Investigate Gene Function in Entomopathogenic Nematode *Heterorhabditis Bacteriophora*

Parasitic nematodes (PN) threaten the health of humans and livestock and cause major financial and socioeconomic burden to modern society. Treatment by periodic de-worming is limited by rapid re-infection rates and the inevitable development of drug resistance. A better understanding of the PN infective process will increase our ability to identify new drug targets and vaccine antigens. The requirement for the vertebrate host has hampered molecular investigations of PN infection mechanisms. *Heterorhabditis bacteriophora* is an entomopathogenic nematode that allows simultaneous monitoring of infection processes and host immune function and offers potential as a tractable model for PN infections. The ability to culture the complete life cycle on plates and the obligatory dauer infective stage permits investigation of molecular events that are inaccessible in other vertebrate host and parasite interactions. However, the molecular tools required for investigating gene function and infection mechanisms are lacking. We report our attempts to use reverse genetics to manipulate the gene function using two different molecular techniques: RNA interference and CRISPR/Cas9. For RNAi, double-stranded RNA of 4 genes (*cct-2*, *nol-5*, *dpy-7*, and *dpy-13*) was injected into the gonad of adult *H. bacteriophora* hermaphrodites. RNAi phenotypes were scored in the F1 progeny on the fifth-day post-injection, and knockdown of gene-specific transcripts was confirmed with real-time quantitative RT-PCR. CRISPR/Cas9 was used to mutate *Hba-dpy-13* gene. Cas9 protein along with guide RNA targeting the first exon of *Hba-dpy-13* was injected into the gonad of adult *H. bacteriophora*. F1 progeny were cloned and F2s were screened for mutants. We observed mutants at a frequency of ~1% for the total F2 progeny. Here we describe for the first time the successful use of reverse genetics tools to manipulate the gene expression in *H. bacteriophora*. These techniques can be used widely to study the molecular basis of parasitism.

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The Impact of HCV Treatment Advances on the HCV Continuum of Care

BACKGROUND

For treatment of chronic Hepatitis C Virus (HCV) infection, pegylated interferon-based regimens were given prior to 2014 and direct acting agents (DAA) were used as preferred therapy since 2014. We compared the Continuum of Care (CoC) for HCV mono-infected and HCV/HIV co-infected patients for those engaged in care and the effect of the DAA on rates of HCV treatment and HCV suppression.

METHODS

A retrospective review of the HCV Clinical Case Registry (HCV CCR) at the Washington, D.C. Veterans Affairs Medical Center (DC-VAMC) was conducted for the pegylated interferon treatment era (2008-2013) and the DAA era (2014-2015). The patients were analyzed based on a modified CoC: HCV diagnosis, engagement in medical care, prescription for HCV medication, and achievement of HCV suppression. HCV diagnosis was based on the HCV CCR confirmation. Engagement in medical care was defined as at least one outpatient encounter at DC-VAMC. Prescription of HCV medication included pegylated interferon during 2008-2013 and simeprevir, sofosbuvir, ledipasvir-sofosbuvir and ombitasvir-paritaprevir-ritonavir with dasabuvir with or without ribavirin during 2014-2015. Finally, HCV suppression was defined as >1 HCV RNA <12 IU/mL after HCV treatment. Chi-square with Yate's correction and Fisher's exact test, depending upon sample size, were used to assess for differences between mono-infected and co-infected patients as well as between treatment eras.

RESULTS

During the DAA era (2014-2015), more HCV/HIV co-infected and HCV mono-infected patients were treated (36% vs 5%, $p < 0.0001$; 23% vs. 6%, $p < 0.0001$) and had HCV suppression (86% vs 19%, $p < 0.0001$; 21% vs. 3%, $p < 0.0001$), when compared to the interferon era (2008-2013). More mono-infected patients achieved HCV suppression than co-infected patients (48.32% vs. 18.18%, $p = 0.007$) in the interferon era (2008-2013). More co-infected patients were treated than mono-infected (36% vs. 23%, $p < 0.0001$) during the DAA era.

CONCLUSION

While more co-infected and mono-infected patients achieved HCV viral suppression with DAAs, HCV/HIV co-infected patients treated in the DAA era achieved similar suppression rates compared to mono-infected patients.

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Emergency Department Approach to Electrical Toothbrush Associated Hand Injury, A Unique Case of Non-Oropharyngeal Injury

Puncture wounds are common injuries treated in the emergency department (ED). Prior studies have shown that toothbrushes are common reservoirs for oral flora, especially in regions near the head of the toothbrush near the bristles. ED providers must be aware of the danger associated with bacterial contamination of the associated wound and should be familiar with different pathogens and options for treatment. We present a unique case of a 30-year-old male with non-intraoral injury who presented to the ED after puncturing his left palm with the metal post of an electric toothbrush.

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Transcriptomic Analysis of the Activated Infective Juvenile Stage of the Entomopathogenic Nematode, *Heterorhabditis Bacteriophora*

Entomopathogenic nematodes [EPN] are a group of nematodes which seek, infect, and kill insect hosts. Due to the ability to grow the entire life cycle on bacterial lawns, entomopathogenic nematodes offer a possible solution to overcoming the problems encountered with studying parasitic nematodes. One EPN of particular interest is *Heterorhabditis bacteriophora*. The life cycle of *H. bacteriophora* has been well reported and contains an obligatory infective juvenile stage similar to the L3 stage of PNs. Additionally, efforts to develop a genetic toolkit have already begun. While the life cycle of *H. bacteriophora* has been well studied, the underlying molecular mechanisms involved in an IJ establishing infection of an insect host are still poorly understood. In order to determine possible genes of importance in IJ development and colonization of a host, transcriptome sequencing was performed on IJs incubated in insect hemolymph for 9 hours. Differentially expressed genes [DEGs] were identified using a trimmomatic-subread-edgeR pipeline and DEGs were further analysed for gene ontologies, KEGG pathways, and orthologue determination by blastp. After analysis, 1641 genes were found to be significantly increased or decreased (fold change ≥ 2 or fold change ≤ -2 , $p < 0.05$). DEGs were found in molecular pathways involving nematode larval development, growth, reproduction, locomotion, and catalytic activity, with a significant number of the genes unique to parasitic nematodes. Further analysis of the transcriptional changes identified a subset of upregulated DEGs as potential parasitism factors.

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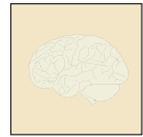
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The Role of Astrocytes in Maintaining the Blood-Brain Barrier

The blood-brain barrier (BBB) is a tightly regulated interface of the central nervous system (CNS) that protects the brain from circulating peripheral blood components while maintaining CNS homeostasis. BBB dysfunction can lead to increased pathogenesis in various neurodegenerative diseases, such as multiple sclerosis, Parkinson's and Alzheimer's diseases due to an enhanced influx of peripheral immune cells and blood-borne neurotoxins. Astrocytes have been implicated in the generation and maintenance of the BBB, however their precise role in BBB dynamics remains unclear. In the current study, we use a loss of function approach to investigate the function of astrocytes in the maintenance of the BBB. Utilizing the GFAP-iCP9 transgenic mouse line, we report that induction of the inducible caspase 9 (iCP9) signaling cascade under transcriptional control of the mouse GFAP promoter leads to apoptosis in GFAP+ astrocytes after treatment with a chemical inducer of dimerization (CID), and this leads to breakdown of the BBB at 48 hours. We i.v inject 40 kDa Dextran 12 hours, 2 days or 8 days after CID induction in the cortex and assess BBB integrity in areas of astrocyte loss. We examine astrocytic GFAP expression and microglial activation using GFAP and Iba1 immunofluorescent staining. Furthermore, astrocyte apoptosis induced in the cortex also leads to an upregulated immune response quantified by increased Iba1+ cells. Together, our data suggests that astrocytes play a vital role in the regulating BBB integrity and as such may be potential targets for restorative therapies under pathological conditions.

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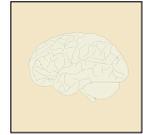
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Endoplasmic Reticulum Stress in the Paraventricular Nucleus of the Hypothalamus During Diet-induced Non-alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD), characterized by an accumulation of hepatic triglycerides, is directly related to obesity. Endoplasmic reticulum (ER) stress and activation of the unfolded protein response (UPR) has emerged as a key mechanism in the pathogenesis of NAFLD. We have recently shown that selectively reducing brain ER stress rescues obesity-induced NAFLD, although the neural regions involved remain unclear. The paraventricular nucleus of the hypothalamus (PVN) is a critical autonomic and endocrine control area, and accumulating evidence suggests a role for the PVN in obesity-related disorders. Taken together, we hypothesized that obesity-induced NAFLD is associated with ER stress in the PVN, particularly in neuron subtypes that project to the liver. PVN ER stress was evaluated using a combination of mRNA measurements, electron microscopy imaging of ER ultrastructure, and immunohistochemical approaches in a model of obesity-induced NAFLD, in which mice were fed high fat diet (HFD; 60% fat) or normal chow (5% fat) for a period of 10 weeks. Gene expression of several ER stress markers indicated 3- to 5-fold increases in UPR activation in HFD fed mice, relative to normal chow (e.g. *p58/PPK*: 1.1 ± 0.3 vs. 3.4 ± 0.2 ; *CHOP*: 1.0 ± 0.2 vs. 4.7 ± 0.8 ; normal chow vs. HFD, $p < 0.05$; $n = 3-4$ /group). We also performed electron microscopy to examine the ultrastructure of the rough ER in PVN neurons ($n = 3$ /group; 3-4 PVN sections per animal). The majority of PVN ER from normal chow animals exhibited flat, tube-like cisternae with dense ribosomal attachment, highlighting minimal evidence of ER stress (4/30 neurons with stressed ER; 15%). In contrast, 58% (16/28 neurons) of PVN neurons from obese animals had ER that appeared bloated with evidence of ribosomal detachment. Building upon this, we investigated whether obesity-induced NAFLD is associated with ER stress in PVN neuron subtypes that project to the liver, including oxytocin and corticotrophin releasing factor (CRF) expressing neurons. Immunohistochemistry analyses of the PVN revealed HFD-mediated upregulation of protein disulfide isomerase (PDI), an ER chaperone that is increased during ER stress situations. Co-localization analysis in obese mice indicated that $91\% \pm 1\%$ and $61\% \pm 3\%$ of PVN oxytocin and CRF neurons, respectively, co-localized with PDI, whereas less co-expression was found in normal chow controls (oxytocin $82\% \pm 1\%$; CRF $53\% \pm 2\%$). Collectively, these findings indicate that obesity-induced NAFLD is associated with PVN ER ultrastructural alterations and robust UPR activation, notably within PVN neuron subtypes that project to the liver. Moreover, these data suggest that PVN ER stress may be involved in the pathogenesis of NAFLD.

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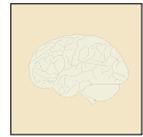
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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Brain Myo-inositol and Glutamine Levels as a Predictor of Neurotoxicity in Ornithine Transcarbamylase Deficiency

The urea cycle is a mechanism of the hepatic detoxification of ammonia, which accumulates within the body as a result of protein metabolism. It also is responsible for de novo synthesis of arginine (Scaglia & Lee, 2006). There are eight known deficiencies in the urea cycle (six enzymes and two transporters) that impair ureagenesis, the most common being ornithine transcarbamylase (OTC) deficiency. Congenital defects of enzymes within this cycle impair the conversion of ammonia to urea, and result in the accumulation of toxic intermediate metabolites. Inborn genetic defects in the metabolism of ammonia can lead to rapid hyperammonemia, which is characterized by symptoms of unexplained lethargy, headaches, seizures, hypoventilation, vomiting, coma, and psychomotor retardation (Ah Mew et al., 2015).

Neurotoxicity can result from a number of mechanisms, such as the accumulation of glutamine (Gln) in astrocytes leading to cellular swelling and cerebral edema (Gropman et al., 2008). As gln levels increase, myo-inositol (ml), an osmolyte, has a tendency to exit the cells in order to maintain astrocyte homeostasis (Gropman et al., 2008). Decreased ml is associated with injury to the deep white matter in the brain, and therefore may be an indicator of changes on the chemical level that may be evident even in clinically asymptomatic patients (Gropman et al., 2008). This present study, a part of an ongoing 10-year research project, focused on patients with OTC deficiency and the elevated levels of brain glutamine during hyperammonemic events, the suspected catalyst of neurotoxicity. Magnetic resonance spectroscopy (MRS) was used to investigate whether the ratio of glutamine to myo-inositol (ml) can be used as a predictor for cytotoxic edema, impairment of white matter tracts, and subsequent cell loss.

The results of this neuroimaging study were generally consistent with previous research findings, indicating that a lower gln and higher ml was correlated with reduced hospitalizations for hyperammonemic episodes and a milder clinical presentation in patients with OTC deficiency. Conversely, most symptomatic individuals showed an elevated gln with a compensatory decrease in ml levels. In patients with an elevated gln and ml, the clinical manifestations appear to be less severe, perhaps due to protective functions of the preserved ml.

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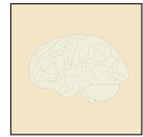
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Characterization and Quantification of Demyelinating Lesions in the Central Nervous System

Localized demyelinating injury has long been a method for studying the time course of central nervous system (CNS) diseases, such as Multiple Sclerosis (MS). Through this well-known and studied disease model, researchers have been able to map a timetable of how demyelinating lesions progress under “normal” conditions; thus allowing for the identification of the diseased form. Through the course of research, several methodologies have been lost or simplified to accommodate their difficulty and to provide for greater reproducibility. The best model of studying demyelination and remyelination in the CNS is a dorsal white-matter lesion in spinal cord, but this method proves to be difficult for some researchers to replicate. Our laboratory has developed and refined methods for the generation of reproducible lesions, as well as accurate and precise analysis of the extent of remyelination. These methods allow for superior data collection and more conclusive results. Here we catalogue how to target the lesion surgically, how to preserve the tissue, how to locate the lesioned tissue, and how to process the samples for final analysis. We also demonstrate how this precise analysis leads to undeniable results when comparing drug treatments with control samples.

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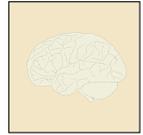
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CHILDREN'S NATIONAL MEDICAL CENTER

Analyzing Autism Spectrum Disorder Through Phenotypic and Genotypic Evaluation in a Preliminary Effort to Develop a Biomarker Screen

Autism Spectrum Disorder (ASD) comprises a broad spectrum of neurodevelopmental disorders characterized by restricted and repetitive behaviors as well as deficits in social communication and interaction. Currently, diagnosis of ASD relies on clinical behavioral assessments and interviews. Given the lack of biological criteria used in diagnosing and treating individuals with ASD, our group utilized existing genotypic and phenotypic data from children affected by ASD in an effort to develop a biomarker screen and to identify genetic susceptibilities specific to ASD. With a pilot participant pool of 342 individuals, 216 of which were children affected by ASD, we built a comprehensive dataset comparing genetic and phenotypic profiles for each participant. Saliva samples for each participant were analyzed for allele specific variants in 16 human genes related to autistic behavior and a battery of neuropsychological testing provided ample behavioral output. With these data, we analyzed relationships between gene variants and scores on tests examining executive function and social communication. Here, we present preliminary findings comparing scores on select neuropsychological measures by gene variants for the 16 genes analyzed.

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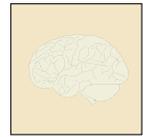
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Insulin Receptor Signaling in the Subfornical Organ Protects Against the Development of Metabolic Syndrome

Metabolic syndrome encompasses a combination of conditions including obesity, diabetes, dyslipidemia, and hypertension. Brain insulin resistance has emerged as a contributor to the development of metabolic syndrome, although the neural regions involved remain unclear. While most investigations have focused on insulin action in the hypothalamus, recent evidence suggests that the subfornical organ (SFO), a putative insulin responsive circumventricular organ well-known for cardiovascular control, is also involved in metabolic regulation. We therefore hypothesized that insulin receptor (IR) signaling in the SFO is involved in cardiovascular and metabolic regulation. In adult male C57Bl/6 mice, we first addressed SFO expression of the IR using immunohistochemistry, and observed that insulin receptor expressing cells are rich in the medial to caudal SFO, while robust IR-ir fibers are detected in the rostral SFO. We next utilized mice harboring a conditional allele of the IR gene, and selectively knocked down the SFO IR via SFO-targeted delivery of an adenovirus encoding Cre-recombinase (AdCre, n=11), or a control vector (AdLacZ, n=7). Both groups remained on normal chow, and cardiovascular and metabolic parameters were continuously monitored for 10 weeks. Selective removal of the SFO IR resulted in a lower mean arterial blood pressure that was evident at 1 week post-surgery and persisted for up to 10 weeks (104 ± 1 vs. 99 ± 1 mmHg, AdLacZ vs. AdCre, $p < 0.05$). This difference was due to a lower diastolic blood pressure (92 ± 1 vs. 87 ± 1 , AdLacZ vs. AdCre, $p < 0.05$), whereas systolic blood pressure was similar between groups. Heart rate was unchanged following ablation of the SFO IR. Removal of the SFO IR did not influence food intake, but resulted in an greater increase in body weight (weekly body weight gain: 0.5 ± 0.1 vs. 1.7 ± 0.4 g, AdLacZ vs. AdCre, $p < 0.05$), with overall elevations in adiposity. Analysis of the liver revealed substantial hepatic steatosis (46 ± 17 vs. 186 ± 29 mg/dl, AdLacZ vs. AdCre, $p < 0.05$) with parallel whole blood hypertriglyceridemia (112 ± 28 vs. 200 ± 20 mg/dl, AdLacZ vs. AdCre, $p < 0.05$). SFO-specific reductions in IR were confirmed by anatomical and molecular verification. These data demonstrate multidirectional roles for IR signaling in the SFO, with ablation of SFO IR resulting in an overall deleterious metabolic state while at the same time maintaining blood pressure at low levels. Moreover, these findings suggest that impairments in IR signaling in the SFO may contribute to metabolic syndrome.

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INSTITUTE OF BIOMEDICAL SCIENCES

Determining the Role of Pre-Synaptic NMDA Receptors in Topographic Map Formation

Efficient processing of sensory information is a critical function of the nervous system. Deficits in sensory processing and integration are commonly seen in neurodevelopmental disorders such as autism. In the visual system, neurons are often organized topographically, such that neighboring neurons monitor adjacent regions of space. Retinal ganglion cells (RGCs) project topographically to the superior colliculus (SC) and dorsal lateral geniculate nucleus (dLGN). During development, spontaneous correlated activity is critical for the establishment of topography in both the SC and dLGN. However, the mechanisms by which activity mediates topographic map formation remain unclear. Previous studies suggest that N-methyl-D-aspartate receptors (NMDARs) play a critical role in the establishment of topography by RGCs, however, it remains unclear if they are required both pre- and post-synaptically. To determine the role of pre-synaptic NMDARs in the development of topography, we used a conditional genetic strategy to specifically ablate NMDAR function in RGCs. We focally labeled RGCs and visualized the termination zone (TZ) of their projections in the SC and dLGN. Our preliminary data suggests that there was no change in TZ size in the SC, but TZs appeared to be larger in the dLGN. Bulk labeling of all RGCs in both eyes showed that eye-specific lamination was similar to controls, suggesting this activity-dependent process is unaffected in the absence of pre-synaptic NMDARs. Together, these data suggest that pre-synaptic NMDARs may play a critical role in retinogeniculate map formation but not in retinocollicular map formation.

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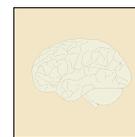
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SCHOOL OF ENGINEERING AND APPLIED SCIENCE

Molecular Analysis of Single Neurons with Known Function in the *Lymnaea stagnalis* Central Nervous System by Capillary Microsampling Electrospray Ionization Mass Spectrometry

The *Lymnaea stagnalis* central nervous system (CNS) is comprised of eleven ganglia containing neurons that regulate various behaviors, such as respiration and feeding, through the formation of neuronal networks. The influence of the cellular metabolite, lipid, and peptide composition on the function of a specific neuronal network can be investigated by single cell analysis. Correlated with their distinct functions, different types of neurons are expected to exhibit specific metabolite compositions.

Mass spectrometry (MS) can be used to obtain the metabolite, lipid, and peptide compositions of single cells. The subsequent addition of ion mobility separation (IMS) sorts gaseous ions based on their collision cross section (CCS), and enhances molecular coverage. Here, capillary microsampling electrospray ionization (ESI) IMS-MS is used for the analysis of neurons with identified functions, e.g., the right pedal dorsal neuron 1 (RPeD1) involved in the central pattern generator of respiration as well as long term memory formation in *L. stagnalis*.

The *L. stagnalis* CNS was removed in saline under a stereo microscope. Neurons were exposed through trypsin dissociation and manual removal of connective tissues. A glass capillary (tip diameter of $\sim 20 \mu\text{m}$) was inserted into a micropipette holder which was attached to a micromanipulator. Under an upright microscope, the capillary was lowered to impale the targeted neuron, and negative pressure was applied to extract the cell contents. The glass capillary was backfilled with electrospray solution and placed in front of the orifice of a mass spectrometer with IMS (Synapt G2S, Waters Co.). A high voltage of $\sim 2000 \text{ V}$ was applied to generate an electrospray containing the ionized cell contents. The produced ions were sorted by the IMS system based on their CCS values, and then analyzed by the time-of-flight mass spectrometer.

Preliminary analyses of single neurons, from multiple different ganglia, have been achieved. For a single neuron, negative ion mode analysis yielded ~ 300 ion species, of which 26 metabolites, e.g., ATP, glutathione, and NAD^+ , and 8 lipids, e.g., PC (16:0/18:1) and PI (18:0/20:4), were tentatively identified based on their accurate mass and CCS values. Peptides, such as polyglutamic acids, were identified by tandem MS. Based on the results from 5 single neurons, the adenylate energy charge (AEC) expressed by $\text{AEC} = \frac{([\text{ATP}] + 0.5[\text{ADP}])}{([\text{ATP}] + [\text{ADP}] + [\text{AMP}])}$ was calculated to be $\text{AEC} = 0.78 \pm 0.07$. The AEC is a measure of the energy state of a cell. Future directions include distinguishing the metabolic differences between neurons of specific function.

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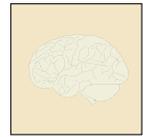
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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Suprasellar Epidermoid Cyst Originating from the Infundibulum: Case Report and Literature Review

Epidermoid cysts account for 1-2% of all brain tumors and are most commonly found in the cerebellopontine angle and parasellar cisterns. The slow growth of these tumors often results in them remaining asymptomatic until their size is large enough to compress surrounding structures, such as the pituitary stalk or optic chiasm. These cysts are believed to develop during the embryonal period of development, more specifically the 3rd to 5th weeks of gestation, with displacement of dorsal ectodermal cells normally residing in the midline. The incomplete separation of the neural and epidermal ectoderm allows for epiblast inclusion in the neural tube, which typically closes during this gestational period. A transsphenoidal approach for the removal of these tumors has been shown to reduce morbidity and mortality in these patients due to the better visualization of the neoplasm and surrounding anatomy and minimal (if any) brain retraction. Tumors and cysts of the pituitary stalk and hypothalamic region vary in presentation depending on their location, progression, and extension into the surrounding anatomy, in addition to the age and comorbidities of the patient; all of these factors must be addressed prior to surgery.

Here we present a rare case of an epidermoid cyst located in the suprasellar region, specifically originating from the infundibulum. Only one additional case with an epidermoid cyst originating within the pituitary stalk has been previously reported in the literature. The patient in this case presented with headaches, diplopia and blurred vision without any endocrinopathy. The only other reported case of an epidermoid cyst occurring within the infundibulum involved a young female patient who presented with a two year history of significant endocrine symptoms including amenorrhea, galactorrhea, polyuria and polydipsia. The similarities and differences between these cases highlight the variety of symptoms and clinical presentations of tumors residing within this region of the brain and the close attention to detail required in diagnosis.

As seen in our patient, tumors involving the pituitary stalk are challenging given the high risk for postoperative endocrinopathy, and management of surrounding structures including the hypothalamus, optic chiasm and vessels within the cavernous sinus. While other cases have presented with lesions intruding into the sellar region, epidermoid growth within the stalk itself is rare and our patient is an excellent example of the neurosurgical management of an epidermoid cyst residing in this specific location.

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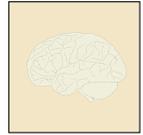
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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Shortage of Neurological Therapeutics: An Escalating Threat to Patient Care

BACKGROUND

Drug shortages are a well-recognized and growing threat to patient care, and can lead to the potential for substitutions of medications that are less effective and may delay critical treatments. Shortages have not been assessed for therapies for neurological conditions.

OBJECTIVE

We assess longitudinal trends in the shortages of generic drugs used for neurological conditions over a fifteen-year period in the United States.

METHODS

Drug shortage data from the University of Utah Drug Information Service (UUDIS) from 2001 to 2015 were analyzed. Medications were defined as those likely to be prescribed by a neurologist to treat a primary neurological condition or critical for care of a patient with a neurological condition. Trends in shortage length were assessed using standard descriptive statistics.

RESULTS

A total of 2,081 drug shortages were reported by UUDIS and 311 (15%) involved medications for neurological conditions. After excluding discontinued products, 291 shortages were analyzed. The median number of neurological drugs in shortage was 21 per month (median 7.4 per month). From 2001 to 2009, the number of neurological drugs in shortage never exceeded 25 in any month. However, beginning in 2009, shortages rose steadily, reaching a high of 50 in December 2012 and 50 again in December 2014. By the end of the study period, 30 neurological drugs remained in shortage. In over half the shortages, manufacturers did not provide a reason for the shortage. When reported, manufacturing delays, followed by supply/demand issues, raw material shortages, regulatory issues and business decisions were cited.

CONCLUSION

Caring for patients with neurological conditions is becoming increasingly compromised by U.S. drug shortages. Manufacturers, together with professional organizations, patient advocacy groups, and the government needs to continue to address this issue, which will escalate with a growing burden of neurological disease.

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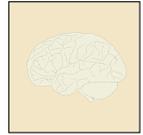
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Local Oligodendrocyte Ablation Leads to Demyelination and Axonal Damage in the Optic Nerve of MBP-iCP9 Transgenic Mice

Demyelination is one of the pathological hallmarks of multiple sclerosis. In order to study the direct effects of oligodendrocyte ablation on demyelination independent of inflammation, we have used intravitreal injections in transgenic mice, in which oligodendrocyte apoptosis is triggered by an inducible form of caspase 9 (iCP9) driven by a fragment of the myelin basic protein promoter and tagged by DsRed. In this model, dimerization of the iCP9 by a Chemical Inducer of Dimerization (CID), which penetrates the central nervous system (CNS), initiates the apoptotic pathway resulting in selective death of MBP-iCP9+ oligodendrocytes without impairing the non-MBP+ cells. Data indicate that 20% of CC1+ cells were DsRed+ in the spinal cord and that systemic CID exposure ablates 96% of this population. Local intravitreal CID injection leads to oligodendrocytes apoptosis, a 32% demyelination, and axonal damage in the optic nerve. Further studies will determine whether demyelination in the optic nerve can cause changes in gene expression of the retinal ganglion cells.

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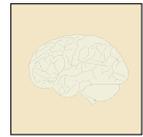
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Diffusion Tensor Imaging Identifies White Matter Dysmaturation in a Hypoxic Porcine Model of Congenital Heart Disease

BACKGROUND

Mortality and morbidity in the severe/complex congenital heart disease population have been significantly reduced due to advances in neonatal cardiac surgery and hospital care. However, even with these successes, congenital heart disease patients are at risk for developing long-term neurological deficits. Non-invasive peri-operative neuroimaging has suggested white matter underdevelopment and/or injury as a possible etiology. Despite these findings, the developmental mechanisms underpinning white matter deficits in congenital heart disease remain largely unexplored due to the technical challenges of in utero brain imaging and ethical concerns regarding the use of invasive technologies. To address these shortcomings, a porcine hypoxia model has been developed to recapitulate the white matter pathologies associated with pre-operative cerebral hypoxia in congenital heart disease. In this preliminary porcine study, diffusion tensor imaging (DTI) was used to assess the extent of white matter macroscopic and microstructural dysmaturation due to hypoxia.

METHODS

Female Yorkshire piglets were housed in a hypoxic environment (10.5% FiO₂) between days 3 and 14 after birth in order to model brain development under hypoxic conditions during the late third gestational trimester and early infancy (normoxic control n=2, experimental n=3). At 14 days of age, DTI images were obtained from postmortem brains using a segmented diffusion echo planar MRI sequence. Volume, fractional anisotropy, and axial diffusivity were computed for the corpus callosum and the internal capsule.

RESULTS

Following hypoxia, corpus callosum and internal capsule volumes were 14% and 22% smaller, respectively, despite a moderate total brain volume difference of 4%. In addition, hypoxic corpus callosum fractional anisotropy values were on average 13% lower than normoxic controls, whereas fractional anisotropy values for the internal capsule were only 2% lower. Hypoxic corpus callosum and internal capsule axial diffusivity values were 9% and 12% lower, respectively, compared with normoxic controls. Low fractional anisotropy in white matter regions has been correlated with reduced structural integrity and hypomyelination in a variety of neurological diseases. Additionally, decreases in axial diffusivity have been associated with axonal injury.

CONCLUSION

The findings of this experiment show that cerebral hypoxia results in reduced white matter maturation during critical periods of brain development. Furthermore, the results strengthen the evidence supporting pre-operative hypoxia as an etiology for the long-term neurologic sequelae of congenital heart disease.

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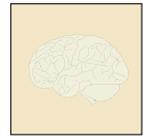
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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Discriminatory Digging Behavior in Mice: A Burrowing Test You Can Dig

Digging behavior is often used to test anxiety and repetitive behaviors in mice. However, digging is also a normal mouse behavior that can be focused toward different goals, i.e. foraging for food, burrowing for shelter, removing noxious stimuli or even for recreation as has been shown for dogs and ferrets. The marble burying test, where digging is measured as related to the number of marbles buried in deep bedding, has become a popular assay for anxiety, obsessive compulsive disorder (OCD) and repetitive behaviors in autism spectrum disorder (ASD) in mouse models. However, this test originated as a test of anxiety in rats looking at species specific defensive behavior in regard to noxious stimuli (e.g. shock rods). This does not necessarily translate to mice, since mice do not actively bury the marbles and do not spend much time interacting or reacting to the marbles at all, suggesting the number of marbles buried is incidental to digging activity and is not part of the defensive behavior exhibited by rats. Here, we present a test to make clear determinations between different types of digging behavior in mice based on the driving motivation for each type of digging. We look at food-seeking digging behavior as well as burrowing digging behavior.

A mutation in the *Cc2d1a* gene has been linked to ASD and intellectual disabilities (ID). We used the *Cc2d1a* mouse model available in the lab to look at their behavior in the burrowing test compared to wildtype (WT) mice. This mouse model has been shown to have cognitive and social deficits as well as hyperactivity and anxiety traits which is reflective of the human disorder.

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MiR-298 Counteracts Mutant Androgen Receptor Toxicity in Spinal and Bulbar Muscular Atrophy

Spinal and bulbar muscular atrophy (SBMA) is a currently untreatable adult-onset neuromuscular disease caused by expansion of a polyglutamine repeat in the androgen receptor (AR). In SBMA, as in other polyglutamine diseases, a toxic gain of function in the mutant protein is an important factor in the disease mechanism; therefore, reducing the mutant protein holds promise as an effective treatment strategy.

In this work we evaluated a microRNA (miRNA) to reduce AR expression. From a list of predicted miRNAs that target human AR, we selected microRNA-298 (miR-298) for its ability to down-regulate AR mRNA and protein levels when transfected in cells overexpressing wild-type and mutant AR and in SBMA patient-derived fibroblasts. We showed that miR-298 directly binds to the 3'-untranslated region (UTR) of the human AR transcript, and counteracts AR toxicity in vitro. Intravenous delivery of miR-298 with adeno-associated virus serotype 9 vector resulted in efficient transduction of muscle and spinalcord and amelioration of the disease phenotype in SBMA mice. Our findings support the development of miRNAs as a therapeutic strategy for SBMA and other neurodegenerative disorders caused by toxic proteins.

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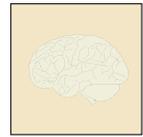
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SCHOOL OF ENGINEERING AND APPLIED SCIENCE
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Experience Dependent Plasticity of Cortical Attention States

Modulation of sensory processing by attention occurs in part through the regulation of cortical oscillations in sensory cortex. The attentive or aroused state is generated by high-frequency gamma oscillations while during inattentive state cortical activity is dominated by low-frequency oscillations. It is unknown how or if this cortical state modulation is affected by changes in sensory experience.

In this research, we study movement modulation of cortical oscillations in the visual cortex of rodents as a model for human selective attention. We use binocular eye-suturing in c57bl/6 mice as a model of visual deprivation in human, such as an early cataract, and study its effects through critical period. In eye-suture (ES) animals both eyelids are sutured before eye opening (EO). To assess cortical state regulation we obtain extracellular recordings of local field potentials (LFPs) and multi-unit activities (MUAs) using multi-electrode arrays in mice trained to run on a treadmill.

Our preliminary evidence suggests that in control animals motion robustly amplifies gamma rhythms and decreases slow wave activities as early as the critical period for ocular dominance plasticity, a key developmental time for organization of thalamic afferent. This modulation of cortical state by movement was negligible in ES animals suggesting that normal visual experience is necessary for the development of cortical states. As expected, firing rates in ES animals were lower than control animals, showing the ES reduced excitatory drive to cortex.

Thus our results suggest that cortical state regulation important for attention is either disrupted or delayed following deprivation of patterned vision. Further experiments will distinguish between these two possibilities and define the role of plasticity in the establishment of normal cortical oscillation.

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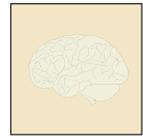
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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Differential mRNA Expression in Ectopic Germinal Centers of Myasthenia Gravis Thymus

Myasthenia gravis (MG) is an autoimmune neuromuscular disorder resulting in weakness of voluntary muscles. It is caused by antibodies directed against proteins present at the post-synaptic surface of neuromuscular junction (NMJ). A characteristic pathology of patients with early onset MG is thymic hyperplasia with ectopic germinal centers (GC). However, mechanisms that trigger and maintain thymic hyperplasia are poorly characterized.

In order to determine the central mechanisms involved in the pathology, thymus samples from MG patients were assessed by histology and grouped based on appearance of GC compared to samples without them. We assessed the differential mRNA expression profiles between the two groups by GeneChip® Human Transcriptome Array 2.0. Partek Genomic Suite 6.6 and Transcript Analysis Console 2.0 programs were used for further analysis. Forty eight annotated mRNA transcripts were identified that were differentially expressed between the two groups with greater than 1.5 fold difference in expression (ANOVA $p < 0.05$). We verified their expression by RT-PCR. We identified Regulator of G protein Signaling 13 or RGS13 that is known to be expressed in GC B-cells and regulate responsiveness to chemokine signaling. Upregulation of RGS13 was found to be associated with specimens having GC. We verified its expression in GC by immunohistochemistry.

Gene ontology (GO) enrichment analysis and Ingenuity Pathway Analysis (IPA) core analysis of differentially expressed genes indicate involvement of immune response regulation and cell proliferation pathways, indicating their importance in GC formation and regulation.

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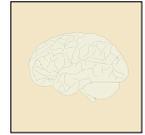
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Central Angiotensin Type 2 Receptor (AT₂R) Stimulation Promotes Enhanced Extinction of Fear Learning Independent of Cardiovascular Measures

Angiotensin II receptor subtypes (AT₁R and AT₂R) are found in regions of the brain critical to the expression and extinction of conditioned fear, however the neurobiological role(s) remain unknown. We propose that brain angiotensin receptors contribute to modulating inhibitory and excitatory conditioned fear circuits, that maybe important in the pathology of posttraumatic stress disorder (PTSD). The objective of this study was to investigate the role of brain AT₂R activation in fear memory. To study learned fear, C57BL/6 J mice (n= 6-10 / group) underwent classical Pavlovian fear conditioning, pairing auditory cues with foot shocks. The neural circuitry underlying the fear response is highly conserved across mammalian species, making rodent models a valuable tool in the study of fear learning disorders, such as PTSD. The percentage of time spent freezing in response to a conditioned stimulus is used to quantify the ability to learn and remember fearful associations. Using this model, the expression of learned fear is tested 24 hours after conditioning, and memory retention one day later. Following the acquisition of fear, AT₂R mRNA expression was elevated in the central amygdala (CeA) (t(22) = 2.5; p<0.05), a critical region involved in the consolidation of fear memory. To further evaluate the functional role of brain AT₂R, we administered (intra-cerebral ventricle-ICV) the highly selective AT₂R agonist Compound 21 (C21-Vicore Pharma). A single ICV injection of C21 at either 0.06ug/ul or 0.1 ug/ul was administered prior to fear expression testing. Acute C21 (0.1ug/ul) treated mice showed a significant reduction in both fear expression (% freezing) (saline-62.5% vs C21-41.2%) (t(27) = 2.8; p<0.05) and fear memory retention (saline-52.9% vs C21-22.6%) (t(28) = 3.8; p<0.05) following the acquisition of fear. Similarly, mice receiving C21 ICV for 2 weeks showed a trend for a reduction in fear memory retention (saline-57.2% vs C21-39.6%) (t(14) = 1.0; p=0.06 and this was independent of behavioral measures of anxiety as determined by open field testing. Moreover, C21 did not affect blood pressure or heart rate in telemetry-implanted mice (Saline-144 ± 3 SBP mmHg, HR 507 ± 13 bpm, n=5; C21 - 136 ± 3 SBP mmHg; HR 518 bpm ± 26, n=4). These data suggest that activation of central AT₂ receptors promote the extinction of learned fear. Further studies are required to determine the neurobiological mechanism(s), which may involve changes in cerebral vascular blood flow and/or modulation of neuronal excitability and plasticity.

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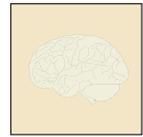
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A Novel In Vivo Model of Selective Focal Schwann Cell Ablation and Peripheral Demyelination

Schwann cells (SCs) are the major glial cells of the peripheral nervous system (PNS), responsible for the production and maintenance of myelin sheaths, which in turn facilitate saltatory conduction in myelinated nerve fibers. SC pathologies are often associated with motor and/or sensory deficits secondary to demyelination and subsequent axonal degeneration. In previous studies, we have shown the ability to selectively ablate cells of specific lineages using transgenic mice and a chemical inducer of dimerization (CID), to manipulate the caspase-9 mediated apoptotic pathway. The enzyme 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNP) is abundantly expressed in myelin-forming oligodendrocytes and SCs. To selectively ablate SCs using CID, we generated CNP-cre;iCP9 double transgenic mice by crossing CNP-cre animals with our inducible caspase 9 (iCP9) flox animals. This model allows for local directed ablation of SCs while minimizing unwanted effects of systemic delivery or global effects expected in other models of apoptosis, such as a heightened inflammatory response. Selective and local ablation of SCs with greater spatial and temporal control will enhance our understanding of the role they play in various demyelinating and non-demyelinating pathologies of the PNS.

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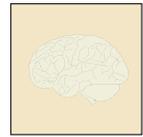
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Neurobehavioral Function in Adults Recovering Consciousness after Severe Traumatic Brain Injury: A Scoping Review

Severe Traumatic Brain Injury (TBI) is a devastating condition that results in significant disability and is a contributing factor to a third of all injury-related deaths in the United States (CDC, 2016). Approximately 1.7 million TBIs occur each year in the US and about ten percent of cases are considered severe (CDC, 2016; Klein et al, 2013). Individuals sustaining a severe TBI may spend extended periods of time in states of disordered consciousness (DOC). The Glasgow Coma Scale (GCS) is the tool most often utilized to assess consciousness and is useful in predicting mortality but has not been found to be effective for predicting prognosis (Lee et al, 2013). Numerous clinical trials for TBI patients have failed over the last two decades (Firsching et al, 2012) and inadequate assessment of neurobehavioral function (NBF) is cited as a key contributor.

This study reports on the findings from a scoping review of current literature examining the assessment of NBF and recovery along the continuum of DOC from coma to full consciousness. This scoping review was designed to capture the constructs researchers have used to measure NBF. The guiding study question for this review was, "What constructs are most frequently used to assess neurobehavioral function in adults recovering consciousness after severe TBI with DOC?"

A scoping review examines the extent and nature of the research, identifies gaps in the literature, and may establish the significance of commencing a full systematic review (Levac, Colquhoun, & O'Brien, 2010). The scoping review methodological framework was followed to conduct this study (Arksey and O'Malley, 2005). Two databases, PubMed and Scopus, were searched using 21 search terms generated from three main concepts: "traumatic brain injury" (n=3), "neurobehavioral function" (n=6), and "outcomes" (n=12), resulting in 229 articles. After removal of duplicates and articles not related to the research question, 58 articles were included in the scoping review that thematically addressed the topics of NBF and recovery of consciousness (Levac et al, 2010).

This inductive approach identified four overarching themes: "Predicting Outcomes", "Treatment", "Neural Pathways", and "Pharmacotherapy". The majority of articles were thematically grouped in two of the four categories, "Predicting Outcomes" (n=29) and "Treatment" (n=16). Across all four themes, clinician-reported outcome assessments and neuro-imaging were utilized most often to understand neurobehavioral function during recovery of consciousness.

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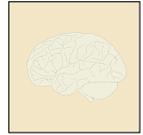
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Brain Angiotensin type 2 Receptor (AT₂R) Distribution and Role in Fear Memory

Previous clinical studies identify the renin-angiotensin system (RAS) as a potential therapeutic target in PTSD, however the mechanism(s) are unknown. Brain angiotensin receptors are expressed in limbic and non-limbic structures and we propose these receptors contributes to modulating inhibitory and excitatory fear circuits important for the consolidation and extinction of fear memory in PTSD. Using a transgenic reporter model (Agtr2-eGFP BAC mouse), these studies aimed to further characterize and identify the role of the brain angiotensin type 2-receptor (Agtr2) in fear related brain regions and behavior. We confirmed that Agtr2 is highly expressed in regions such as prefrontal cortex (PFC), bed nucleus of the stria terminalis (BNST), central amygdala (CeA), medial amygdala (MeA) and periaqueductal gray (PAG). The average cell density in these brain regions is 277.7 ± 24.2 neurons/mm², which is significantly higher than non-limbic areas such as dorsal striatum (3.8189 ± 0.4929 neurons/mm²). Moreover, Agtr2-eGFP positive cells are neuronal, non-glutamatergic as they are highly co-localized with the neuronal specific marker NeuN, but not with the astrocytic, microglia and glutamatergic markers GFAP, Iba-1 and Tbr-1 respectively. To further investigate the possible function of brain Agtr2, we used Pavlovian fear conditioning, an animal model commonly used to study PTSD (pairing of auditory cues with footshocks). Using C57BL/6J mice (n= 6 / group) we injected the highly selective AT₂R agonist Compound 21 (C21) bilaterally into the CeA, a critical brain region for the consolidation and extinction of fear memory. Mice receiving C21 into the CeA prior to fear extinction, displayed a trend for enhanced extinction (C21 group - 43% freezing vs. saline - 55% freezing; p=0.19) compared to control. Together, these data provide further evidence characterizing the role of Agtr2 in brain regions important for the consolidation and expression of conditioned fear, which may lead to novel drug targets for the treatment of PTSD and fear related disorders.

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Correlation of 1-Hour Post-Load Plasma Glucose and Pediatric Cardiometabolic Risk

As more children develop obesity, they are at increasing risk for developing type 2 diabetes mellitus, and dyslipidemia at earlier ages. Individuals with obesity and T2DM are at risk for metabolic dyslipidemia, which is characterized by various markers of inflammation and atherogenesis. Altered adipocytokines, dyslipidemia, and the hyperglycemia of T2DM can initiate endothelial injury and an inflammatory process, accelerating the progression of atherosclerosis. One commonly used method for ascertaining risk of T2DM is an oral glucose tolerance test. There is insufficient research on the use of this test in the pediatric population, and how the result interpretation may differ from the adult population. This study compares the lipids, inflammatory factors, adipocytokines, and subclinical atherosclerosis in four groups of adolescents: Lean Controls, Obese Insulin Sensitive, Obese Insulin Resistant without T2DM, and Obese with T2DM. Comparison of these groups will allow differentiation of the effects of obesity, insulin resistance, and insulin secretory defects causing hyperglycemia. The goal is to identify which adolescents are at the highest CVD risk, and what factors may be contributing to that risk.

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In-Person Clinic-Based versus Smartphone Application-Based Plans for Weight Loss among the Overweight and Obese

BACKGROUND

The prevalence of obesity in the United States (US) among adult men and women continues to rise. Obesity is a major health problem among the US population commonly increasing the risk of significant comorbidities such as type 2 diabetes mellitus, dyslipidemia, and cardiovascular diseases. While in-person interventions that address the dietary, exercise, and behavioral aspects of obesity are common, a new wave of weight loss strategies has emerged with a greater emphasis on technology and internet-based approaches.

METHODS

This study compared the efficacy of a traditional in-person weight loss approach utilized by the Johns Hopkins Weight Management Center to a weight loss treatment via the smartphone application (app), Loselt!. It was hypothesized that the comparison between the Johns Hopkins Weight Management Center protocol and the Loselt! App program over a 12-week period would show no difference in the percent of actual weight loss compared to theoretical weight loss i.e., compliance. Using a case-control analysis, 92 Johns Hopkins patients were matched to 3,380 Loselt! App participants based on gender, age, starting weight, starting BMI, caloric restriction level, and estimated total daily energy expenditure with light activity.

RESULTS

Clinic patients achieved 94.1% of their theoretical weight loss compared to Loselt! users who achieved 62.8% after matching. In addition, clinic patients achieved 10.5% total weight loss compared to Loselt! users who lost 6.1% after matching. Overall, clinic patients showed a significantly greater percent of realized theoretical weight loss or compliance (mean = 28.6, SD = 9.6, $p > 0.003$) compared to Loselt! users. Moreover, clinic patients showed a significantly greater percent of total weight loss (mean = 3.2, SD = 0.9, $p > 0.001$) compared to Loselt! users.

DISCUSSION

While weight loss programs are ubiquitous, historically, long-term compliance to these programs is often limited. We found that both clinic-based and technology-based weight loss programs provided a degree of weight loss success when participants are matched for demographic and biologic characteristics. These findings suggest that application-based weight loss programs may have a place in weight control. However, as shown here, they may not be as efficacious as a clinic-based intervention. Nonetheless, this technology may be particularly helpful as a cost-effective means for influencing patient dietary and exercise behaviors. Future studies should examine whether smartphone applications like Loselt! would produce an additive benefit when used in combination with more traditional approaches to weight control.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES
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Increased Visceral Adiposity in Obese Adolescents with Hyperglycemia Compared to Normoglycemic Obese Peers

BACKGROUND

The increase in pediatric obesity in recent decades has led to an increase in the prevalence of type 2 diabetes (T2DM) in children and adolescents. Obesity increases insulin resistance, a known risk factor for T2DM. However, not all adolescents with insulin resistance go on to develop T2DM. Other risk factors, such as family history, also play a role. Excess visceral fat as opposed to subcutaneous fat has been associated with increased metabolic abnormalities.

OBJECTIVE

To investigate the relationship between visceral adiposity and abnormal glucose tolerance in obese adolescents.

METHODS

This observational cohort study enrolled pubertal children (Tanner stage >1), ages 12 -19 years, BMI $\geq 95^{\text{th}}$ percentile, and compared those with abnormal glucose tolerance by oral glucose tolerance test (OGTT) or previous diagnosis of T2DM (n=34) (Abnl Gluc Tol), to those with normal glucose tolerance by OGTT (n=80) (NI Gluc Tol). Visceral fat area (VFAT) was measured by dual x-ray absorptiometry (DXA). VFAT was square root transformed to achieve a normal distribution.

RESULTS

Groups were similar in age (14.51 years \pm 1.41 (Abnl Gluc Tol) vs 14.49 years \pm 1.41 (NI Gluc Tol), $p = 0.94$), sex (50% male vs 39% male, $p = 0.27$), and race (79% African American vs 80% African American, $p = 0.77$). VFAT was significantly higher in the Abnl Gluc Tol group compared to the NI Gluc Tol group (90.68 \pm 25.22 vs 76.54 \pm 25.41, respectively, $p = 0.009$) by t-test. Linear regression analysis demonstrated that this difference persisted after adjusting for BMI Z-score, age, sex, and race ($\beta = 0.892$, $p = 0.000$). Greater BMI z-score, age and male sex were also associated with increased visceral adiposity.

CONCLUSIONS

Obese adolescents with abnormal glucose tolerance have significantly greater visceral adiposity compared to normoglycemic obese peers, even after adjustment for BMI z-score, sex and age. Future longitudinal studies are needed to determine whether increased visceral adiposity predicts conversion to abnormal glucose tolerance among obese adolescents.

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Performance of Non-invasive Tests to Predict Significant Liver Fibrosis in Patients with Morbid Obesity

Non-Alcoholic Fatty Liver Disease (NAFLD) affects more than 90% of patients with morbid obesity (MO) and approximately 30% have significant liver fibrosis and/or cirrhosis. Liver biopsy is the gold standard for diagnosis of significant liver fibrosis and cirrhosis; however, several non-invasive tests have been suggested to predict the presence or absence of significant liver fibrosis and to avoid liver biopsy in these patients. The aim of this study was to determine the ability of these tests to predict significant liver fibrosis, specifically in patients with MO.

METHODS

Liver biopsies from patients with MO undergoing gastric bypass surgery were studied in retrospective sequence from 2016 to 2014 and determined by histology to show either no significant fibrosis (NSF) or significant fibrosis (SF) based on the presence of no bridges or bridges of fibrosis, respectively; to increase representation of biopsies with SF, additional biopsies with SF were added from 2013-2004. Inclusion criteria after EMR review were diagnosis of MO (BMI ≥ 40 kg/m² or > 35 kg/m² with Diabetes or hypertension) and availability of data concerning sex, age, BMI, Diabetes, platelet count, AST, ALT and albumin within 6 months before surgery; exclusion criteria were no other potential causes of liver pathology. The non-invasive tests used to estimate SF on liver biopsy included NAFLD fibrosis, BARD, APRI (0.7 cut off) and Fib4 scores, based on combinations of age, BMI, Diabetes, AST, ALT, platelets, and albumin. Test cut-off scores for SF were set using available on-line calculators.

RESULTS

One hundred fifty-five patients with MO met study criteria, 31 with SF. Patients were 45 ± 11 years of age, with BMI 46.7 ± 8.6 kg/m² and 83% female; no significant differences between patients with SF and NSF. Diabetes was more prevalent in patients with SF vs NSF (83 vs 54%, $p < 0.0001$). Non-invasive test results for Sensitivity and Specificity found:

NAFLD - Sensitivity 41.9% (13/31) and Specificity 86.3% (107/124);

BARD - 90.3% (28/31) 29.8% (37/124);

FIB-4 - 3.2% (1/31) 100% (124/124);

APRI - 16% (5/31) 99% (123/124).

CONCLUSIONS

No single non-invasive test showed sufficient sensitivity and specificity to recommend it as a test to predict SF in patients with MO; however, results suggest that a combination of these non-invasive test results might improve their predictive value. Diabetes was associated with SF in patients with MO and is likely to be a risk factor for progressive liver fibrosis in these patients.

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Variables Associated with Overweight/Obesity among African American Women with Hypertension and Diabetes

BACKGROUND

Obesity is the second leading cause of preventable death next to tobacco use. It is a contributing factor to chronic diseases such as hypertension and diabetes. Although it is prevalent in all populations regardless of age, sex, race, ethnicity, socioeconomic status, education level, or geographic region, it disproportionately affects African Americans (AA), in particularly AA women. Overweight/obesity increases AA women's chances of developing chronic illnesses such as diabetes, hypertension, heart disease and stroke, and decreases their life expectancy. It is imperative to identify modifiable risk factors that relate to overweight/obesity among this population so health care providers can develop interventions to decrease the rate of overweight/obesity. The purpose of this study was to explore variables associated with overweight/obesity among AA women with hypertension and diabetes.

METHODS

This was a secondary data analysis using descriptive-correlational design to analyze cross sectional data obtained from the 2013 Behavioral Risk Factor Surveillance System (BRFSS), the nation's premier system of health-related ongoing telephone health survey of adults ages 18 years and older. AA women (n = 1823) with high blood pressure and/or diabetes were included in the analysis. The dependent variable was overweight/obesity. Independent variables included demographics (age, education, marital status, and household income), physical activity, consumption of fruits/vegetables, life satisfaction, perceived emotional support, and inadequate sleep. Descriptive statistics were performed on all study variables. Chi-Square analysis was used to study the relationship between each independent variable and the dependent variable. For all analyses, alpha was set at 0.05.

RESULTS

The majority of the sample of 1,823 AA women were 44 years of age or younger (97.2%). This group also had a significantly higher percentage of those in the overweight/obese category $\chi^2(1) = 13.32, p < .001$ versus those 45 years and older. There were no statistically significant results for any of the independent variables.

CONCLUSIONS

Despite the lack of statistically significant results for this study, it is important to note the significant missing data on the emotional support and life satisfaction scores. The lack of responses could steer the need for further studies where obtaining this information is made possible within a more sensitive and trusting manner. Thus, further identifying lasting interventions that decrease the rate of overweight/obese AA women, as the interventions would require a multifaceted approach.

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Hepatic Sympathetic Denervation Reduces Non-alcoholic Fatty Liver Disease in Diet-Induced Obese Mice

Non-alcoholic fatty liver disease (NAFLD), characterized by elevated liver triglycerides, is directly associated with obesity and a significant contributor to metabolic and cardiovascular diseases. We have recently demonstrated that hepatic sympathetic nerve activity is significantly elevated in mice that were fed a high fat diet (HFD, 60% fat), relative to normal chow controls (NC, 5% fat) (0.24 ± 0.02 vs. 0.36 ± 0.03 v*s/min, NC vs. HFD; $p < 0.05$). These findings indicate a state of hepatic sympathetic overactivity during diet-induced NAFLD; however, the role of the hepatic sympathetic nervous system in NAFLD pathology remains unknown. Therefore, we tested the hypothesis that selective removal of the hepatic sympathetic nerves would rescue obesity-induced NAFLD. Male C57B1/6 mice were fed a HFD or NC for 10 weeks. Liver sympathetic denervation was performed by applying 10% phenol in ethanol to the hepatic nerve bundle, whereas saline was used as a sham control. Hepatic denervation did not influence body mass, caloric intake, water consumption, metabolic rate, and ambulatory activity in NC or HFD mice. As expected, HFD feeding resulted in significant elevations in hepatic triglyceride levels, when compared to NC (2.4 ± 0.5 vs. 6.4 ± 0.6 nmol/mg of liver tissue, NC Sham vs. HFD Sham; $p < 0.05$). Following liver denervation, hepatic steatosis was partially reduced in HFD fed mice back towards normal chow levels (2.4 ± 0.4 vs. 4.5 ± 0.7 nmol/mg of liver tissue, NC Sham vs. HFD Denervation; $p > 0.05$). In line with this, histological examination (H&E and Oil Red O) revealed widespread and severe lipid accumulation in the liver of HFD sham animals, which was reduced following liver denervation. Interestingly, real time PCR analysis revealed that liver denervation in obese mice was associated with a reduction in markers of hepatic free fatty acid uptake (e.g. *FAT/CD36*, 8.2 ± 1.6 vs. 2.8 ± 0.6 fold NC sham; HFD Sham vs. HFD Denervation; $p < 0.05$) and gluconeogenesis (e.g. *G6Pase*, 23.1 ± 5.3 vs. 9.2 ± 2.7 fold NC sham; HFD Sham vs. HFD Denervation; $p = 0.15$). Examination of tissue norepinephrine levels, as an indicator of sympathetic nerve activity, confirmed an ~70% reduction in the liver ($p < 0.05$ for all). Collectively, these findings demonstrate that selective ablation of hepatic sympathetic nerves partially ameliorates hepatic steatosis in diet-induced obesity, independent of changes in body weight, food intake and adiposity. Moreover, these data suggest that targeting hepatic sympathetic overactivity may provide a novel therapeutic strategy to treat NAFLD.

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Artificial Sweetener such as Sucralose May Promote Inflammation in Human Subcutaneous Fat-derived Mesenchymal Stromal Cells (MSCs)

Artificial sweeteners are extensively used as alternatives for caloric sugars, particularly among individuals with obesity and diabetes, who have an increased cardiovascular disease (CVD) risk. Sucralose is a common artificial sweetener used as a low calorie sweetener (LCS) in multiple food products. MSCs are multipotent mesenchymal tissue derived cells, which differentiates into fat, bone, muscle and cartilage depending on the body's repair needs, cell environment or culture media conditions. Based on human epidemiological studies that shows an association with LCS use and obesity, we decided to investigate whether varying concentrations of sucralose in an obesogenic environment alter differentiation of MSCs more towards adipogenesis and promote inflammation in MSCs. We cultured commercially obtained MSCs (Lonza, Inc) in Adipogenic Media (Lonza, Inc) with sucralose (0, 0.2, 0.45, 1.0 mM) for 12 days. After 12 days MSCs were stained with Oil Red O stain for imaging and lipolysis quantification using a plate reader (520nm). Rest of the cultured MSCs were collected for RT-PCR.

RESULTS

Lipolysis and staining experiments indicate that intracellular fat droplet accumulation increased in parallel with increasing sucralose concentrations. Using RT-PCR, we noted higher expression of adipogenic genes such as CEBPa (1.32x fold), and FABP4 (1.04x) at 0.2mM of sucralose concentration (a high but physiological concentration). In comparison, 1mM sucralose (reflecting supra-physiologic concentrations) showed markedly increased expression of CEBPa (3.45x), and FABP4 (4.06x). MSCs cultured in sucralose (1mM) upregulated the antioxidant glutathione peroxidase-3 (2.00x) possibly in response to increased superoxide accumulation and cellular inflammation. Increased expression of sweet taste receptor subunit T1R2 (2.45x) was also noted. In summary, upregulation of adipogenic genes such as CEBPa and FABP-4 in hMSCs, cultured in near physiological concentrations of sucralose, indicate possible causality between increased fat deposition and sweetener use. Further studies at physiological concentrations of sucralose using multipotent cells like MSCs in-vivo along with human studies are needed to establish whether sucralose use leads to increased fat deposition particularly in a high CVD risk population of obesity, prediabetes and diabetes.

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Loss of HDAC11 in Mice Regulates Hepatic Lipid Metabolism via AMPK/ACC1/CPT1 Pathway

HDAC11 is a member of histone deacetylases (HDACs) family, but its biological functions and molecular mechanisms are poorly studied. In this study we have identified that *HDAC11* knockout mice had resistance to high-fat diet induced obesity, fatty liver, hyperlipidemia and glucose intolerance. Also, our results indicated that loss of HDAC11 activated the thermogenesis and oxygen consumption. Mechanistically, in hepatocyte HDAC11 negatively regulated Carnitine palmitoyltransferase I (CPT1) activity. Our data further showed that HDAC11 could inhibit CPT1 activity from dephosphorylation of ACC1 and AMPK. These findings established HDAC11 regulated hepatic lipid metabolic progress and suggested that HDAC11 stimulates AMPK/ACC1/CPT1 pathway activity through regulating its phosphorylation.

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Rate of Patients WITH Moderate & Severe Binge Eating Habits in an Outpatient Adult Medical Weight Management Clinic

New patients to the Weight Management Clinic at GWU MFA were the participants of this study. The purpose of the study was to evaluate the rate of new patients whom had binge eating like habits. All new patients were self-administered the surveys, which included a consent form, a demographics survey, and an eating habits questionnaire. Approximately, 50 participants completed the study and data will be analyzed by the team with a statistician. The data will be analyzed looking for variables that correlated between the patient's demographics and results of the eating habits questionnaire. Patients who obtained greater than 18 points on the eating habits questionnaire were given a handout on resources in the area to help with habits that are often seen in binge eating. They were not diagnosed with an eating disorder from this study. The key statistical analysis will focus on the rate of participants that score >18 on the eating habits survey, and gender, BMI, psychiatric condition, and alcohol intake, correlates with the eating habits score.

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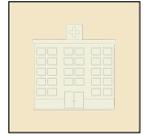
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PREVENTION AND COMMUNITY HEALTH



SCHOOL OF MEDICINE AND HEALTH SCIENCES

Telemedicine in Urgent Care: A Review

Acute urgent care is an area in which the rapid expansion of telemedicine has been relatively recent. The development of internet and smartphone capabilities has created the opportunity for patients with low-acuity conditions to be examined, diagnosed, and treated, all without having to schedule in-office medical visits. A growing number of telehealth companies such as AmericanWell, MeMD, and Teladoc, in addition to established medical centers and offices, are offering these telemedicine services to patients. The following literature review seeks to examine the claims made by the aforementioned telehealth companies, medical centers, and accountable care organizations, regarding their urgent care telemedicine services, and subsequently examine whether these claims are supported by published studies in the literature on telemedicine. We performed an automated electronic search for studies and review articles on the use of telemedicine for acute urgent care, using the following search terms: telemedicine for urgent care, online urgent care, efficacy of telemedicine for acute care, cost-effectiveness of telemedicine for urgent care, convenience of telemedicine for urgent care, quality of care of telemedicine for urgent care. These search terms were used as keywords in PubMed, MEDLINE, CINAHL, and Scopus. A manual search was completed by checking the reference lists of selected documents and selecting relevant articles from these lists.

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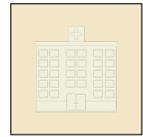
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MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH

School-Level Disadvantage Moderates Individual-Level Tobacco Cessation Failure

BACKGROUND

Over half of adolescent smokers desire to quit, but the majority fail. Most adolescent cessation programming conventionally focuses on individual-level factors and mainly highlight successful outcomes. While understanding factors that lead to successful individual smoking cessation outcomes is necessary in adolescents, it is also essential to determine factors and conditions that contribute to treatment, or cessation, failure. The present study posits that adolescents' proximal environments-such as schools-may influence cessation treatment outcomes.

PURPOSE/OBJECTIVE

The purpose of this study is two-fold: a) Determine the individual level (Level 1) predictors of tobacco cessation failure in adolescents, b) Determine how the school environment level (Level 2) moderates the influence of level 1 predictors of tobacco cessation failure.

METHODS

Using aggregated data from multi-year (1998-2010) school based cessation trials (Not on Tobacco (N-O-T) in 5 states, we created a socio-spatial database comprising of linked individual-level and school-level data. By applying a tobacco-specific socio-ecological framework and Hierarchical Linear Modeling, the present study examined the interplay of individual level (n=8,855) and school level (n=807) factors associated with cessation treatment failure among adolescent cigarette smokers. Treatment (participation in N-O-T) was deemed as failing to meet its primary goals if participants continued to smoke cigarettes, measured 3-months post baseline.

RESULTS

At the individual level, greater self-efficacy predicted a higher likelihood of cessation success and nicotine dependence predicted a greater likelihood of failure. Ten percent of the variation in individual tobacco cessation failure was attributable to school-level variables. Adolescent smokers were more likely to experience failed treatment in a) school districts with large percentages of the population having less than high school education and b) schools with a higher ratio of students to teachers. Moreover, the influence of individual level self-efficacy on cessation was weakened among adolescents attending schools with higher percentages of students eligible for free and reduce lunch program.

CONCLUSION

Findings suggest school-level socio-economic disadvantage as a significant factor inhibiting cessation, regardless of adolescent motivations to quit smoking. Understanding such interplay of proximal environments, such as schools, and individual-level factors will provide insights to educators, policy makers, and practitioners into the complexities that inhibit or strengthen an adolescents' smoking cessation treatment experience. Cessation programming should consider the interplay between individuals and school-level socio-economic disadvantage. Tailored strategies that buffer the effects of disadvantage may enhance adolescent cessation treatment outcomes.

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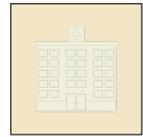
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MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH

Neighborhoods and Health: The Implications of These Relationships

BACKGROUND

Racial and ethnic minority groups have a higher prevalence of both diabetes and hypertension, which may be influenced by neighborhood-level food environment and sociodemographic factors. We evaluated whether the imbalance between available healthy and unhealthy food options was associated with cardiometabolic markers (A1C and Systolic Blood Pressure [SBP]) in an urban adult patient population.

METHODS

We analyzed data from 4,729 patients from a hospital and outpatient system in Washington, DC with valid A1C, SBP, and home address data. We operationalized individuals' neighborhood food environment using the Centers for Disease Control and Prevention's modified retail food environment index (mRFEI) reported at the census tract level, which ranged from 0 in the least healthy food environments to 33 in the healthiest in our study sample. We used Geographically Weighted Regression to predict A1C and SBP levels separately based on mRFEI controlling for age, neighborhood socioeconomic status, neighborhood racial composition, and distance to the primary care center.

RESULTS

Overall, there was a small, but significant relationship between neighborhood food environments both clinical outcomes. For both A1C and SBP there was a slight negative relationship with improved food environment scores (β -0.00627, p-value: 0.00; β -0.39284, p-value: 0.00). However, after adjusting for additional covariates, the impact of food environments decrease for both A1C and SBP (β -0.00023, p-value: 0.21; β -0.1169, p-value: 0.01). For A1C, the impact of food environment decreases as additional neighborhood variables are added into the model.

CONCLUSIONS

We found that neighborhood-level variables are correlated with particular clinical outcomes. Food environments may be important in managing chronic disease. However, this impact solely may be clinically minute, but important on a population level. Identifying the relationship between food environments, additional neighborhood variables, and cardiometabolic outcomes could be instrumental in improving the health conditions of urban residents.

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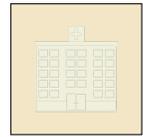
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PREVENTION AND COMMUNITY HEALTH



SCHOOL OF MEDICINE AND HEALTH SCIENCES

The Impact by Community Health Workers on the Health of Adults with Chronic Illness Living in Rural Communities: A Scoping Review

Community Health Worker (CHW) programs have been used globally to facilitate access to primary care, especially in low-resource and rural communities. CHW programs have even been developed to increase health education and health promotion in communities experiencing growth of chronic, non-communicable diseases. Despite the resurgence in the use of CHW programs, formal evaluation of programs and publications of the evaluation reports are believed to be limited. As program funding is often tied to the availability of evidence, a scoping review was completed to explore the available literature. The objectives of this scoping review were:

1. To understand the breadth of the literature on the impact by CHWs on the health of adults with chronic illness residing in rural communities
2. To explore what the literature informs about prevention and health promotion for chronic illness using CHW-led interventions with identification of knowledge gaps

Searches were limited to English-language, published, indexed, full-text available from the George Washington University Library System using the Web of Science, CINAHL Plus with Full Text, Scopus, and Global Health via Ovid databases. The selection process excluded CHW programs on maternal & child health, reduction in mortality, and cost-effectiveness. This scoping review found a scarcity of published, indexed literature on the impact on health by CHWs. The variation in the titles and roles for Community Health Workers likely contributed to the inability to quantify and qualify the impact on participant health. This is further complicated as the framework for evaluating the process, program, and outcomes of CHW programs is not consistent from program to program. In exploring the literature, it was found that recognition of the CHW's role in promoting, preventing, and supporting the self-management of patient and community health care through policy and/or legal changes were key to the strength of some CHW programs. Additional research for non-English publications and grey literature is recommended to further evaluate the research question.

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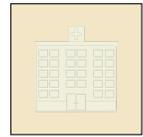
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PREVENTION AND COMMUNITY HEALTH



MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH

An Exploration of First-Generation College Graduate Health Outcomes in Early Adulthood

Chronic diseases and conditions such as heart disease, stroke, and obesity are among the most common, costly, and preventable illnesses prevalent in the United States. Understanding the social and economic factors that influence individual and community health has become important as growing evidence points to the effect of the interplay of the social, physical, health services, and structural environment on one's health. Education is one such factor that has become increasingly recognized as an important social determinant of health, and parental education has been shown to be associated with educational and occupational outcomes in children. Guided by the Ecological Model of Health, this research sought to understand first-generation college status as a social status factor. Almost one-third of the national undergraduate population is first-generation college students—those whose parents did not earn a postsecondary degree; they are an important, growing, but often hidden population. The current study is a secondary analysis of data collected as part of the National Longitudinal Study of Adolescent to Adult Health (Add Health). This research investigated the relationship of first-generation college graduate status to health (measured by Body Mass Index and blood pressure) of individuals aged 24-32 years old, as well as potential mediators of the relationship—health behaviors, stress and social support. Results indicated that approximately 44% of college graduates are first-generation and were 1.6 times more likely to be from a minority group than their continuing generation peers (95% CI: 1.27, 2.25) ($p = 0.000$). They were 3.91 times more likely to come from families with incomes below the median for college graduates (\$51,000) than their peers (95% CI: 2.97, 5.15) ($p = 0.000$). First-generation college graduates had statistically significantly higher mean BMIs than their peers (28.41 and 26.62, respectively); first-generation college graduate status had a significant association to BMI, even while controlling individually for health behaviors, social support, and adolescent family income. Health behavior and social support did not mediate the relationship between first-generation college graduate status and health, but social support differed significantly between first and continuing generation college graduates. The findings have implications for national policies concerned with support of first-generation college graduates while in college and with the transition into early adulthood. This is the first study, to the author's knowledge, to use a nationally-representative dataset (Add Health) to generate a profile of first-generation college graduates in early adulthood and to explore the health outcomes of first-generation college graduates.

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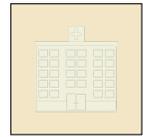
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MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH

E-Cigarettes and Smoking Cessation Among Pregnant Women: Insights From a Secondary Analysis of a Randomized Controlled Trial

BACKGROUND

The use of electronic cigarettes is a rapidly expanding phenomenon. Currently, there is a scarcity of data to help guide decisions regarding the potential harm and benefits of e-cigarettes. This study examines whether pregnant smokers who used e-cigarettes are more likely to quit smoking than those who had never used e-cigarettes.

METHODS

Data were drawn from the Quit4Baby study, a text-message-based smoking cessation randomized controlled trial. The sample was comprised of 481 participants with complete follow-up data at 1 month follow-up. Linear and logistics regression models to control for confounds were conducted to evaluate the association between e-cigarette use and smoking cessation outcomes.

RESULTS

21.83% of pregnant smokers reported past 30-day use of e-cigarette at baseline or 1 month. E-cigarette users differed from non-users on baseline characteristics including Fagerstrom score, and self-efficacy to quit smoking. At 1 month follow-up, a larger decline in cigarette smoked per day was observed in e-cigarette users (mean decline = 3.95 cigarettes/day) compared to non-users (mean decline = 3.16 cigarettes/day); however, it was not statistically significant. Compared with pregnant smokers who never used e-cigarettes during pregnancy, smokers who ever used e-cigarettes were less likely to quit smoking for 30 days at 1 month follow-up after controlling for intervention effect (AOR=0.466; 95% CI = 0.191, 1.135; $p = 0.09$) and approached the level of significance.

CONCLUSIONS

Pregnant smokers who have used e-cigarettes during pregnancy may be at increased risk for not being able to quit smoking. Longer-term cohort studies need to be conducted to confirm findings and future studies should employ better measures of patterns of and reasons for e-cigarette use, and frequency of usage.

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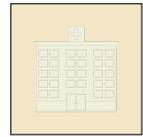
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SCHOOL OF MEDICINE AND HEALTH SCIENCES

MLP Interventions within the Length of Stay Variance Patient Population

BACKGROUND

A medical legal partnership (MLP) is a coalition formed by a healthcare organization contracting a legal service organization to meet patient health harming legal needs (e.g., housing not to code). This study seeks to expand MLP interventions to a new patient group: Length of Stay (LoS) variance patients. LoS variance refers to a hospital stay beyond medically necessary due to lack of safe and appropriate discharge location. LoS variance negatively impacts patient experience, institutional cost control, bed capacity, and overall capacity to respond to surges in patient demand. The study's objectives were to: describe, assess health harming legal needs, integrate an existing MLP, and assess the efficacy of MLP intervention within this population.

METHODS

This was an eight-week prospective cohort study focused on the adult LoS variance patient population at an urban safety net hospital. Medical records of 110 LoS variance patients were statistically analyzed, tracking demographic markers and discharge barriers. In addition, 18 patients were assessed for health harming legal needs via interview and questionnaire; and five staff social workers were surveyed to determine familiarity with MLPs, perspectives on the population, and potential interventions. Finally, institutional and policy interventions were investigated via interview with key LoS variance staff members and a hospital system representative.

RESULTS

Demographic analysis of the LoS variance population supported associations between decreased LoS with non-Medicaid/non-Medicare insurance coverage; absence of psychiatric/behavioral issues; and Asian race. Of the 18 patients surveyed, the majority possessed health harming legal needs, with 50% pertaining to housing and benefits/services. Seven received legal counsel, and the MLP attorney took three on as clients with successful resolution of barriers to discharge for two. Findings from the staff surveys showed the majority of staff had referred patients to civil legal services previously, but only a minority had received any training in MLP, expressing interest in further training.

CONCLUSIONS

Our findings indicate that LoS variance patients have unmet civil legal needs which may contribute to their LoS variance. MLP can be an appropriate and effective intervention in this population. While providers are aware of some of the health harming legal needs of this population, patient care could improve with further provider training in MLP, and the standardized usage of legal screenings to help identify patients for intervention. Further research into this population's health harming legal needs and the best MLP interventions to address them is warranted, particularly at other institutions.

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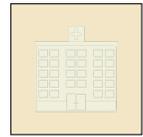
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PREVENTION AND COMMUNITY HEALTH



SCHOOL OF NURSING

Implementation of a Falls Prevention Plan Among the Community-dwelling Seniors of Ward 8

With the exponential rise of the aging population due to the number of baby boomers reaching 65 years of age, the United States healthcare system needs to modify socioeconomic structures to meet the growth in healthcare demands. Many older adults want to age in place, which can also reduce the need for long-term institutional care. But this requires increasing community-based resources and support to adequately meet their health needs (Lehning, 2012).

A community needs assessment was conducted to analyze the current unmet resource and support needs of the community-dwelling senior population (≥65 years old) to reduce the risk of falls. They cause a significant adverse event among this population with potentially long-term detrimental health outcomes. Data for this project was collected from the Ward 8 neighborhood of the District of Columbia (DC), which has the highest concentration of poverty and the lowest amount of community-based resources available, using windshield and walking surveys, information from the DC Office of Aging Needs Assessments, and an expert interview with Dr. Beverly Lunsford, PhD, RN, CNS-BC, Director of Health and Humanities at the Center for Aging in Washington, DC, Director of the Washington Area Geriatric Education Center Consortium (WAGECC), and Assistant Professor at The George Washington University School of Nursing.

Based on the data collected the major risks for falls among the 65 years and older population residing in Ward 8 was predominantly related to lack of local resources, increased environmental hazards, declining infrastructures, inadequate access to transportation, lack of local government funding, and physical hazards both external and internal to the home. To address these unmet needs, several interventions were proposed including: a) dissemination of informational packets on how to reduce falls among the residents, b) establishing the evidence-based program called Matter of Balance, c) addressing polypharmacy through medication reconciliation, and d) partnering with Safe at Home. The short-term goal of this project is to increase awareness of fall prevention methods and resources available among 40% of the specified population after 1 year of implementation. The long-term goal is to reduce reported falls by 30% after 3 years.

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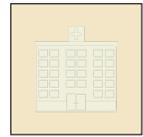
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PREVENTION AND COMMUNITY HEALTH



MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH

An Evaluation of the Effectiveness of the Black Women's Health Imperative (BWHI) #LetsTalkAboutPrep campaign among Black women living in Washington D.C.

BACKGROUND

Black women in the District of Columbia (D.C.) are 50% of the female population, but account for 92% of women living with HIV. Pre-Exposure prophylaxis (PrEP) can reduce the risk of HIV infection by up to 92% when taken consistently by people who are at high risk of HIV infection but research suggests that very few Black women are aware of PrEP as a prevention option. This study tests the effectiveness of a culturally sensitive public health communication campaign to promote PrEP awareness among Black women in D.C., as part of the Black Women's Health Imperative (BWHI) #LetsTalkAboutPrep media campaign.

METHODS

One hundred ninety two sexually active, HIV negative Black women ages 20-69 who live in D.C. who reported at least one HIV risk factor were surveyed about their knowledge of PrEP, uptake behaviors and sociodemographic characteristics. Participants also reported exposure to the #LetsTalkAboutPrep campaign (5 ads). We tested the relationship between exposure to the campaign and intention to use PrEP, as well as other outcomes related to uptake (i.e. discussion of PrEP with friends/physician). The independent variable was the sum of 5 dichotomous campaign exposure variables. The dependent variable was the sum of 5 dichotomous PrEP uptake behaviors, including considering to use PrEP and seeking more information about PrEP. Multivariate linear and logistic regressions were performed to assess the association between exposure to campaign ads (range 0-5) and PrEP uptake behaviors (range 0-5), controlling for sociodemographic variables. We hypothesized that there would be a dose response in which exposure to more ads is associated with increased intention to use PrEP.

PRELIMINARY RESULTS

The independent and dependent variables were significantly correlated at $r = 0.26$. The multivariate linear regression shows that with each additional campaign ad exposure, there is a $B = 0.51$ unit increase in the number of prep uptake behaviors, when controlling for education, marital status, income and age ($p < 0.05$). This model explains 22% of the variance in the outcome variable.

CONCLUSION

There is evidence that exposure to the #LetsTalkAboutPrep campaign is associated with Black women's intention to use PrEP behaviors. Further analysis is required to build on this research to create similar culturally sensitive communication campaigns to increase Black women's awareness, knowledge and use of PrEP nationwide.

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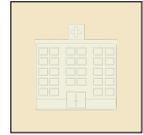
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PREVENTION AND COMMUNITY HEALTH



MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH

Risk Factors for Youth Prescription Drug Misuse: Screening Opportunities in Clinical Settings

BACKGROUND

Nonmedical prescription drug use has become a pressing concern in the U.S. Though prescription drugs have medicinal value when taken on a short-term basis, many prescriptions are demonstrating to be problematic with long-term use due to a likelihood of addiction. There has been less focus on primary prevention and youth's consumption and abuse of prescription drugs early in the lifespan. The current objective was to assess risk factors associated with prescription drug misuse by high school students in the U.S.

METHODS

The present study is a secondary analysis of the 2015 Youth Risk Behavior Surveillance System survey data among high school students (grades 9-12). Two dependent variables were used for multivariate modeling, both stemming from an ordinal prescription drug misuse item. Serial logistic regression was employed to assess behavioral risk factors associated with lifetime and high prescription misuse (40 times or more). Covariate selection was identical for both models, including demographics and behaviors which align with routine clinical screening opportunities. Variables included race, gender, grade level, sports team engagement, sexual intercourse before age 13 and ever receiving HIV testing, electronic cigarette and marijuana lifetime use, and depression symptom (suicide injury resulting in hospitalization during the last 12 months).

RESULTS

Results from models of lifetime ($N=10,763$, $F=101.23$, $p<.001$) and high ($N=1,855$, $F=8.80$, $p<.001$) prescription drug misuse among youth demonstrated both parallel and distinct risk factors in the present sample. The distinct features of being a high prescription misuser, compared to a less frequent misuser, are higher odds of being male ($OR=2.10$, $p=.001$), receiving HIV testing ($OR=2.10$, $p=.002$), as well as lower odds of engaging in sports teams ($OR=0.69$, $p=.03$), keeping all other variables in the model constant. Additionally, reviewing similarities across the lifetime and high misuse models demonstrates as frequency of misuse increases, there are consistently high odds of experiencing suicide injury, having sexual intercourse before age 13, and using marijuana (all $ps<.05$).

CONCLUSION

Results provide current insights on factors associated with lifetime and high prescription drug misuse among U.S. students. This study complements and reinforces intervention efforts in clinical settings for substance use prevention. In particular, the literature demonstrates those with suicide injury are reoccurring health care users. These individuals may be more easily identified and reached by way of linking screening data for common risk factors (e.g., STD testing). Cost-effective prevention efforts in clinical settings to expedite multidimensional screening for high-risk youth should be explored.

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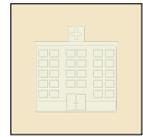
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PREVENTION AND COMMUNITY HEALTH



MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH

Exploring the Rights of Breastfeeding Students on Campus: A Qualitative Analysis of Support for Student Lactation Within Higher Education

BACKGROUND

All women have a right to meet their breastfeeding goals, which ultimately impact their health and the health of their children. For female students who are also new mothers, the lack of lactation accommodations within the academic environment is a barrier to both breastfeeding continuation and academic degree completion, and consequently hinders efforts to promote women's educational attainment. Title IX provisions, which provide pregnancy discrimination protections for female students, do not specifically outline lactation support accommodations, increasing the need for supportive policies on campus. While provisions within the Affordable Care Act on workplace lactation have led to an increase in female employee based lactation support programs (LSPs) within universities, little is known about how these programs support university students. The aim of this study is to describe how lactation accommodations for female students are conceptualized and integrated within the provisions of university based LSPs and policies.

METHODS

First, a content analysis of 55 university LSP practice documents and 31 policies identified within a sample of 88 universities within a large study on university lactation support was employed to determine the degree to which students were present and assimilated within these services. Five universities were then selected to serve as case studies for student lactation support, and a constant comparative analysis of documents and interviews collected from these cases was utilized to determine how students were perceived within university LSPs.

RESULTS

About 1/3 of lactation policies included students as beneficiaries of lactation space and none provided for lactation breaks for students. Universities view students as interdependent beneficiaries of campus lactation services along with employees, as a function of clear student need and advocacy for lactation support. The provision of lactation services is perceived to support student retention and recruitment, and enhance efforts towards creating a campus that is both inclusive and supportive of healthy norms. The lack of lactation policies related to female students was seen as a barrier to meeting their specific needs, and the inclusion of student provisions within lactation policies can also insure that students are aware of available services.

IMPLICATIONS

Understanding how students are conceptualized and integrated within university lactation accommodations will inform the development of campus lactation guidelines that call for the inclusion of students within current and future services and policies. Such efforts aim to support female college students who are parents, and improve women's access to postsecondary education.

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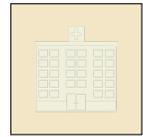
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MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH

Influence of Parietal Cortex on Motor Surround Inhibition in Healthy Adults—A TMS Study

Surround inhibition (SI) in the motor cortex is a phenomenon necessary for controlling fine, focal movements wherein the excitability of synergist muscles is enhanced and that of surrounding muscles is inhibited.

Patients with focal hand dystonia (FHD) have less/absent SI, suggesting that SI might contribute to the disease pathophysiology. Hence studying this phenomenon in detail is likely to enhance our understanding of the pathophysiology of FHD. It has been postulated that the parietal-premotor-motor network is crucial in FHD. As a result, past studies from our group^{1,2} evaluated the role of the premotor cortex in SI, yet neither the dorsal nor ventral premotor cortex influenced SI.

In this exploratory study, we aimed to determine the influence of the posterior parietal cortex, specifically the anterior inferior parietal lobule (aIPL) on SI using transcranial magnetic stimulation (TMS) and electromyography (EMG). We recruited 11 healthy volunteers, out of which 4 completed the study.

Participants performed an auditory-cued simple index finger movement task and single-pulse TMS was applied either at rest or movement onset. Motor-evoked potentials (MEPs) were recorded from the synergist and surround muscles. Peak-peak MEP amplitude served as our primary outcome measure.

Our preliminary results show that the posterior parietal cortex is probably not involved in SI, as SI did not change by conditioning the aIPL. We are recruiting more subjects to obtain more reliable results.

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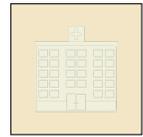
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PREVENTION AND COMMUNITY HEALTH



SCHOOL OF MEDICINE AND HEALTH SCIENCES

Care Conundrum in the ED: The Gap Between Clinician Awareness and Patient Expectations about Advance Directives

BACKGROUND

Initiation of the palliative process in the ED with preliminary advance care discussions contribute to reducing the length of hospital stay, overall cost, ED recidivism, ICU utilization, and improving patient and caregiver satisfaction.

OBJECTIVES

To assess if elderly ED patients have advance care directives, to identify the patterns and incidence of advance care discussions in the ED between patients and providers, and to gain an understanding of patients' perceptions and expectations of such discussions.

METHODS

Trained research assistants surveyed ED patients (Emergency Severity Index 2 or 3) over age 65 or their caregivers in an urban university hospital. Patients were asked about advance care planning documents and whether they had discussed goals of care with ED staff, primary care physicians, or their families.

RESULTS

248 out of 426 patients completed surveys. 89% of patients lived independently and 4% resided in assisted living facilities. 42% of patients reported completing an advance care document; with 62% of these located at their home. 23% reported previous advance care discussions with their primary care physician and 57% had discussions with their family. 82% of patients thought ED providers should know about their end of life wishes, but only 40% wanted to talk to ED clinicians about advance care planning. 7% of patients reported that EM physicians and nurses asked about advance directives.

CONCLUSIONS

Most older ED patients expect emergency clinicians to be aware of their care preferences in the event of a critical illness yet over half of patients do not have an advance care document and most are not asked about their advance care preferences by emergency physicians and nurses. The large gap between the desire to have their preferences known and any systematic way to discuss or record these desires suggests the need for system improvements (better communication of advance directives across care systems) and more targeted discussions by ED clinicians. The ED may be a place to initiate advance care discussions in patients who have not prepared an advance directive. The limited awareness that ED clinicians have of patients' advance directives suggests that future studies should explore barriers to advance care planning in the ED.

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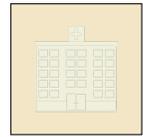
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Integrated Health Behavior Models Illustrate How Positive Attitudes and Low Risk Perceptions Drive Young Adult E-Cigarette Use

Given increasing rates of e-cigarette use among young adults, research is needed on the attitudes and beliefs that drive use among this age group. Tobacco control approaches used to prevent cigarette smoking may not work as effectively for preventing e-cigarette use. To address this research gap, the present study applied the Integrated Behavior Model (IBM) encompassing the affect heuristic theory to examine the individual-level determinants (i.e., attitude, perceived norm, personal agency, intention, and e-cigarette risk perception) of young adults' e-cigarette use. The 2013-2014 Population Assessment of Tobacco and Health (PATH) Study Wave 1 baseline adult dataset consisted of 9,112 young adults (ages 18-24). A total of 3,887 (42.7%) reported ever having used an e-cigarette even one or two times, and reported now using e-cigarettes every day (n=160), some days (n=947), or not at all/non-users (2,780). Structural equation modeling (SEM) indicated that both the affect heuristic theory and constructs adapted from the IBM were significant drivers of e-cigarette use among young adults. The final structural model demonstrated acceptable fit (CFI = 0.935; TLI = 0.925; RMSEA = 0.024, 90% CI: 0.022-0.026). As expected for the IBM, as young adults' positive feelings, perceived benefits, and normative beliefs of e-cigarettes increased, their intention to quit e-cigarettes decreased; which increased the likelihood of currently using e-cigarettes. As perceived benefit and positive feelings increased, young adults' risk perceptions decreased resulting in a higher likelihood of using the device. These findings suggest that future communication, educational, and policy strategies to prevent e-cigarette use among young adults should highlight the health risk of e-cigarettes to address the high perceived benefits and low risk perceptions reported by young adults in this study.

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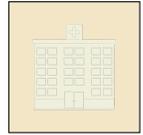
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Assessing the Mental and Physical Health Impacts of Self-Defense Training for Young Women: A Critical Analysis

BACKGROUND

Women are continuously at risk of being sexually assaulted and even with more stringent laws and increased prevention efforts, the number of assaults has not significantly decreased in the past forty years. This study sought to examine effective and ineffective rape prevention techniques, determine the efficacy and benefits of women's self-defense training, understand perspectives opposing self-defense and sexual assault prevention programs, and determine whether a high school setting may be promising to help improve overall gender equality and women's health outcomes.

METHODS

A literature review of peer reviewed research published after 1980 was performed in October 2016. The review only included papers available in English and with full-text availability.

RESULTS

There were 57 studies examined for this paper. Overall, self-defense programs were found to be effective in reducing the rates of sexual assault and completed rape. The most effective techniques discussed were forceful physical resistance, non-forceful physical resistance, and forceful verbal resistance. Opposition against self-defense typically believed that women are either not strong enough or more likely to be injured if they fight against their attacker; both viewpoints were demonstrated to be untrue. The research also found that there were other benefits from these programs such as increased self-esteem and reduced rates of self-blame. Finally, the research demonstrated that self-defense programs could be effectively taught in high schools.

CONCLUSION

High school and college aged females alike face high rates of sexual assault and rape. Therefore, these programs should be taught in high schools as a prevention technique, improving both physical and psychological health outcomes in this vulnerable population.

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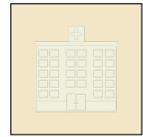
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How the Media Frames a Crisis: Emotion of Ebola in Liberia

Liberia made headlines in 2014 due to the Ebola Virus Disease epidemic that recorded over 11,000 confirmed cases and 4,800 deaths. The crisis was sudden, unexpected, and threatened the stability of a country that was recovering from a decade of civil unrest. In this context, local populations mainly relied on traditional media to obtain news information and learn about health behaviors. Risk communication research has shown that emotion affects attitude, which in turn influence behavior. It is known that during crises such as health emergencies, members of the public display a range of emotions that can affect their level of action toward the adoption of prevention practices. Yet, distinct emotions yield distinct outcomes; for instance, fear increases risk perception while anger decreases risk perception. Moreover, previous research has estimated that emotional frames used by news media can cause similar emotions in their audiences. Positive emotions tend to calm anxiety and reduce perceived threat. This study assessed the range, frames, and intensity of emotions communicated by news media during the Ebola epidemic in Liberia. The analysis is based on a large random sample of newspaper articles from Liberian dailies (n=745) and local radio programs (n=182 audio files) from January 2014 to December 2015. Six coders, deemed to have high inter-coder reliability, $K \geq .85$ coded communication materials produced in English and based on definitions drawn from a theoretically-guided codebook. Results showed that hope and fear were the main emotions expressed in both radio and newspapers. More than 70% of radio programs and about half of newspaper articles communicated hope as the primary emotion while fear appeared as the primary emotion in about 30% of print articles. The analysis suggests that the media had a large imprint on the emotional tone of the crisis; and understanding of emotional responses can potentially inform the design and implementation of risk communication efforts during crises that are supported by the public and thus, become more likely to yield harm reduction. Therefore, the design of effective risk communication tools can be enhanced by efforts that utilize an emotion-based perspective to decode the emotional states different publics are experiencing during any given crisis.

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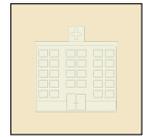
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Assessing PVST Completion Rates of Infants Born to Hepatitis B-Infected Mothers

PURPOSE

Hepatitis B virus (HBV) is a serious bloodborne viral infection and can lead to premature death from hepatocellular carcinoma. Pregnant women with chronic HBV pose a serious threat to their infants; hence, post-exposure immunoprophylaxis is necessary. Post-Vaccination Serological Testing (PVST) is also recommended to test an infant's immune response to the HBV vaccinations. The Perinatal Hepatitis B Prevention Program (PBHPP) aims to prevent transmission of HBV from infected mothers to babies born in the United States. Although, the majority of cases can be traced to the Western Pacific and African regions, there is limited knowledge on factors that affect PVST completion among cases managed by the Houston Health Department (HHD). This project aims to assess the PVST completion rates among infants born between January 1, 2015 to December 31, 2015 to HBV-positive mothers managed by HHD.

METHODS

Infants born in 2015 to hepatitis B-infected women living in Houston/Harris County, and case-managed by Houston PHBPP were exported from the HHD surveillance system. Maternal race/ethnicity was analyzed for infants who were immune to understand if it influenced PVST completion.

RESULTS

In accordance to the Centers of Disease Control recommendations, infants born to HBV infected women should complete PVST between 9-18 months of age. After analysis of the 232 infants case-managed by the program, 64 infants were excluded. Of the 168 infants eligible for PVST, 76% (n=129) have completed PVST; 84.5% (n=109) infants completed PVST within the recommended interval and 15.5% (n=20) completed PVST after 18 months of age. 54.2% (n=70) are Asian/Pacific Islander (API), 29.5% (n=38) are Black Non-Hispanic, 7% (n=9) are White Hispanic, 6.2% (n=8) are White non-Hispanic, and 3.1% (n=4) are of unknown ethnicity. Of the 39 eligible infants who did not complete PVST, 38% (n=15) are API, 33% (n=13) are Black non-Hispanic, 15% (n=6) are White Hispanic, 8% (n=3) are White non-Hispanic, and 5% (n=2) are of unknown race/ethnicity.

CONCLUSIONS

Though the Houston PHBPP PVST completion rates are improving, targeted interventions are needed to focus on increasing the PVST completion rates amongst the API and Black, non-Hispanic groups. Further analysis will be conducted on the 39 infants who have unknown immunity, to fully understand the Houston PHBPP program practices and the factors that affect PVST completion among different racial and ethnic groups.

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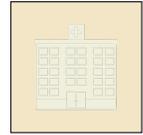
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Short-term Effects of Climate Change Communication: How Political Party Affiliation Affects Receptivity to Environmental Messages

BACKGROUND

Media are often conceptualized as agents of either positive or negative social change. Their differential effects on climate change beliefs and behaviors among those with different political party affiliations have not been investigated through randomized studies. Using a tightly controlled laboratory experiment, we asked how political party affiliation affects people's susceptibility to and learning from pro-environmental messages.

METHODS

Participants were randomly assigned to watch one of three episodes on climate change and other environmental issues ("Years of Living Dangerously" broadcast on the National Geographic channel: treatment video) or a control video on the Zika virus. Pre, immediate post, and one-week post exposure measures were obtained to assess beliefs, intentions, and behaviors.

RESULTS

Data collection is ongoing at the time of writing. Preliminary findings (N=130; objective=600) indicate that watching any of the treatment videos resulted in greater self-reflection on one's role in climate change, $F(3,125)=15.46, P<.001$, than watching the control video. Beliefs in the negative future consequences of climate change did not vary by treatment or control video, but they were strongest among Democrats and weakest among Republicans $F(3,125)=2.88, P<.05$. Republicans, compared to others, were least likely to believe the US could take effective steps to combat climate change, $F(3,125)=4.91, P<.01$. In a multivariate model, individual efficacy (but not video type or political party affiliation) was associated with intentions to engage in more environmentally friendly behaviors, $F(1,124)=21.13, P<.001$.

CONCLUSIONS

Media effects are not uniformly experienced; their messages are conceptually refracted according to audience members' prior beliefs. For environmental issues, political party affiliation serves to produce differential meaning and therefore different outcomes for Republicans, who do not believe as strongly in the negative consequences of climate change, than for others. Climate education will be more effective if tailored according to people's political beliefs. Failure to make this distinction may result in boomerang effects.

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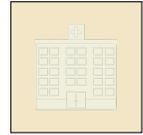
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Developing a Self-Scoring Mechanism for the Motivation Assessment for Team Readiness, Integration, and Collaboration (MATRICx)

OBJECTIVE

To develop a translational self-scoring sheet for the Motivation Assessment for Team Readiness, Integration, and Collaboration (MATRICx) instrument for individuals and teams to be able to use the tool in team reflection and maintenance.

METHODS

A review of the team science literature was used to compile a list of motivators and deterrents to collaboration that were developed into 6 domains of collaborative functioning in health and biomedical teams. This list informed the development of 55 indicators representing a hierarchical spectrum of collaboration. Rasch analysis was used to investigate the rating scale structure, unidimensionality, and person-item fit of responses from 150 participants. Items were analyzed applying a 1-parameter Rasch model using Winsteps® 3.80.1. Pilot data analysis provided a hierarchy of motivators and threats which make up the MATRICx framework.

RESULTS

Several iterations have contributed to the development of a self-scoring scale that maps individual participant motivators for collaboration against degree of collaborative experience and along the domains of collaborative functioning in a graphical context. This is usable by individuals and teams to establish the degrees and depth of collaborative motivation in order to improve collaboration for all team members.

SUMMARY OF FINDINGS

The self-scoring sheet provides the basis for technological advancement of the MATRICx tool to be designed and promoted as a mobile application for use by teams and to collect data for further research. Ultimately, the self-scoring graphical framework will be used as part of the technical development of the MATRICx mobile application.

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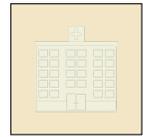
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PREVENTION AND COMMUNITY HEALTH



SCHOOL OF MEDICINE AND HEALTH SCIENCES

Exercise Capacity and Hospitalization Rates in Veterans

BACKGROUND

Cardiorespiratory fitness, or exercise capacity, has been shown in multiple retrospective studies to be inversely correlated with cardiovascular and all-cause mortality, even after adjustment for potentially confounding cardiovascular risk factors. Given the correlation of poor cardiovascular fitness with poorer medical outcomes (including mortality), it is likely that poor exercise tolerance is associated with a higher incidence of medical hospitalizations. In addition, lower exercise tolerance has also been associated with higher perioperative complication rates and prolonged length of stay after major elective surgery. This study evaluates fitness levels of veterans that underwent elective stress testing and assessed whether the highest fitness levels correlated with the lowest hospitalization rates and least severe illnesses in both cardiovascular and non-cardiovascular diagnoses. Factors such as length of hospital and ICU stay and inpatient mortality were used to assess this potential correlation.

METHODS

This study is a retrospective chart review of all Veterans admitted to the general acute medicine, medicine telemetry, PCU or MICU services that underwent a symptom-limited exercise tolerance test at the Washington DC VAMC between January 1, 2000 and January 1, 2010, within a pre-existing database. Patients with an implanted pacemaker, those who failed to achieve at least 80% of predicted maximum heart rate and those who were unstable, developed a left bundle branch block or required emergent intervention during the stress test were excluded. Differences will be evaluated using a Pearson's chi-square test and a one-way ANOVA.

RESULTS

The results of this study are pending.

POTENTIAL IMPLICATIONS

Physicians generally understand that regular exercise and cardiorespiratory fitness help protect against cardiovascular diseases, but a correlation between higher fitness and fewer hospitalizations for non-cardiovascular diseases would be an interesting new finding and one which might help guide physicians' clinical decisions (placing more emphasis on exercise even in veterans without cardiovascular risk factors) as well as guide future research at the DC VAMC.

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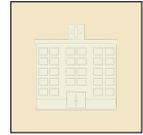
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Shifting Beliefs and Practices around Family Planning in Rural Ethiopia

BACKGROUND

Over the last ten years Ethiopia has substantially increased uptake of family planning methods. As a result, most regions of the country experienced a decrease in fertility. The aims of this study are to: (1) Describe the current family planning beliefs in one rural district in Ethiopia; (2) Identify which beliefs promote or hinder the uptake of family planning; (3) Acquire insights into how these beliefs may be changing through time; and, (4) Specify the social influences involved in the diffusion of information and ideas related to fertility and family planning.

METHODS

In July 2016, in collaboration with our Ethiopian research partners, we conducted five focus groups and twelve individual interviews (n = 59) with adolescents, men, women and key informants in Oromia, Ethiopia. We used a random sampling protocol to recruit participants. Focus group and interview questions covered childbearing, gender roles, decision-making, and modern contraceptive use. We analyzed data using thematic analysis and Nvivo v.11 qualitative software.

RESULTS

All participants knew of and accepted modern contraception to space childbirth. Adults considered it a positive change within their community and adolescents considered it a common part of the community for married women. We also found that there are two decision-making networks in regards to family planning: (1) one that pertains to basic decisions about having children, which remains patriarchal; and (2) a second network that pertains to family size and spacing decisions which includes the Government Health Extension Workers who are perceived as trusted community members who helped bring family planning methods and health education to the community. Adolescents described use of contraception among married women as commonplace but did not discuss it for themselves. Some key informants reported a need for improved adolescent sexual health services.

CONCLUSION

While marriage and initial childbearing remain patriarchal, Government Health Workers have helped to increase contraception uptake among married women who space births after their first birth. Focusing efforts on spacing after first birth among married women could be an effective first step to increase contraception uptake within a community.

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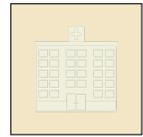
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Improving Lung Cancer Screening in Primary Care

The most common cause of mortality from malignancy is lung cancer. Unfortunately the overwhelming majority of lung cancers is detected in advanced stages, which is likely the driving factor for poor survival rates. There is evidence that early detection of lung cancer by screening high risk patients with annual low-dose CT scans can improve the survival rate by 20%. However, low dose CTs are not ordered by primary care physicians as routinely as other screening tests such as mammography. In the resident clinic at the Medical Faculty Associates at George Washington University Hospital, only 4.3% of physicians documented whether or not a patient met criteria for lung cancer screening. Documentation remained low despite both residents receiving information on lung cancer screening as well as forms distributed in clinic highlighting those meeting screening criteria. The initial thought was residents were not coached by attending physicians to screen for lung cancer in comparison to other screening tests during health maintenance exams. Preliminary surveys in January 2017 with attending physicians in primary care clinic indicated reasons for low screening rate may include lack of knowledge of guidelines, lack of habitual practice of new guidelines, obtaining insufficient smoking history to assess risk, overlooking high risk of former smokers, and concerns about insurance coverage. No physicians surveyed stated disagreement with lung cancer screening guidelines. Therefore, the major barrier to appropriate documentation may be increasing knowledge and emphasizing importance of lung cancer screening in primary care clinic. Our aim is to increase the rate of evidence-based documentation of candidacy for lung cancer screening by twofold over a six month period among Internal Medicine residents in the outpatient setting during the annual physical. Future strategies to reach this goal include education on appropriate screening steps and documentation, including lung cancer screening into health maintenance exam note macros, and reinforcement of guidelines by attending physicians.

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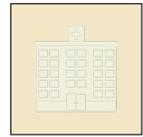
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The Effect of Early Palliative Intervention in Patients with Sepsis: A Retrospective Review

BACKGROUND

Severe sepsis is the leading cause of in-hospital death and the most expensive condition treated in U.S. hospitals. Reassessing the goals of treatment with patients and their families with early palliative care consultations and advance care planning discussions has the potential to improve care and better utilize hospital resources.

OBJECTIVES

To evaluate if early vs. late advance care planning discussion with severe sepsis or septic shock patients or their caregivers affects hospital length of stay, disposition, ICU utilization, mortality, exposure to invasive procedures, and cost.

METHODS

A retrospective chart review was performed for all patients over the age of 65 who presented to the emergency department fulfilling criteria for severe sepsis or septic shock in an urban university hospital. Data abstraction points included advance directive and advance care discussion documentation and outcomes such as length of stay, cost of hospitalization, in-hospital mortality, and use of invasive procedures. Patients were categorized into 4 groups: those with a palliative consult less than or equal to 4 days from admission, those greater than 4 days, those having a non-palliative physician discuss goals of care, and those having no palliative consult.

RESULTS

Of 104 patients, 50 were female. 59% were African American and 31% were Caucasian. 62% resided in a private home. 61% had documentation of advance care directives in the chart. 46% of all sepsis patients had advance care planning discussions. 89% had co-morbidities that qualified them for palliative care yet 55% received no palliative consult. 77% of patients who received a palliative consult after 4 days were noted to have a length of stay of 16+ days. Each of the other groups was less than 25% with a length of stay of 16+ days. 67% of patients died after receiving a palliative consult after 4 days, compared to the other 3 groups where each was less than 40%. Hospital cost was over \$150,000 in 89% of patients receiving a palliative consult after 4 days compared to the other 3 groups which were all under 25%.

CONCLUSION

The utility of early palliative consults and advance care discussions may be the greatest during the first four days of hospital admission as these patients had shorter stays and lower costs. Early palliative consults may present an opportunity to alter the trajectory of septic patients and improve overall outcomes.

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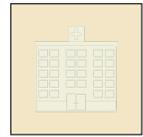
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Adverse Childhood Experiences as a Moderating Factor between Healthy Days and Amongst Adults with Obesity

BACKGROUND

Adverse childhood experiences (ACEs) are known to be linked to a myriad of health consequences. There is also plentiful research finding that people with obesity experience poorer health. Much research has been done finding an association between ACEs and chronic diseases such as obesity; yet there have not been any studies to date examining if there is an interaction between ACEs and BMI that is significantly associated with the number of poor health days an individual experience. This study utilizes secondary analysis of cross sectional Behavioral Risk Factor Surveillance System (BRFSS) data to examine this relationship.

METHODS

A total of 25,085 respondents of the BRFSS survey from years 2009-2015 in 4 different states (Alaska, Arkansas, New Mexico, and Washington) were used during analysis. Descriptive and linear regression analysis were used with weighted data to describe findings.

RESULTS

Analyses show that there is a significant interaction between BMI category and ACE experienced when looking at the outcome of poor health days both before controlling for demographic factors (p value= 0.0145), and after controlling (p value=0.0214).

CONCLUSION

Future public health interventions must be centered upon holistic prevention of both mental health and chronic disease. Having a high BMI in conjunction with ACEs may result in higher unhealthy days due to an inability to manage the disease effectively. As such, preventative measures against ACEs must take place, and treatment for Obesity must encompass more than dietary and exercise regulations.

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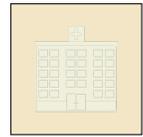
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“Dey Sey teachers are pay agents to contaminate children with Ebola”: Rumor Spread and Control During the Ebola crisis in Liberia

The Liberian Ebola epidemic had a devastating impact on one of the world’s poorest countries, with over 4,800 dead due to the disease and more than 10,500 infected. The severity of the epidemic, coupled with widespread misunderstanding about Ebola by Liberian citizens, led to the exponential growth of rumors. Spread of rumors during health crises typically begins at the interpersonal level through informal channels due to the large amount of uncertainty about the facts. The media can then pick up these rumors and circulate them further, leading to a larger reach. This can hinder preventative health messages and can also lead to widespread panic and extreme public reactions. Rumor control during outbreaks is imperative to reducing the public’s fears about a disease. In Liberia, a rumor tracker system was developed during the epidemic to detect and control rumors as quickly as possible through SMS text messaging. The focus of this study was twofold, first to assess the number of rumors that were circulated by distinct channels over time and second to assess rumor control communicated by these channels over time. The primary research method used in this study was a quantitative content analysis of print and audio communications collected from Liberian newspapers, SMS messages from the “Dey Sey” tracker, and radio programs from January 2014 to March 2015. The final dataset included 745 newspaper articles, 135 SMS messages, 182 radio programs to be evaluated using an a priori codebook. A six person coding team with an intercoder reliability score of 0.85 and above analyzed the data. There were 142 total rumors sent to the rumor tracker by SMS, with the most common rumor being about “new Ebola cases”. The source for the majority of SMS rumors was a community member (92%). The total number of rumors circulated was higher in newspaper than in radio, but a greater percentage of mentioned rumors were stated to be myths through radio. The most common rumor spread and debunked through both radio and newspaper was “Ebola was not real”. The findings of this study provide an important start into how rumors and rumor control can affect an epidemic, showing how rumors are indeed first spread interpersonally and then picked up by the media. With careful training and coordination between public health officials and local media, health crises and public fear can be curbed by controlling rumors.

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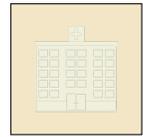
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Current Knowledge of Obesity Treatment Guidelines by Healthcare Professionals

BACKGROUND

Despite the high prevalence of obesity among U.S. adults, provision of recommended counseling and treatment modalities remains low. The primary objective of this study was to assess healthcare professionals' (HCPs) beliefs and knowledge regarding current clinical guidelines for obesity treatment modalities.

METHODS

Primary care physicians (PCPs), obstetricians/gynecologists (OB/GYNs), and nurse practitioners (NPs) completed a web-based survey during June 2016. Respondents included a nationally-representative sample of U.S. medical professionals (n = 1,506) who were randomly selected to participate from SERMO's Global Medical Panel (480 family practitioners; 523 internists; 250 OB/GYNs; 253 NPs). The 144-question DocStyles survey was administered by Porter Novelli Public Services and included eight obesity-specific questions developed by George Washington University researchers.

RESULTS

The majority of respondents (51%) did not recognize that the minimum level of physical activity for adults to achieve substantial health benefits is at least 150 minutes of moderate-intensity activity per week. Only 16% of respondents correctly identified the USPSTF and guideline-recommended intensity of behavioral weight-loss counseling as approximately bi-monthly for at least six months. Only 15% of respondents correctly identified that BMI ≥ 27 kg/m² is the appropriate indication threshold to prescribe obesity pharmacotherapy among patients with an obesity-associated comorbid condition. Fewer than one-third of respondents correctly identified when long-term pharmacotherapy is indicated, with nearly one-quarter responding that obesity medications should never be prescribed beyond three months of use, regardless of weight loss. PCPs were more likely than OB/GYNs or NPs to be familiar with the correct guidelines for pharmacotherapy.

CONCLUSIONS

These findings suggest many HCPs are not familiar with the clinical guidelines for obesity management. Limited understanding of how or when to deliver evidence-based treatments prevents providers from effectively addressing obesity with their patients. As coverage for behavioral counseling services and pharmacotherapy expands, it is imperative that HCPs understand how to leverage these treatment modalities to support healthy weight management and improved health outcomes for patients with obesity. Comprehensive medical education on obesity treatments could increase HCP rates of behavioral counseling and pharmacotherapy.

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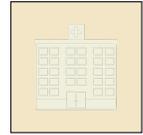
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PREVENTION AND COMMUNITY HEALTH



MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH

Doing Our “Best”: The Presence of Crisis Communication Best Practices in Liberian Radio and Newspapers during the Ebola Crisis

The most recent global outbreak of Ebola virus disease (EVD) persisted for two years, resulting in 29,000 diagnosed cases and 11,000 reported deaths across Liberia and several other West African countries. Unlike previous outbreaks, this one spread to crowded and medically ill-equipped urban areas, which exacerbated the transferability of EVD. Additionally, widespread misunderstanding of EVD and social concerns about the incompatibility of prevention methods with traditional social and burial rites intensified fear and anxiety among residents in affected areas, further fueling public health concerns.

In contexts like this, it is imperative that risk and crisis communicators rely on best practices for communicating with the public. Practices such as pre-crisis planning, displaying credibility, communicating compassion and efficacy, and accepting uncertainty are vital. Yet, the public is mostly influenced, during a crisis, by mass media (e.g. radio programming). Mass mediated communication can create credible perceptions—and perception is reality.

This study employed a content analysis a random sample of Liberian radio programs (audio tapes, N = 182) and newspaper articles (print, N = 745) from the top outlets in the country to determine the extent to which these outlets communicated the use of best practices. A theoretically guided codebook based on best practices was developed and intercoder reliability scores of $K > .85$ were attained by the six-member coding team.

Results showed significant discrepancies between radio and print in communicating the imminent contagion risk to their respective audiences. Newspaper articles overwhelmingly denoted (85.8%) the “dynamic and ongoing” nature of the risk compared to only 22.1% of radio programs. Communication of response efficacy and self-efficacy across both channels was low, 15% and 10.6% for newspapers, 14.6% and 18.9% for radio, respectively. Communication of compassion and empathy, an important component of building stakeholder and public perception of credibility during a crisis, was similarly low, mentioned in 11.1% of radio programs and 17.2% of newspaper articles. Generally, newspapers were more likely to utilize crisis communications best practices than radio programs were. The ability and readiness of media outlets to communicate according to best practices can impact the public’s “buy-in” during a crisis and influence outcomes. The potential of future EVD outbreaks demands increased focus on methods for facilitating newspapers’ and radio programs’ inclusion of and effective use of best practices in their messaging.

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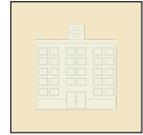
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Overlooking the Obvious: Communication of Efficacy by the Mass Media during the Ebola Crisis in Liberia

BACKGROUND

March 2014 heralded the largest Ebola outbreak in history set in West Africa. Of the over 21,000 confirmed cases, more than 11,310 deaths were recorded. It is axiomatic that during health emergencies, the public should learn about the harm reduction steps to take, have confidence in themselves, and believe these steps will yield positive outcomes. Yet, it is questionable whether mass-mediated outlets aid with these efforts.

METHODS

Content analysis methodology was employed. A codebook was developed based on existing knowledge of efficacy. Clear definitions were devised and each record was systematically coded.

Data was acquired for each medium through different processes. For radio content, available Ebola-related radio programs from major radio stations were acquired. Additionally, content from three radio programs, Radio Cape Mount, Radio Joy and Youth talk Radio; specifically created to address the unfolding Ebola crisis were obtained. For newspapers, content from three major newspapers were obtained. The analysis timeframe runs from January 2014 to January 2015.

All coders (six) underwent extensive training on applying the codebook used for capturing data. Coders were broken into three teams (radio team, newspaper team, SMS and chalkboard team) and asked to code a random set of 10% of the recordings and documents to assess inter-coder reliability. Coders' reliability ranged from $K = .85$ to $.99$. Disagreements were handled in a team meeting with team leader. Coders were split up to code the remainder of the documents only after the agreement rate was deemed satisfactory.

RESULTS

Prevention Steps communicated. Over twenty-one prevention steps were mentioned in both radio programs and newspaper articles. The five most frequent messages were careful hand washing (14.7%), prompt notification of suspected cases (9.6%), no touching (9.4%), practice safe burial (9.2%), do not touch someone with signs of Ebola (8.6%).

The five most frequent steps communicated in print content were as follows: avoid contact with contaminant (16%), practice safe burials (12.8%), no touching (12.1%), wash hands carefully (11.9%), and do not touch someone with signs of Ebola (9.1%).

Self-efficacy. Messages of self-efficacy were identified in 18.9% of radio content. This rate was almost halved at 10.6 % in newspaper content.

Response efficacy. Response efficacy was communicated at approximately the same rate across both channels. 14.6% of radio messages and 15% of newspaper articles communicated response efficacy.

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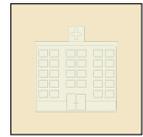
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Evaluating the Effects of Maternal Smoking on Infant Birth Weight

BACKGROUND

Prenatal maternal smoking is associated with 20-30% increased risk of low birth weight (LBW). Quitting smoking during pregnancy has almost immediate health benefits for both mothers and their babies, with longer term benefits being a function of sustained cessation. Despite this fact, many women find it difficult to quit when they learn about their pregnancy. This study investigated the relationship between maternal smoking and infant birth weight (BW) using a cohort of pregnant women from a randomized controlled trial.

METHODS

Data was drawn from Quit4Baby study, a text-message-based smoking cessation trial. The sample comprised of 307 participants who had their baby by the end of 6 month follow-up interview. Bivariate analysis were performed to evaluate the association between maternal smoking and BW.

RESULTS

Out of the 307 participants who have had their babies, 15.6% reported having LBW babies (<2500 grams). Results from Pearson's correlation showed no relationship between number of cigarettes smoked per day at pre partum and BW ($r= 0.014$ $p= 0.832$). Other smoking variables like living with a smoker, smoking status in the past 7 days and 30 days, and pre partum cigarette reduction were also not associated with LBW. Demographics like Black/ African American race and yearly income of up to \$15,000, which previously have shown association were also not associated with LBW.

CONCLUSIONS

Small sample size and nature of the Text4Baby sample from which this study's participants were recruited, could have been the reasons for observing results that do not match previous literature. Future studies may conduct analysis using a larger sample size of pregnant smokers to better explain the association between maternal smoking and infant birth weight.

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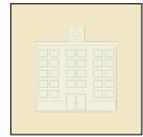
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PREVENTION AND COMMUNITY HEALTH



MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH

Applying Precision Medicine Concepts to Prevent and Early Diagnose Cancer: A New Hypothesis

'Precision Medicine' (PM) is the latest name that has been coined to convey 'personalized medicine.' PM has been defined as 'the right [drug] treatment for the right patient at the right time'. Current approaches to managing diseases are designed for an 'average patient'; this leads to some problems with our current approach to the treatment of illnesses. For example, the efficacy and efficiency of outcomes are not uniform; only a fraction of patients respond. The side effects can be inflicted on those who do not respond. PM will avoid these shortcoming.

THE HYPOTHESIS

Cancer is a complex and multifactorial, chronic, genetic, mutational disease in the majority of cases. Genomic Medicine, 'Big Data' initiatives and Electronic Health Records (EHRs) are being already leveraged to provide precision cancer care to improve outcomes. Our premise is that these efforts can and should be extended to prevention / early detection areas.

RESULTS

PM encompasses a combination of enomic medicine, big data and EHR. However, there is a paucity of the application of PM concepts in the cancer prevention. Further details will be presented in our presentation as a white paper.

SUMMARY AND RECOMMENDATIONS

At least eight steps are recognized in implementing health care policies.

1. **Describe the problem** - This white paper is the first step in that direction.
2. **Assess readiness for policy development**
3. **Develop goals, objectives, and policy options** - An expert panel has to be invited to develop these goals, objectives and policy options.
4. **Identify decision-makers and influencers** - The panel to be invited will be represented by experts from the following fields:
 - Genomic Medicine Scientists
 - Big Data Analysts
 - EHR Experts
 - Precision Medicine Oncologists
 - Public Health Policy Implementation Experts
 - Representatives from NCI (National Cancer Institute)
 - Representatives from IOM (Institute of Medicine)
5. **Build support for the policy** - this will be one of the charges to be given to the 'Expert Panel'.
6. **Draft and revise the policy**
7. **Implement the policy** - one of the major tasks will be finding the funding.
8. **Evaluate and monitor the policy**

In this white paper, a new paradigm has been developed – a novel idea that 'precision medicine concepts can be applied to cancer prevention initiatives. These initiatives will apply some of the states-of-the-art ideas from Genomic Medicine, Big Data and EHR to a new area of application – Cancer Prevention.

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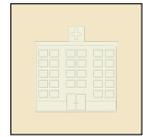
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MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH

Involvement of Romantic Partners in Prostate Cancer Patients' Treatment Decision

PURPOSE

The central aim of this study was to identify ways prostate cancer (PCa) patients' female romantic partners are involved in their treatment decision and how partners might influence the treatment decision.

METHODS

Twenty-five men (21 partnered/married, 23 White Non-Hispanic, mean age = 66) with clinically localized PCa were interviewed by telephone about their treatment decision-making experiences. The semi-structured interviews were transcribed verbatim and transcripts were coded by three or more coders using a codebook generated through an open-coding process. Discrepancies were resolved via discussion.

RESULTS/DISCUSSION

Unless the relationship was strained, partners were the primary support person involved in men's treatment decision. Men described partners' involvement as collaborative, active, or passive. Most men expressed satisfaction with the support they received. The most common way partners were involved was by seeking information about the disease and treatment options from sources such as the Internet and by asking questions at physician consultations. In some cases, partners urged men to choose more aggressive treatment. Partners also provided tangible and emotional support.

CONCLUSION

Contrary to earlier studies, most of the men reported that their wives/ partners were involved in the PCa treatment decision process, and believed their support was helpful. We also identified potential explanations for why married men have relatively better survival rates for PCa, including partner support for aggressive treatment. Also, partner support may reduce logistical burdens of aggressive treatment and adherence to follow-up protocols.

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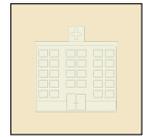
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MILKEN INSTITUTE SCHOOL OF PUBLIC HEALTH

Road Traffic Behaviors by Gender in Serbia

BACKGROUND

Road traffic injuries constitute one of the leading causes of death globally, the majority of which occur in low and middle income countries. It is important to understand the most vulnerable group of road users in order to successfully reduce the number of road traffic injuries. Gender differences are important in understanding driving patterns as optimistic bias in male youths results in a failure to understand their own vulnerability to safety hazards. Behaviors, experiences, risk perception, and social norms surrounding road traffic safety were investigated before the implementation of a road traffic safety educational program.

METHODS

Surveys were administered to 3rd and 4th graders in various types of schools across Belgrade (N=1,449). Respondents were asked questions regarding their previous experiences on the road, practice of safe road behavior, and aspects of risk perception. Responses to the surveys were stratified by gender and males (n=711) and females (n=738) were compared across these variables.

RESULTS

Consistent with previous research, senses of false security were disproportionate across genders. Gender also was found to play a role in accuracy of risk beliefs, risk exposure, sense of false trust, and injunctive norms. Males had a greater sense of false security than females, as well as greater risk exposure and a sense of false trust. Females were more likely to have accurate beliefs about road traffic behaviors as well as greater perceptions of injunctive norms.

CONCLUSIONS

These findings provide support for idea that gender is a major social determinant of road traffic safety and thus must be considered in the implementation of road traffic policy and programs. Within youth populations, males have a poorer sense of the consequences they may face for risky road traffic behavior. These findings are generalizable outside of Serbia as optimistic bias has been found in many high-risk behaviors outside of this population. Due to their greater levels of optimistic bias, male youths would most likely benefit from an educational campaign that made them aware of their risk.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Improving Patient Experience in Hospitalized Patients Through a Music Listening Program

INTRODUCTION

Identifying and treating frequent psychiatric problems facing patients entering critical care units, including delirium, depression, and anxiety are important to decrease patient suffering and improve morbidity and mortality. Music programs have been studied in various populations as a means to alleviate symptoms of depression or anxiety. Music therapy provides an alternative modality to get in touch with emotions, but there are limited studies that examine impact of receptive music listening on mood and patient satisfaction (Erkkla, 2011).

OBJECTIVE

The primary goal of the study is to determine the effect of music listening on hospitalized patients' anxiety, pain perception, as-needed medication usage, and patient satisfaction compared to standard care provided by a psychiatric consult service.

METHODS

Participants include patients who are identified by the primary team to require a psychiatric consult. Participants must be 18 years or older and must have capacity to participate in surveys. Participants were randomly assigned to either the music program group (intervention) vs. standard care after consent. Pre-test surveys and post-test surveys are completed in both groups at enrollment and 24 hours after enrollment. This study was approved by Institutional Review Board of George Washington University Hospital.

RESULTS

At baseline, there is no statistical difference between the control vs. intervention group due to randomization in terms of age, sex, employment, education, marital status, whether they own their own music ($p>0.10$), pain score ($p>0.10$), frequency of as-needed medication, or type of as-needed medication used in last 24 hours ($p>0.10$). At baseline, intervention group had higher anxiety score and a sub-scale score after randomization ($p<0.10$). Of 84 people approached, 39.3% ($n=33$) agreed to enroll in either the music intervention group ($n=16$) or control ($n=17$). The music intervention group shows decrease in Trait Anxiety sub-scale but not total anxiety score at baseline and follow-up ($p=0.10$). In terms of patient satisfaction, 62.5% of patients ($n=10$) rated the music as "good" or "excellent" and provided positive comments about the program. In terms of nurse satisfaction, 43.8% of nurses ($n=7$) rated the music program as "good" or "excellent" and 50.1% ($n=8$) "agreed" or "strongly agreed" that as-needed medication usage decreased in intervention group, and provided positive comments about the program.

CONCLUSION

Preliminary results suggest that music listening program may decrease a sub-scale on self-anxiety rating. Qualitative feedback from patients and nurses suggest that music listening may also improve patient experience during hospitalization and reduce as-needed medication usage. Further studies are needed to determine the effectiveness and feasibility of implementing music listening program in hospitalized patients.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES
CHILDREN'S NATIONAL MEDICAL CENTER

Depressive Symptoms and Patient-Provider Communication in Adolescents and Young Adults with Type 1 Diabetes

Depressive symptoms are prevalent in adolescents and young adults (AYAs) with type 1 diabetes (T1D) and may impact communication between AYA patients and health care providers (HCPs). This study evaluates associations among depressive symptoms and objective indicators of patient-provider communication, including patient-centered care.

Seventy-six AYAs (53.9% female; M age=17.77±1.22 yrs; 50% non-Hispanic white) with T1D were recruited to participate in a longitudinal study of health communication. Participants completed the Center for Epidemiological Studies Depression Scale (CES-D). Clinic visits were audio-recorded and communication quality was coded using the Roter Interactional Analysis System (RIAS), a system for evaluating medical interactions; clinic visit duration, mean number of utterances by AYAs and HCPs, and an overall index of patient-centered communication were used for current analyses. Hemoglobin A1c (M = 8.89%±2.25) values were extracted from medical records.

On the CES-D, 30.3% of participants reported clinically elevated symptoms of depression (M = 13.16±9.75; range 0-44). CES-D scores were positively associated with HbA1c ($p<.05$) and objective rating of patient-centered communication ($p<.01$). Clinic visit duration, amount of provider to patient talk, and total patient talk were not significantly associated with depressive symptoms.

The prevalence of depressive symptoms and association with glycemic control supports the importance of routine depression screening in this population. AYA-HCP communication may also be impacted by mood, as HCPs engaged in more patient-centered communication for patients endorsing greater depressive symptoms. This association implies that providers might have responded to patient mood by encouraging more active patient participation during the clinic visit. Future studies should examine this relationship over time.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Parent/Child Discrepancies in Irritability Reports

In the context of a large-scale NIMH-supported RDoC clinical trial of Cognitive Behavioral Therapy for disabling levels of irritability in adolescents who have been referred for care because for aggressive behavior, we are examining the extent to which parents and children provide similar or different reports of irritability and affective reactivity. In a sample of 109 participants with functional neuroimaging data as a primary outcome measure, we will test the similarity/difference in parent versus child irritability ratings. We are identifying 3 groups: High Parent/Low Child, Low Parent/High Child and High Parent/High Child and comparing these groups on the ratings of key psychopathology variables: ADHD, depression and anxiety. We are also examining the effects of age and gender on self-report discrepancies. We are predicting that girls and children with higher level of anxiety will have higher ratings of self-reported irritability. Finally, we are evaluating the effect of callous-unemotional traits on irritability.

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Agreement between Parents and Children regarding Child Mental and Behavioral Health Symptoms in Pediatric Allergy, Immunology, and Hematology Clinics

BACKGROUND

The purpose of this project was to evaluate agreement about mental health among parents and children who participated in a mental health screening program in pediatric allergy, immunology, and hematology clinics.

METHODS

Patients aged 8-17 and their parents ($n=70$) treated in the Division of Allergy and Immunology and the Division of Hematology at Children's National Health System completed the PROMIS Pediatric Profile 25, a mental and behavioral health measure of physical functioning, anxiety, depressive symptoms, fatigue, peer relationships, and pain interference. Patients with asthma and their parents also completed the PROMIS Asthma Impact module. T scores were calculated for each patient and parent.

RESULTS

Patients were 57% female with a mean age of 12.08 years ($SD=2.89$). Most patients identified as African-American (56%) or Caucasian (23%); 58% had asthma. Parent and child T scores for the Pediatric Profile domains were positively correlated, r range=.28-.60, $ps<.05$. Parents estimated that asthma had a greater impact than child raters. Overall, parent-child agreement was unrelated to patient age, race, or sex, all $ps>.05$. However, male patients were less likely to agree with parents regarding their anxiety than females; parents underestimated male patients' anxiety and overestimated female patients' anxiety, $F(1,68)=5.05$, $p<.05$.

CONCLUSIONS

Children with chronic illnesses and their parents generally agreed about child mental and behavioral health symptoms. Mental health discussions should include children, especially regarding anxiety, as parent-child agreement may be less likely.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Effects of Essential Oil on Fear Memory and the Immune Response: A Potential Alternative Therapy for Post-traumatic Stress Disorder (PTSD)

Chronic stress plays an integral role in activation and exacerbation of inflammation in the peripheral immune system. Peripherally circulating immune cells are also capable of crossing the blood-brain barrier and can promote inflammation in the central nervous system (CNS), which has been suggested to contribute to mental health disorders, such as posttraumatic stress disorder (PTSD). However, the association between fear memory and the immune system is not well characterized. Moreover, there are only two FDA-approved medications currently for PTSD. Therefore we sought to examine orange essential plant oil (OEPO), previously been found to have CNS depressant-like effects, on fear memory and immune cell activation in a mouse model of PTSD (Pavlovian Fear Conditioning). The treatment group (n=8) was administered 25% OEPO via olfactory exposure prior to and after fear conditioning. Mice exposed to 25% OEPO showed no difference in percent freezing during fear acquisition compared to controls. However, when tested for extinction retention 48 hours later the treatment group experienced a significant decrease in freezing behavior ($17.1 \pm 1.6\%$ ($p < 0.01$) versus control ($3.67 \pm 2.13\%$), suggesting that OEPO affects extinction of fear memory in mice. Next we examined the peripheral and central immune response following extinction of fear memory using flow cytometry analysis. A significant decreased in the number of effector memory T cells CD62loCD44hi $7.955(\pm 0.48)\%$ was observed in the treatment group relative to control $12.05(\pm 0.708)\%$ ($p < 0.05$).

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CHILDREN'S NATIONAL MEDICAL CENTER

Addictions and Substance Abuse in the LGBT Community

As we focus on addictions and substance abuse in the LGBT community, it is vital to heed advice to avoid the stigmatization, stereotyping or pathologizing of the LGBT community. Data from the largest nationally representative sample of sexual minorities, to date, makes clear that most *had not* engaged in substance use, and most *did not* meet criteria for problematic substance use. Both in the United States and globally, the majority of the members of the LGBT community do not use substances, and among those who do use substances, the majority are able to do so without any associated harm. Yet, this paper will present a body of evidence documenting the manner in which sexual minority adults present a particularly high prevalence and heightened risk for substance involvement (e.g., alcohol, drugs) in comparison to heterosexuals, including across the lifespan. More specifically, this paper will cover the following topics: 1) the diagnosis of substance use disorder and prevalence patterns among sexual minority groups; 2) club drug, poly-drug, alcohol, cigarette, prescription drug, and opioid use patterns; and, 3) meeting the needs of diverse clients—such as those presented in a series of illustrative cases—via new approaches and advances in treatment, including future directions in research.

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Improving the Screening Process for Sleep Apnea in the Internal Medicine Residents' Clinic

INTRODUCTION

Sleep apnea is a common medical problem and is associated with multiple comorbidities. However, screening for this condition is not systematic in our resident medical clinic and is left up to the physician's suspicion. There are validated screening tools that are widely available for use and Berlin Questionnaire is one of them. It is 86% sensitive and 77% specific in primary care settings.

AIM

Over a period of five weeks, we will increase the percentage of appropriate patients referred for sleep study in the internal medicine residents' clinic by 50% through implementing the use of Berlin Questionnaire.

METHOD

Baseline data on appropriate referral rates were gathered by chart review and use of the Berlin Sleep Apnea Questionnaire, without involving the primary care physician. Our intervention was the use of the screening tool during appointments scheduled for physicals. We did two PDSA cycles to determine the best way to implement this tool. In the first cycle, the form was available to all patients coming for their annual physical visit. In the second cycle, the physicians were given the screening tool to use with patients as they deemed appropriate.

RESULTS

At baseline, 7 of 14 sampled patients (50%) screened positive on the Berlin Questionnaire. Three of the seven patients (43%) were referred by their physicians for sleep testing. During the first PDSA cycle, no forms were returned, so no data were collected. In the second cycle, two of the three sampled patients screened positive; however, 50 percent of those screened positive were referred.

DISCUSSION

We found a low uptake on using the screening forms in both cycles. In the first cycle, it was one of many forms the patients need to fill and discuss with their physicians and none were returned to the investigator. In the second cycle, residents were asked to use the screening form when they deemed it appropriate. There was still a low uptake on using the form.

CONCLUSION

Screening for sleep apnea is challenging despite being a common problem and having screening tools readily available. A complicated form filled during a visit in a busy clinic may not be ideal for screening. Likewise, utilizing multiple forms during a single visit may decrease the likelihood that patients and physicians will complete them. Further PDSA cycles using different visit types or different screening tools, are needed to determine easier ways to increase rates of appropriate referrals for further testing.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Improving HIV Screening Rates at an Academic Teaching Institution Internal Medicine Resident Clinic

INTRODUCTION

Human immunodeficiency virus (HIV) affects over a million individuals in the United States. Thirteen percent of people with HIV don't know they have the virus. Washington DC has among the highest rates of HIV in the nation. An important step in the fight against HIV is screening tests, which everyone is recommended to have at least once in his/her life. The goal of this study is to increase HIV screening during annual physical examinations at the George Washington University Internal Medicine Residents Clinic by 25%.

METHODS

We performed a retrospective chart review of all patients who presented for annual physical examination from July 2016 to January 2017. Rates of HIV screening were determined by search for any laboratory record of an HIV test or documentation by the provider in the clinic visit note. Baseline rates were determined and rates after four subsequent interventions (PDSA cycles) aimed to increase screening rates: email reminders, macro utilization education, patient education posters in rooms, and pocket cards of recommended screening guidelines for residents.

RESULTS

Baseline data revealed that 67.6% of patients had ever had HIV screening. In order to meet our predetermined goal of a 25% increase in screening rates, rates would need to increase to 85% of patients. Post-intervention #1 (email reminder to providers), the rate was 64.8%. Post-intervention #2 (macro utilization education), the rate was 69.6%. Post-intervention #3 (posters in patient rooms), the rate was 77.0%. Preliminary results for post-intervention #4 (pocket cards of recommended screening guidelines for residents), the rate was 90%, though a final numbers of this last intervention are still pending analysis.

DISCUSSION

HIV screening is a known effective tool in preventing the spread of sexual transmitted diseases. In addition to patient education, focusing on reminding providers of this importance is essential to increasing the rates of testing. Our study demonstrated that direct patient education/exposure and reminder tools for physicians are two possible ways to increase the rate of HIV screening. While preliminary data shows promise in provider reminders such as pocket cards, final analysis of this effect is currently underway. The effects are compounded and do not reflect any single intervention at a time, demonstrating the importance of a multi-focal approach towards increasing screening rates.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Introducing Patient-Centered Documentation of Treatment Plans During Clinic Visits

BACKGROUND

When improving patient outcomes, an important tenant is ensuring patient understanding of the treatment plan. However, up to 40-80% of information provided by practitioners is immediately forgotten by the patient. One important method of ensuring patients' comprehension is the "teach back" method. The purpose of our study is to increase the number of patient-centered treatment plans by providing a form that engages patients while incorporating the "teach back" method.

METHODS

The "My Visit" form was placed in resident clinic rooms before each clinic day. Forms were counted at the end of the week to calculate the number of forms used and the number of patients seen each week was determined retrospectively. Multiple interventions were used to increase use of the form, including adding a colorful element to the clipboard, placing "primer" sheets in the waiting room, and attaching pens to the clipboards.

RESULTS

Initial introduction of "My Visit" forms resulted in 17.6% use, with additional interventions leading to 19.4% and 18.9% use.

DISCUSSION

After introduction of the "My Visit" form, the rate of patient-centered documentation during clinic visits remained stable. Despite new interventions introduced each cycle, these did not significantly increase in the percent of patients using the form.

The series of interventions were aimed at better exposing patients to the "My Visit" form, as well as facilitating ease of use. Because the rate of patient-centered documentation remained stable with each added element, it is evident that the increased exposure did not lead to increased acceptance of this new procedure. Nevertheless, it is important to note that nearly one-fifth of patients consistently used the visit forms during the course of this project. This suggests that "My Visit" forms may be a reliable method to engage a subset of patients and that alternative methods for patient engagement should be explored.

The ultimate goal of this project is to improve patients' experiences and personal health literacy. By encouraging patients to create their own record of the visit, resident physicians can actively engage patients and assess their understanding of the treatment plan. This facilitates communication and allows the patient to ask further questions, as well as provides patients with a detailed note to serve as a reminder of the plan between clinic visits.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Reducing Readmissions: Findings from an Urban Academic Medical Center

BACKGROUND

Hospital readmission rates are increasingly being utilized as a measure of quality and to modify hospital reimbursement. Many have argued that a significant proportion of readmissions can be prevented if modifiable factors had been intervened upon, but recent studies suggest that the majority of readmissions are most likely not preventable. In order to reduce overall hospital readmissions, clinicians and administrators should target factors which specifically address these preventable readmissions.

OBJECTIVES

This study seeks to identify trends in readmissions at the George Washington University Hospital and to identify factors which are associated with preventable readmissions. Results of this study will be compared with previously published national data. Results suggesting any unique characteristics of this institution's systemic, clinician, or patient-based factors contributing to early hospital readmissions can then be used to identify and prioritize targets for future improvement projects with the aim of reducing hospital readmissions.

DESIGN

A cross sectional survey was used to determine the proportion of readmissions which are preventable and identify associated risk factors. The survey used was modified from previously validated tools.

METHODS

All attendings in the division of hospital medicine attended a brief orientation session. Patients presenting as 30-day readmissions were identified using weekly readmissions reports. For each of those patients, the most recent attending physician was asked to indicate whether the readmission was more likely than not a preventable readmission. If yes, they were asked to select from several possible factors which may have contributed to that readmission.

RESULTS

To date, the survey response rate is 98%. Of the 163 responses available in the preliminary analysis of this ongoing study, 57% of readmissions were thought to be potentially preventable. Of those preventable readmissions, the most frequently identified associated factors were patient or caregiver's inability to adequately manage condition (49%), patients' non-medical social issues (29%), patients' failure to keep follow up appointments (13%), patients' uncertainty of whom to contact for outpatient care or when to return to ED (11%).

CONCLUSIONS

Initial analysis indicates that GWUH may have higher levels of preventable readmissions when compared to other similarly conducted studies, in which rates of preventable readmissions ranged from 26.9% to 38%. Potential reasons for this finding range from the subjective nature of defining preventability to institutional or patient-population specific causes. The factors driving readmissions at GWUH are largely patient-related rather than hospital process-related, adding to the growing debate over whether readmissions are a reliable measure of hospital quality.

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What's the Plan? Improving Physician Patient Communication in the Hospital

OBJECTIVE/BACKGROUND

For hospitalized inpatients, the medical plan of care often changes throughout the day based on the results of lab work, imaging, and consultant recommendations. What is presented as the plan of care to the patient by the medical team at the start of the day may differ by the end of the day. These changes, while expected, may be perceived as miscommunication and serve as a source of anxiety and confusion for patients and their families. In addition, duty hour regulations create additional handoffs of patient care between day and night teams, further emphasizing the need for proper and consistent communication.

AIM STATEMENT

To reduce the number of overnight cross cover team phone calls regarding patient plans of care by 50% by June 15, 2017.

METHODS

Plan-do-Study-Act (PDSA) cycles were completed using pre-printed templates, referred to as plans of care (PC) that included spaces to fill in patient-specific plans that were the most pertinent sources of overnight questions by the patient, nursing staff, and families. PDSA cycle 1 consisted of the complete plan of care distributed to one patient on one day. PDSA cycle 2 consisted of this PC being handed to family members present during rounds on four separate occasions. PDSA cycle 3 involved adjusting the time of handing out the PC as well as adjusting how the PC was distributed. Ultimately the PC was posted to the patients' rooms for PDSA cycle 4.

RESULTS

Initially handing the PC to the patient was unsuccessful; however on incorporating the PC onto the patient room wall, families that knew about the update were overall more satisfied with the care provided. Families stated "this is very helpful", patient's expressed gratitude, and both responded to the PC being easily visible at all times with quotes such as "thank you for leaving this here" and "I will look at that when I forget everything you just said".

CONCLUSIONS

Communicating with patients and their families with reinforcement of a document that outlines major points in the plan of care for the day leads to less anxiety, concern, and overall increased satisfaction of care in the hospital. Analysis will next include assessing the numbers of times cross cover teams are contacted overnight by patients and/or families about their plans of care. Subsequently, we hope to evaluate patient satisfaction through a post hospital discharge survey to patients and a family member.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Osteoporosis and Fracture Reduction in the Primary Care Setting at GW MFA

Osteoporosis is a disorder characterized by deterioration in bone mass and bone architecture, leading to bone fragility and a predisposition to fracture. Among older patients, hip osteoporotic fractures are a major cause of morbidity, mortality, and health care costs. Currently, osteoporosis results in over 1.5 million fractures per year in the United States. With the aging of the population, the rate of fracture is expected to increase by 48% in the next 25 years, making the current fracture rate rise from 1.5 million to greater than 3 million fractures in the United States. Most osteoporotic fractures occur in women, primarily due to postmenopausal estrogen deficiency, leading to increased trabecular bone resorption. With osteoporosis becoming an increasingly significant public health burden, it is critically important to identify and treat at-risk patients.

The focus of our QI project is to improve the rate of osteoporosis screening in the primary care setting for women equal to or greater than the age of 65, in accordance with the United States Preventive Services Task Force (USPSTF) recommendations. Specifically, we aim to increase the percentage of screening dual-energy x-ray absorptiometry (DXA) scan orders by a total of 10% for female patients age 65 or greater in the primary care setting through the use of education.

Our initial PDSA cycles focused on collecting baseline data for two cohorts of residents to determine the percentage of patients in our study population who have existing or new DXA scan orders. Among the two cohorts of residents, we found a significant variability in the percentage of DXA scan orders (53% and 82.5%, respectively). Interventions included providing verbal reminders as well as email reminders and educational material regarding screening guidelines. In one of the resident cohorts, we see a 3% increase in percentage of new or existing DXA scan orders for a given week compared to baseline.

With future PDSA cycles, we intend to incorporate education in the form of oral presentations, reminders, and encourage the use of documentation templates among resident cohorts with a low percentage of DXA scan orders.

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Incorporating NSQIP into Surgical Morbidity and Mortality Conference: Promoting an Environment of Education, Transparency, and Accountability

INTRODUCTION

Surgical Morbidity and Mortality Conference (M&M) nationwide lacks a standardized structure. We compared implementation of NSQIP definitions to structure our M&M versus our current system of self-identification and review.

METHODS

A prospective study was performed to compare the identification of adverse events and the educational value of our M&M conference before and after implementation of NSQIP definitions over 10 weeks. Chart review was performed of all cases to identify NSQIP defined M&Ms. Surveys were administered before and after intervention to assess educational value. All presented M&Ms were evaluated for adequate reporting of adverse events and areas for improvement. Survey and presentation data were compared using Student's T or Mann-Whitney testing as appropriate. P-values <.05 were considered significant.

RESULTS

Pre-intervention, 15% of occurrences were identified compared to 81% post-intervention. One of three deaths pre-intervention was identified versus four of four identified post-intervention. Faculty, residents, and students found improved clarity and education content in cases presented as well as improved identification of etiology, learning points, and prevention of future adverse events (all $P < .01$). Residents and faculty found the post-intervention model better identified and communicated adverse events ($P = .02$), opportunities for prevention ($P = .04$), and promoted improved transparency ($P < .01$) and inclusion of all adverse events ($P < .01$). 85% of participants supported the changes in M&M conference.

CONCLUSION

Incorporation of NSQIP into M&M standardizes identification and discussion of adverse events thus identifying opportunities for improvement and augmenting educational content. Consideration of the use of NSQIP should be given to other surgical departmental M&Ms.

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Removing Barriers to Care for the Underserved: Provider and Patient Perception of Direct to Consumer Telemedicine

PURPOSE OF STUDY

Lack of access to pediatric subspecialty care is a major barrier to pediatric health for underserved populations in the Washington DC, Virginia and Maryland area. Lack of access to transportation, long office wait times, and missed school and work are barriers that prevent access to subspecialty care. Direct to consumer (DTC) telemedicine provides this service to our underserved population by bringing care into their own home through use of computers, tablets, and smart phones.

METHODS USED

Structured interviews of parents and providers were performed prior to implementation of a subspecialty DTC telemedicine program for underserved children in Washington DC, Virginia and Maryland. Participating subspecialties included providers in neuropsychology, neurology, diabetes, and gastroenterology.

SUMMARY OF RESULTS

Pre-implementation structured interviews demonstrated a need for a more time-effective and convenient solution to the current model for subspecialty care. Parents reported telemedicine could save them time and cost while eliminating driving, parking, and waiting for an in-person appointment. Parents also reported home observation and management of certain conditions, such as feeding disorders, would reduce stress/anxiety. The two most positive aspects of telemedicine reported by providers were follow-up education in the families' homes and coordination of multiple specialties/personnel in a single visit.

CONCLUSIONS

Parents desire an expansion of DTC telemedicine subspecialty services. DTC subspecialty care in a patient's home may improve parent satisfaction and eliminate current barriers that exist.

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Medical Resource Utilization of Outpatient Care for Children with Neurofibromatosis Type 1

BACKGROUND

Neurofibromatosis Type 1 (NF1) is an autosomal dominant syndrome with manifestations affecting the central nervous system, musculoskeletal system, peripheral nervous system, and cognitive/behavioral functions. Many of these manifestations persist throughout life and require medical/surgical interventions.

The resource utilization and economic burden of caring for children with NF1 is unknown. Prior research has inherent selection bias and does not accurately reflect the incidence/resource utilization of morbidities. In order to identify which disease manifestations are in the most need of improved clinical algorithms and novel therapeutics, the frequency/type of resources utilized (i.e., diagnostic imaging and specialty visits) must be determined.

The current study sought to identify which manifestations of NF1 utilize the most healthcare resources and to validate the accuracy of using International Classification of Diseases, Ninth Revision (ICD-9) diagnostic codes to identify patients with NF1.

METHODS

The electronic health record at The Children's Hospital of Philadelphia was queried to identify patients seen between January 2011-December 2015 with the ICD-9 code 237.71. Subjects were excluded if the clinical/genetic diagnosis could not be confirmed. For eligible subjects, the frequency of disease manifestations, MRI scans, and specialty visits over the five-year study period were recorded. The positive predictive value (PPV) of identifying subjects using the ICD-9 code was calculated.

RESULTS

Nine-hundred-eleven subjects with NF1 were included (ages 0.7-69.5 years, median = 12.9; 51% female). Fifty-four patients could not be confirmed and were excluded. The most common manifestations were cognitive/behavioral (42%), CNS abnormalities (37%), plexiform neurofibromas (32%), MSK (21%) and other (19%).

A total of 13,643 outpatient provider visits occurred with Ophthalmology (18%) and Oncology (23%) being the most frequent. Subjects underwent a total of 4,527 MRI scans, 63% required sedation. Brain MRIs were the most common (N = 2,161). Treatment with prescription medications occurred in 13% of subjects for cognitive/behavioral disorders.

The 237.71 ICD-9 code accurately identified subjects with a confirmed diagnosis of NF1 (PPV = 94.4%) if the code was present once in the subject's chart. The PPV increased to 98.2% if at least two subject visits were coded.

CONCLUSIONS

To our knowledge, this is the first study to describe medical resource utilization, based on disease manifestation, in children with NF1. CNS manifestations required the highest frequency of MRI acquisitions and specialty visits. The ICD-9 code 237.71 accurately identified subjects with NF1.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Patient Preference to Participate in Shared Decision Making for Performing a CT Scan in the Emergency Department

BACKGROUND

CT scans are widely used in US emergency departments and represent a major source of carcinogenic radiation. Shared Decision Making (SDM) is the principle of including the patient in the decision process regarding diagnostic and therapeutic options. SDM has been used successfully in decisions such as hospital admissions for chest pain and surgery for appendicitis. It is unknown if shared decision making is beneficial in the decision to order a CT scan in the ED. Our objective was to assess the desire of ED patients to participate in the decision process regarding CT scan use and describe differences in patients who want to participate versus those who do not want to participate.

METHODS

Patients who were receiving a CT scan in a tertiary care urban ED were approached from June to August 2016 and asked to participate in the study. If verbally consented, subjects were interviewed in the ED by a research assistant blinded to the objectives of the study after a CT scan had been ordered but prior to ED disposition.

RESULTS

Of the 102 subjects who were enrolled, 58% were female, the median age was 46.5, and 48% received an abdominal CT scan. 48% of all patients desired to “participate fully in the decision to perform CT scan,” compared to 44% who “did not want to participate in the decision to perform CT.” Of those who wanted to participate fully, there was no difference in median age, sex, type of CT, discussion of risks by physician, or explanation of alternatives by physician. Patients who wanted full participation were more likely to have concerns about CT scans (23% versus 11%, $p=0.02$) but also felt more involved in the decision process (31% versus 20%, $p=0.04$).

CONCLUSION

Approximately 50% of ED patients want to participate in the decision to perform a CT scan and among those patients, they are more likely to have concerns about CT scans. There was no increase in discussion of risks or alternatives for patients who wanted to participate in the decision.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Case Report: Tension Pneumothorax and PEA Arrest During Elective Colonoscopy

Approximately 1.3 million elective colonoscopies are performed each year in the United States. Whereas minor gastrointestinal symptoms may develop in approximately 33% of patients after a colonoscopy, severe complications are much more uncommon. We present a case of a 63 year old woman who experienced PEA arrest in the context of a tension pneumothorax which developed as a result of a perforated viscera during an elective outpatient colonoscopy for follow-up evaluation of polyps and diverticulosis.

Bowel perforation is one of the most dangerous complications of a colonoscopy as insufflation of gas into the peritoneum or retroperitoneum may track along tissue planes including subcutaneous tissue and the pleural space, leading to life-threatening pneumothoraces. This case illustrates a potentially lethal consequence of colonic perforation and aims to raise awareness among anesthesiologists who may be the first medical providers to recognize early signs and symptoms of colonic perforation. When this potential complication is identified early, life-saving interventions may also be implemented early.

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Effects of a Comprehensive Bariatric Program Implementation on 30-Day Readmission and 30-Day ER/Infusion Clinic Visit Rates Due to Dehydration

BACKGROUND

Program accreditation requires adherence to MBSAQIP standards to assist patient in making needed changes to his/her diet and lifestyle. However, literature provides conflicting information regarding the value of a comprehensive bariatric program accreditation and its effects on 30-day readmission and 30-day ER/infusion clinic visit due to dehydration development.

OBJECTIVES

To examine the effects of implementing a comprehensive bariatric surgical program on 30-day readmission rates, and 30-day emergency room (ER) and infusion clinic visit rates due to dehydration for bariatric surgical patients.

METHODS

Our study was a retrospective separate sample pre-post intervention chart review. The data were collected before and after implementing a comprehensive bariatric program using a convenience sample of 180 adult patients (age ≥ 18) that had bariatric surgery at an acute care hospital. We conducted Chi-square analyses with significance levels set at 0.05.

RESULTS

Among the 180 patients, majority had laparoscopic gastric bypass ($n=112$, 62.2%). Among the 180 patients, 55 (31%) were in the pre-intervention and 125 (69%) were in the post-intervention group. A total of 7 (3.9%) had 30-day readmission. Significantly more patients ($n=5$, 9.1%) in the pre-intervention group had 30-day readmission compared to those in the post-intervention group ($n=2$, 1.6%; $X^2=5.73$, $p=0.03$). Among the 180 patients, 8 (4.4%) had 30-day ER/infusion clinic visit due to dehydration. No difference was found in 30-day ER/infusion clinic visit between the pre-intervention ($n=5$, 9.1%) and the post-intervention groups ($n=3$, 2.4%; $X^2=4.03$, $p=0.06$).

CONCLUSION

Implementation of comprehensive bariatric program was effective in lowering 30-day readmission rates.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Vancomycin Trough Quality Improvement Project: Aiming to Improve Correctly Timed Troughs

Vancomycin is one of the most widely used intravenous antibiotics in the United States for the treatment of severe gram-positive infections, specifically methicillin-resistant *Staphylococcus aureus*. Troughs are used to guide dosing of vancomycin in order to maintain a therapeutic concentration (between 15 and 20 mcg/mL) that achieves a steady-state before the administration of the fourth dose. Therefore, a vancomycin trough must be timed just prior to the fourth dose to ensure that a therapeutic steady-state has been achieved. It is important for any medical facility to implement a system to determine whether medications are within their therapeutic window to reduce the risk of such complications. We aim to improve quality of care by increasing the percentage of appropriately timed vancomycin troughs through physician and nursing education. The initial analysis of this project has revealed that only 34% of vancomycin troughs were timed properly on select floors of the university hospital. This demonstrates a large deficit in our aims to provide safe and effective patient care. We hope to show that implementation of a nursing education program on medical wards will lead to a great proportion of appropriately completed vancomycin troughs.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Improving Plan of Care Communication Between Primary Resident Teams and Nursing Staff

BACKGROUND

Ineffective communication between physicians and nurses can compromise patient care. The aim of this project was to encourage resident physicians to provide daily, verbal updates to nursing staff regarding their patients' daily plan of care.

METHODS

The study took place at the George Washington University Hospital. It involved five internal medicine resident teams and the nursing staff on 4-South. Baseline data was collected with a questionnaire that assessed the number of patients that the nurses received a verbal plan of care. PDSA cycle 1 was distributing the nursing radio frequency phone numbers to the residents before morning rounds, and PDSA cycle 2 was posting a written reminder in the team rooms to call with the following details: diagnosis, goals for the day, labs or procedures, and discharge status. Post-intervention data was obtained with the same questionnaire used at baseline.

RESULTS

Our data did not show a significant increase in the amount of plan of care updates given by the resident teams to the nursing staff. Baseline and intervention data were each collected over a course of 4 days. At baseline, there were a total of 5 reports called to the 31 nurses that completed the survey. During PDSA cycle 1 and 2, a total of 7 reports and 5 reports were called to the 33 and 36 nurses who filled out the survey, respectively. Of note, a separate survey was performed amongst the nursing staff to identify the specifics to include in the plan of care update.

CONCLUSION

The benefits of constructive communication between physicians and nurses is well established in both medical and nursing literature. Literature reviews have found that physicians and nurses hold different attitudes regarding the importance and quality of such collaboration (1). Our experiences underscore this effect when considering the differences in what physicians felt was most important (providing a daily care plan update) and what nurses felt was most important (and expanded list, covering diagnosis, lab and procedure updates, and discharge planning). High workloads and burnout (2) are commonplace in residency, and may have had an adverse effect as resident physicians may have felt too overburdened to take on any additional responsibilities or allocate any more time from their already long work days to engage in collaborative efforts with the nursing staff. Future research should focus on the barriers to physician-nurse communication and collaboration, and identify ways to address them.

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Electronic Medical Record Discharge Template Use Improves Resident Efficiency

George Washington University internal medicine residents are challenged to deliver evidence-based, humanistic, and high-quality medical care. However, much of their time is spent on documentation instead of direct patient care or scholarly activities. The introduction of electronic medical records (“EMR”) has provided an opportunity for the improvement of both efficiency and quality of patient care. In reality, capitalizing on this opportunity has been particularly difficult in academic settings that experience high patient turnover and employ resident physicians at varying levels of training.

The discharge instruction (“DCI”), which details the reason for a patient’s hospitalization, is among the most important documentation that a resident is responsible for. Despite this, only 16% of internal medicine residency programs have a discharge planning curriculum. This was addressed in a prior quality improvement (“QI”) project at George Washington University. The results of that project showed that DCI standardization through the use of templates led to a decrease in drafting time in addition to an increase in quality. Subsequently, the EMR system at the site of the project was changed. The present QI project aimed to adopt those previous instructions and replicate those results in the new system.

Our aim was to increase the use of DCI templates by 25% in 4 months on the cardiology service. Templates were created for common diagnoses: acute heart failure exacerbation, syncope, noncardiac chest pain, and acute coronary syndrome. Initially, only 35% of respondents were using templates, however, after our final PDSA cycle 100% of respondents were using templates. This increase in use correlated with a decrease in the amount of time spent writing DCIs. The number of residents able to complete discharge instructions in less than 10 minutes increased by 28%. Despite the decrease in time, residents surveyed did not perceive a reduction in quality.

Our study shows that the use of DCI templates or macros increases efficiency while maintaining quality. This will permit residents to devote more time to other aspects of patient care as well as to their pursuit of knowledge. Further PDSA cycles can be target the creation of additional templates for the cardiology service, and the expansion of template use to other services.

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Resident Wellness Quality Improvement Project

BACKGROUND

Physician burnout is a well-known phenomenon among health workers that has become the subject of widespread investigations over the past several years. Multiple studies have shown an increased prevalence of burnout among both medical students and residents in all specialties. Increasing evidence of the negative impact of physicians' burnout on patient health care and the health care system in general has led to the establishment of many programs to address these concerns and to minimize the consequences. The aim of this quality improvement (QI) project was to lower physical / mental burnout among Internal Medicine (IM) residents at The George Washington University Hospital by 25% over a six-month period.

METHODS

A modified burnout questionnaire was distributed to IM residents and interns to assess pre-intervention burnout level. Then several quality-improvement initiatives were developed and provisional plan-do-study-act (PDSA) cycles were devised. The first cycle was comprised of 2-3 minutes of breathing exercise during the morning report. The second cycle required a medical team to perform a group breathing exercise before starting their medical rounds. The third cycle involved residents in a 10-15 minutes of mindful eating at noon conference. The fourth cycle included playing classic music in medical team room. Verbal feedback was acquired from study participants following the completion of each task during each cycle. At the end of the project, a modified burnout questionnaire will be distributed to assess post-intervention burnout level.

RESULT

Initial burnout questionnaire was sent to a126 residents with 43.7% (n=55) response rate. Twenty-five percent of the participants reported a moderate to severe burnout level while the majority reported no to mild symptoms of burnout. Difficulties in time management, and sleep deprivation were identified as factors contributing to burnout by 63.6% and 70.2% of participants, respectively. Constructive feedback (42.6%), meditation (42.6%), and listening to music (46.8%) were the most suggested interventions. Further results pending completion of PDSA cycles.

DISCUSSION

Findings from the initial survey suggest that most IM residents are not experiencing high level of burnout, which could be related to factors that are intrinsic to the medicine residency program or to the time of the year when the survey was assessed. Future analysis will be conducted to determine whether the PDSA interventions that were tested will yield any changes in resident burnout levels.

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VETERANS AFFAIRS MEDICAL CENTER

“Are Healthy Veterans More Health Literate?”: Implementing a Novel After Hospital Care Plan to Improve Patient Understanding and Facilitate Efficient Follow-Up Care at the Washington D.C. Veterans Affairs Medical Center

All too often, patients are discharged without a complete understanding of their medical plan. Patients also feel burdened with coordinating their own care which may contribute to dissatisfaction with their medical care. A new, comprehensive discharge booklet, hereby referred to as the After Hospital Care Plan (AHCP), was piloted at several Veterans Affairs medical facilities nationwide. Prior studies have shown the AHCP improves patient understanding of their medications, medical conditions, and importance of follow-up visits. The object of this study is to address barriers to implementation of the AHCP for medical floor patients at the Washington D.C. Veterans Affairs Medical Center (DC VAMC).

AIM

Implement AHCP on discharge for 25% of all patients cared for by medical teams by June 2017, while maintaining or improving patient satisfaction through progressive quality improvement cycles.

METHODS

The software for the AHCP was tested multiple times on individually discharged patients to evaluate for technical barriers and to ensure that the AHCP would be accessible to all medical teams. The text and format of the AHCP booklet itself was also updated to ensure compliance with smoking/addiction counseling requirements. After technical success of the booklet was achieved, we developed educational materials for involved healthcare providers on how to use the new booklet. For monitoring of results, we selected several relevant inpatient satisfaction scores to assess improvements in patient understanding of their medical plan upon discharge.

DISCUSSION

We postulated that improving the vehicle of delivering health information to patients (the discharge booklet) would improve both patient comprehension and health outcomes.

While many of our initial barriers were technical, many of the subsequent obstacles were related to redefining provider roles. Emerging technologies will continue to strive to make changes to established hospital processes and culture change is crucial to making way for newer and more efficient tools. The support of departmental leadership has been invaluable in garnering support from other departmental staff. Our next steps will be continuing to work with nursing and pharmacy staff to incorporate standardized training of the AHCP to be used for all patients being discharged from the medical floors.

This project demonstrated the ease of implementing a new component of the discharge process among a small group of trainees within only a few months. We aspire to broaden education for all resident physicians to use the AHCP by the end of the academic year.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Care Team Face Sheets: A quality improvement project to enhance patient-provider communication

BACKGROUND

Inability to name one's physician has been shown to be associated with diminished patient understanding of plan of care, medication changes, and discharge instructions. We believe that the creation of a Care Team Face Sheet ("Face Sheet") provides a novel means to help patients identify their inpatient providers and improve patient-provider communication.

AIM

We sought improvement of over 10% in three different scores of patient perception of care and communication with their hospital physicians after completing our intervention over the time period from July 2015 through February 2017.

METHODS

Our intervention involved distribution of a Face Sheet, which is a document that provides labeled photos of each member on the primary inpatient medical team and describes each team member's role. These sheets are printed by a member of the primary team and handed out to patients at admission or shortly thereafter.

We began our project in July 2015 with a survey of 100 hospitalized internal medicine patients to collect baseline data on patient demographics, whether they were able to name one of their physicians, and their satisfaction scores around communication, understanding their plan of care, and their overall hospital experience, using a 1-5 Likert scale.

Over the following 18 months, we completed several PDSA cycles aimed at increasing the distribution of Face Sheets by the residents to their patients. After each intervention, which usually lasted 2-3 weeks, we performed a random survey of 10 patients to see if they had received a Face Sheet.

At the conclusion of our intervention, we collected 50 surveys of patients to compare with our baseline data.

RESULTS

We found that distribution of the Face Sheets was lower than anticipated, persisting around 10%, despite several months of PDSA cycles and various interventions. Assessing the barriers to distribution in a qualitative fashion, we found that residents overwhelmingly believed Face Sheets to be useful to their patients, however they cited an overwhelming amount of small tasks and things to remember during the days as barriers to adopting a new workflow process.

We found modest improvements in patient satisfaction scores including 6.7% for understanding plan of care, 9.4% in satisfaction with communication, and 4.2% in overall satisfaction with hospitalization.

DISCUSSION

Barriers to implementing a new work flow process included frequent resident turnover, resident burnout, and need for support from physician leadership. We still believe that increased distribution would lead to lasting improvements in patient provider communication.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Lapse in In-Line Stabilization in Pediatric Trauma Patients

BACKGROUND

Cervical spine (C-spine) injuries occur in 1.5% of injured children sustaining blunt injuries who are seen at trauma center, with a mortality rate approaching 20%. To prevent worsening of a C-spine injury in at-risk patients, the neck should be immobilized in a "neutral position" to minimize movement until it can be examined. We previously observed that failure to maintain C-spine stabilization is a frequent error during pediatric trauma resuscitations.

OBJECTIVES

The objectives were to identify the different types of lapses in C-spine stabilization during trauma resuscitations and to determine tasks associated with the lapses. Our secondary objective was to evaluate patient and resuscitation features associated with lapses in C-spine stabilization.

METHODS

Fifty-six videos of trauma resuscitations performed at Children's National Medical Center were reviewed to identify lapses in C-spine stabilization. Patient features, including Glasgow-Coma Scale (GCS) motor score, and resuscitation features, including time of resuscitation (weekday vs. weekend), were obtained from the trauma database and medical chart review. Tasks associated with lapses were identified through video review. The presence, duration, and number of lapses were analyzed using logistic and linear regression models for associations with patient and resuscitation features.

RESULTS

Two types of lapses were observed: incorrect in-line stabilization C-spine ($n=52$, 75.4%) and complete lapse in stabilization ($n=17$, 24.6%). The most common task performed during a lapse was C-spine collar manipulation ($n=43$, 50.6%). C-spine collar manipulation was associated with a higher likelihood of a lapse (OR 6.82; 95% confidence interval (CI) 1.74, 26.64; $p<0.01$). The lapse duration decreased by 138.31 seconds for a GCS motor score of 6 compared to a lower GCS motor score (95% CI -217.30, -59.32; $p<0.001$). The number of lapses increased by 0.91 for a resuscitation performed during the weekend (95% CI 0.22, 1.59; $p<0.01$), by 0.04 for each additional task related to oxygen delivery performed (95% CI 0.01, 0.08; $p<0.01$), and by 0.62 for each instance of C-spine collar manipulation (95% CI 0.37, 0.87; $p<0.001$).

CONCLUSIONS

Lapses in C-spine immobilization are frequent errors during pediatric trauma resuscitations. Most lapses are due to improper C-spine stabilization rather than a complete lack of stabilization. Tasks performed near the head and neck, including oxygen delivery and collar manipulation, have a high association with C-spine immobilization errors. These results suggest education focused on high-risk patient factors, resuscitation factors, and specific resuscitation tasks may reduce the likelihood of lapses in C-spine stabilization that occur during pediatric trauma resuscitation.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

ConnectER Usage: Are Physicians Comfortable Using Telemedicine for Follow Ups on Non-Visual Diagnoses?

The ConnectER program provides recently discharged ED patients telemedicine follow up consults. This service minimizes patient burdens of time and travel, and provides patients an alternative if a follow up with a primary care physician is not available in a timely fashion. ER physicians recommend patients to the program based on whether they think a virtual follow up would be medically appropriate and convenient for the patient.

A quality improvement study was initiated to analyze the program's usage so that we might improve marketing and education for physicians and patients. ED providers, especially those unaccustomed to telemedicine, often think of "visual" diagnoses (e.g skin rash, lacerations, etc.) to be more appropriate for telemedicine follow up than "non-visual" illnesses (e.g. chest pain, headache, etc.). We hypothesized that as physicians gained comfort with ConnectER, the ratio of non-visual to visual diagnoses patients would increase. We analyzed approximately 700 ConnectER referrals, first classifying diagnoses as visual or non-visual. Then we compared the non-visual/visual ratios for each month from the beginning of the program in July 2015 to January 2017.

Our results demonstrate wide month to month variability in the non-visual/visual ratio, but on average the ratio is greater than 1. We will present further analysis of our data and quality improvement plan to enhance ConnectER referrals by ED providers. Critical analysis of telemedicine program utilization is important to enhance engagement by both providers and patients.

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A Videographic Assessment of the Quality of EMS to ED Handoff Communication during Pediatric Resuscitations

BACKGROUND

The National Association of EMS Physicians emphasizes the importance of high quality communication between emergency medical services (EMS) providers and emergency department (ED) staff for providing safe, effective care. The quality of handoff communication from EMS to ED teams for critically ill pediatric patients needs further exploration.

OBJECTIVE

This study assessed the quality of handoff communication during pediatric resuscitations.

METHODS/DESIGN

This study was conducted at a level 1 pediatric trauma center. We retrospectively reviewed video recordings of pediatric patients who required critical care ("resuscitations") in the ED between 1/1/2014 and 2/2/2016. All events that had video recordings with EMS to ED provider handoff communication were included. Handoff quality parameters included critical patient information (chief complaint, age, medical history, vital signs, weight, exam findings, pre-hospital interventions) and inefficient communication patterns (ED staff interruptions, ED attending questions to repeat previously communicated information, and ED staff questions on information not communicated by EMS). Times involving the handoff process were also collected [handoff time= arrival to ED bed; report time=complete EMS report]. Our institutional review board approved this study.

RESULTS/DISCUSSION

68 resuscitations were reviewed; 25% were cardiac arrests. 78% arrived by ground transport; 22% by helicopter. The median handoff and report times were 50 seconds [IQR 30,74] and 108 seconds [IQR 62,252] respectively. EMS handoff included: chief complaint (88%), interventions (81%), exam (63%), medical history (59%), age (56%), and weight (20%). Communicated vital signs included: respiratory rate (53%), heart rate (43%), oxygen saturation (39%), and blood pressure (31%). Inefficient communication occurred in 87%, including ED staff interruptions (51%), ED attending questions on previously reported information (40%), and ED staff questions on information not communicated (65%).

CONCLUSION

We described the quality of EMS to ED handoff communication during pediatric resuscitations in a single pediatric ED. We have identified multiple opportunities to improve the content and efficiency of this process.

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Reducing Resource Utilization and Improving Efficiency Using A Separate Activation for Emergent Large Vessel Occlusion Ischemic Strokes

OBJECTIVE

To improve the acute stroke management process in light of recent advancements in acute endovascular therapy.

BACKGROUND

Earlier treatment of acute ischemic stroke with both intravenous (IV) tPa and endovascular therapy results in better clinical outcomes. We performed a quality stream analysis (QSA) to develop an acute stroke management protocol to more efficiently deliver IV tPa and endovascular therapy.

DESIGN/METHODS

A process mapping QSA was designed and implemented to improve the acute stroke management process in light of the recent evidence supporting acute stroke intervention for large vessel occlusions. Major changes included (1) partitioning the work flow between cases requiring only IV tPA and probable cases for endovascular therapy (2) implementing a new separate activation system for probable large vessel occlusions - "LVO Attack" and (3) implementation of a door Straight-to-CT approach. Prior to the QSA all brain attack cases were reflexively getting a CTA head and neck to screen for LVO.

We compared outcomes between pre- and post-QSA epochs including door-to-tPA (DTT) time, door-to-groin (DTG) time, utilization of any vascular imaging during hospitalization (i.e. CTA, MRA, IR, or carotid ultrasound), and symptomatic hemorrhagic transformation. Non-parametric statistics were used with $p < 0.05$ required for significance.

RESULTS

A total of 215 patients were included (97 in the pre- and 108 in the post-improvement epoch). Median DTT time improved (57 to 27 min, $p=0.013$). There was a trend towards shorter median DTG time in the post- compared to pre-QSA, however, the difference was not statistically significant (131 to 65 min, $p=0.51$). There was a 39.8% absolute reduction in vascular imaging. There was no difference in symptomatic hemorrhagic transformation between the two epochs.

CONCLUSIONS

Partitioning of the acute stroke management process with a separate activation for probable large vessel occlusions resulted in a reduction of vascular imaging utilization and did not result in slower door-to-groin times.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Increasing Nursing Participation in Morning Rounds for Hospitalized Patients at GWUH

OBJECTIVE/AIM

Improve communication of the plan of care to all team members, particularly the patient's bedside nurse, by increasing nursing staff participation in bedside rounds to 75% by January 2017.

BACKGROUND

Internal medicine patients hospitalized at George Washington University Hospital have multiple medical conditions that necessitate complex plans of care. The discussion of the plan of care occurs during morning rounds. In a previous study, we found that calling the nurse was effective at raising the number of nurses notified to greater than 50%. This study attempts to achieve a higher percentage of nurse participation in bedside rounds by leveraging a continuous quality improvement methodology.

QUALITY IMPROVEMENT METHODS

PDSA cycles were conducted on the Internal Medicine Green Team on non-call days. Day one was observational. The first PDSA cycle was to call the nurse from the number written on the white board in each patient's room. The second PDSA cycle was to assign the medical students to collect the nurse's number for each of their patients prior to rounds. The third PDSA cycle was to collect the distribution sheet listing the nurse's numbers for the unit.

RESULTS

During the day of observation prior to starting a PDSA cycle, only 36% of nurses aware of rounds with only 27% present at rounds. The first PDSA cycle using the phone number on the patient white board resulted in 100% of nurses notified of rounds on their patients with 66% present at rounds. The second PDSA cycle using medical students to collect phone numbers resulted in 75% of nurses aware and present at rounds. The third PDSA cycle using the nurse's distribution paper resulted in 100% of nurses notified and 66% present at rounds.

DISCUSSION

Our goal was to increase attendance to 75% through PDSA cycles that changed the way that nurse phone numbers were acquired by our team. We found that the most effective method of contacting nurses was whenever the phone numbers were available in advance, which gave the medical team more time to place the call and gave the nurses more time to plan to attend rounds. They are not currently available through the electronic medical record at George Washington University Hospital. Future PDSA cycles will focus on the time involved in each method of notification.

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REHABILITATION AND RECOVERY



SCHOOL OF ENGINEERING AND APPLIED SCIENCE

Robot Therapist for Assisting in At-Home Rehabilitation of Shoulder Surgery Patients

Annually in the US, there are 53,000 shoulder replacements, 650,000 rotator cuff injury surgeries, and 4.5 million doctor visits for “extreme shoulder pain”. The mean age of shoulder surgery recipients is increasing (currently 50.9 years old), along with the number of surgeries performed. Of these surgery patients, 76% of traditional patients who do not fully adhere to their physical therapy regimen due to soreness, lack of supervision, and/or lack of incentive. Older patients are less likely to complete their post-surgery therapy regimen than younger patients. Patients are more likely to complete their exercise under supervision. However, patients prefer to exercise at home over traveling to a session.

To resolve the abovementioned issues, we propose the use of an autonomous, interactive robot for patient rehabilitation as they recover from shoulder surgery. This robot introduces customized training and encouragement regimens, to increase physical therapy adherence and improve the patient’s recovery experience from the comfort of their own home.

The initial range of motion and patient pain levels are recorded during calibration. OP2 guides the user through the physician prescribed rehabilitation program and movements. OP2 first demonstrates the exercises, then observes the user’s performance and gives performance feedback. The movements targeted for the purpose of this study include internal rotation, glenohumeral abduction, glenohumeral flexion, and passively performed pendulum movements.

Research shows users respond positively to robots when they exhibit and respond to social cues. OP-2 provides active verbal feedback to the user based on performance. Role model systems: promotion (positive feedback) and prevention (negative feedback) vary in their effect on individual user motivation. Feedback style is altered throughout the rehabilitation program as OP-2 learns user preference and observes which styles generates the most patient improvement.

Initial feasibility studies have proven promising. After completing the primary programming phase, the robot is currently able to: Perform calibration routines, demonstrate movements, retain user calibration information including pain values and initial range of motion of the joint, automatically generate a custom rehabilitation program based on initial calibration, track user movement, provide verbal feedback, and adapt feedback style based on patient performance.

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REHABILITATION AND RECOVERY



SCHOOL OF MEDICINE AND HEALTH SCIENCES

A Comparison of Narcotic Usage and Length of Post-Operative Hospital Stay in Open Versus Minimally Invasive Lumbar Fusion

INTRODUCTION

Lumbar fusion can be accomplished through open or minimally invasive surgery (MIS). While the open technique involves a long central incision through skin and muscle, MIS utilizes multiple small incisions and is generally associated with less muscle damage. MIS has also been shown to be cost effective, have a shorter length of stay, and a decreased need for perioperative blood transfusion. However, both techniques regularly require narcotics for management of post-operative pain. Given the ongoing opioid epidemic in the United States, the focus of this study was to compare perioperative narcotic usage between open and MIS to evaluate how narcotics are being used in the hospital setting. Additionally, the study examines the length of post-operative hospital stay associated with the two techniques.

METHODS

Institutional board approval was obtained for a retrospective review of medical records for patients who underwent lumbar fusion at George Washington University Hospital from 2010 to 2015. Although 1600 patients were identified, data sets were only available beginning in 2012 due to a change in the medical record system. Additionally, data concerning patient controlled anesthesia (PCA) was inconsistently documented in the medical record. Therefore, we took a consecutive cohort from 2014 to conduct our study. A retrospective analysis was performed for 41 patients that underwent MIS and 69 that had open surgery. Data were collected on inpatient narcotic usage and length of stay. Inpatient narcotic usage was defined as narcotics used intra-operatively and narcotics used during the post-operative recovery period. Opioid use was standardized using an equi-analgesia chart and total dose was calculated for each patient. Average total dose and length of stay were compared using t-tests and p-values were calculated.

RESULTS

Average narcotic usage post-operatively was significantly lower for the MIS group relative to those who underwent open lumbar fusion (average equi-analgesic dose 278 mg vs. 442 mg, $p = 0.03$). A comparison of intra-operative narcotic use did not reveal a statistically significant difference. (26 mg vs. 33 mg, $p = 0.06$). Additionally, the average length of post-operative hospital stay was significantly shorter for patients who underwent MIS compared to those who had an open procedure (4.1 days vs. 6.2 days, $p = 0.02$).

CONCLUSION

From this study, the authors demonstrate that minimally invasive lumbar fusion decreases the overall use of opioids in the perioperative period relative to the open procedure. However, intraoperative narcotic usage was not statistically different between the two groups. Additionally, the minimally invasive technique leads to significantly shorter hospital stays when compared to open surgery. This study supports evidence from the literature that have shown MIS to have better short-term outcomes in terms of pain control and length of hospital stay relative to open surgery.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Are We There Yet?: Teen Pregnancy Rates in the District of Columbia from 2006-2014

Preventing teen pregnancy is a critical, high leverage intervention that can expand opportunity for every family in Washington, DC. It is far more effective, and far less costly, than after the fact efforts to deal with neighborhood instability, developmental disabilities, child abuse, school failure, violence, and the continuing cycle of poverty that traps all too many young people. The national teen pregnancy rate has declined continuously over the past two decades, from 61.8 births for every 1,000 adolescent females, compared with 24.2 births for every 1,000 adolescent females in 2014. Rates of teen pregnancy in the District of Columbia have followed this downward trend, but remain well above the national average. In 2007 the DC Campaign for the Prevention of Teen Pregnancy, a grant released a report on the trends of teen pregnancy rates in the District of Columbia. The purpose of this study is to assess the rates of teen pregnancy since the publication of this study. We utilized data from the District of Columbia Department of Health to assess pregnancy rates, live births, abortions, and fetal deaths among females age less than 15 and females ages 15 to 19 from 2006-2014. In this time, we found that pregnancy rates in the 15 to 19-year-old age group has declined by 39% from 58.7 to 35.8 per 1,000. While the cause of this decline is likely multifactorial, it is encouraging news for the many local community organizations dedicated to adolescent health. Teen pregnancy rates remain higher than the national average, however, so continued efforts are necessary to help improve the social and economic health of our nation's capital.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Healthcare Provider and Patient Knowledge, Attitudes and Practices (KAP) Regarding Zika Virus

INTRODUCTION

Zika virus emergence in the western hemisphere has prompted the critical need for tailored risk counseling. Our team created a KAP survey in order to assess provider and patient awareness of Zika virus symptoms, transmission, treatment, and current and future concerns in order to inform local risk counseling efforts.

METHODS

The cross-sectional survey was issued in Medical Faculty Associates (MFA) clinics and via online link to healthcare providers and community members. The REDCap Data Collection tool was used to capture responses with subsequent SAS data analysis.

RESULTS

A total of 172 responses were collected. Most respondents (97%) were aware of a link between Zika virus and microcephaly. 89% think that a vaccine is important. 52% will restrict travel to Zika endemic regions. 51% will take mosquito protective measures in the US versus 91% in Zika endemic areas. 35% of pregnant women would abstain from sex if their partners traveled to a Zika endemic area whereas 25% would if they themselves were the traveler. 37% plan to delay pregnancy and 58% are concerned about eventually having a child with microcephaly. Of the healthcare providers sampled, about one-fifth could not identify Zika infection symptoms, 16% were unaware of symptom treatment options and 5.4% did not know that Zika virus could be passed transplacentally. 34% believed DEET to be unsafe in pregnancy and 52% were unsure about permethrin safety in pregnancy. Of the 172 survey respondents, most (97%) were aware of a link between Zika virus and microcephaly. 89% think that a vaccine is important. 52% would restrict travel to Zika endemic regions. 51% would practice mosquito safety in the US versus 91% in Zika endemic countries. 35% of pregnant women would abstain from intercourse if their partners traveled to Zika endemic areas whereas 25% would if they themselves were the traveler. 37% plan to delay pregnancy and 58% worry about future children with microcephaly. Of the healthcare providers, 20% could not identify Zika infection symptoms, 16% were unaware of symptom treatment options, 5% were unaware that Zika virus passes transplacentally, and 34% believed DEET to be unsafe in pregnancy.

CONCLUSION

The survey results provide novel insight into the KAP of patients and healthcare providers regarding Zika virus. This data will be used to optimize information distribution to our community, address large knowledge gaps in both patients and providers, and prepare medical providers to offer needed counseling.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Provider Beliefs, Knowledge and Training on Gestational Weight Gain and Exercise During Pregnancy

BACKGROUND

Gestational weight gain (GWG) and exercise during pregnancy have strong influences on the health of mother and child long after birth. Studies suggest a patient-provider communication gap regarding these important health topics exists. This gap could be due to a variety of factors, including a provider deficit in knowledge and training. Addressing this communication gap could improve maternal and child health.

OBJECTIVES

The purpose of this survey study was to assess provider beliefs, knowledge and training on GWG and exercise during pregnancy.

METHODS

Providers at GW MFA OB/GYN clinic were recruited for a voluntary survey. Descriptive statistics of responses are reported.

RESULTS

A total of 36 provider questionnaires were analyzed. Most providers believed determining a woman's BMI was important for making an appropriate recommendation for GWG (91.7%) and gaining an inappropriate amount of weight during pregnancy had a negative impact on mother (97.2%) and child (88.9%). Almost all providers (96.9%) agreed with the benefits of exercise for 30 minutes/day at least 4 times per week during pregnancy. In clinical scenarios, a majority of providers recommended a GWG consistent with Institute of Medicine (IOM) guidelines for "normal" (82.9%) and "overweight" BMIs (54.2%), however, a majority (52.8%) recommended GWG below IOM recommendations for obese women. In all three BMI scenarios providers were more likely to recommend below rather than above IOM recommendations. Almost all providers reported some form of formal training regarding GWG (82.4%), most often during Residency (69.4%). Few providers reported training through continuing medical education (CME) courses or lectures (11.1%). A third of physicians reported not receiving formal training on exercise during pregnancy. Providers reported monthly or annual use of medical journals, academic books, and ACOG Bulletins/Committee Opinions. Almost all providers agreed a GWG tracker or calculator placed into an electronic medical record would be beneficial.

CONCLUSIONS

Our findings suggest while most providers receive training regarding GWG at least once during their initial training, continued medical education seems to be limited. Providers are accessing available resources to keep current with accurate guidelines; however, their use is infrequent. Future research should study whether implementing CME lectures or courses on GWG would benefit providers and enhance practice. Providers generally follow IOM recommendations, though they appear to believe the recommendations are too generous for obese women. Implementing a GWG calculator or tracker into Electronic Medical Records in Office Systems was supported by providers and should be considered.

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SCHOOL OF MEDICINE AND HEALTH SCIENCES

Predictors of Postpartum Hemorrhage Following Cesarean Delivery: A Model for Calculating Risk of Transfusion

OBJECTIVE

Postpartum hemorrhage (PPH) is one of the leading causes of morbidity and mortality in obstetrics worldwide. There has been an appreciable rise in the severity of PPH requiring more transfusions in the United States. Our objective is to better define patients at greatest risk for severe PPH in order to identify cases for early intervention and monitoring.

STUDY DESIGN

Using the MFMU Network's Cesarean Registry, we identified cases of PPH defined as 1) non-severe (nsPPH): requiring <4 units pRBCs or 2) severe (sPPH): requiring ≥ 4 units pRBCs or ICU admission. We used a reference group of no transfusion (no txf) for comparison. We compared prevalence and severity of hemorrhage associated with maternal, fetal, and socioeconomic risk factors. Multivariate logistic regression models were used to identify predictors that were independently associated with either 1) nsPPH vs no txf, 2) sPPH vs no txf, and 3) any hemorrhage vs no txf. A risk calculator was developed for predicting the need for blood transfusion.

RESULTS

We included 56,967 women, with 983 cases of nsPPH (1.7%) and 726 cases of sPPH (1.3%). Race was identified as an independent risk factor for all PPH with Asians having the highest risk for hemorrhage (OR 2.02, 95% CI 1.35-3.01), followed by Hispanics (OR 1.47, CI 1.26-1.71) and African Americans (OR 1.25, CI 1.09-1.44). General anesthesia (OR 7.57, CI 6.35-9.02), preeclampsia (OR 2.44, CI 1.66-3.58), >3 prior term deliveries (OR 1.51, CI 1.22-1.88) and failed TOLAC (OR 1.92, CI 1.51-2.25) are significant risk factors for severe PPH. Variables that were found to be protective against sPPH were higher starting hematocrit (OR 0.68, CI 0.64-0.72) and being a term gestation >38 weeks (OR 0.51, CI 0.42-0.61). This model has good discrimination for predicting nsPPH and sPPH with AUC being 0.82 and 0.81, respectively.

CONCLUSION

Different risk factors exist predisposing women to non-severe and severe PPH among this large cohort who required cesarean section. Using our data, we were able to create a risk calculator for identifying patients at highest risk for postpartum hemorrhage requiring a blood transfusion. With an accurate prediction model, those at risk for severe PPH could be identified prior to delivery leading to interventions to improve patient outcomes through preparedness, preoperative planning, and patient counseling.

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