Eastern Regional Meeting Abstracts

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EFFECT OF PERIODIC STAFF EDUCATION ON PERFORMANCE IMPROVEMENT IN ASSESSMENT AND EDUCATION OF HEART FAILURE PATIENTS

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Purpose of Study: To assess the effect of staff education on the performance of the assessment of daily weights, intake/output (I/O) measurements, and heart failure education in a population of patients admitted with heart failure.

Methods Used: We conducted a single center interventional study on patients with known heart failure who were admitted for a minimum of 24 hours in the hospital. We recorded documented weights, whether intake/output was measured, and the incidence of heart failure education (in the form of pamphlet distribution and/or verbal teaching, done by the nursing staff). The first set of data was considered to be the baseline (index), and subsequently there were 3 interventions of paramedical staff regarding the importance of daily measurements of I/Os and weights, and HF teaching; data was collected several months after each intervention. Finally, data was collected several months after the last data period to determine if there was a change without intervention (FOLLOW-UP).

Summary of Results: We found that there was a significant improvement in the measurements of daily I/Os and weights, and heart failure education following each intervention (Table 1: p value refers to comparison with the Index).

Conclusions: Periodic interventions with the paramedical staff in the form of emphasizing the importance of daily measurements of I/Os and weights, and HF teaching lead to better outcomes in patient assessment and patient education.

	Index	After 1st Intervention	After 2nd Intervention	After 3rd Intervention	FOLLOW-UP
Daily weights	51%	69% (p<0.01)	70% (p<0.01)	92% (p<0.01)	83.25%(p<0.01)
I/O recorded	44%	76% (p<0.01)	67% (p<0.01)	88% (p<0.01)	72% (p<0.01)
HF education	45%	67% (p<0.01)	73% (p<0.01)	89% (p<0.01)	64.5% (p<0.01)

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FIVE YEARS MORTALITY PREDICTION PERFORMANCE AND OPTIMIZATION OF A NEW ARTIFICIAL INTELLIGENCE MODEL FOR CARDIOVASCULAR RISK

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Purpose of Study: Prevention strategies to reduce cardiovascular (CV) complications in patients with renal disease may benefit from noninvasive vascular testing and risk models evaluations.

We have studied common carotid intimae media thickness (CIMT), plaque and stenosis and tested endothelial function by brachial flow mediated dilatation in chronic kidney disease and end stage renal disease (ESRD) patients. After one year we evaluated the value of CV risk factors for predicting end point events (EP) with an artificial intelligence model. After five years we have "retrained" its network system, optimized its architecture and calculated the mortality prediction performance of our model.

Methods Used: Ultrasound examinations were performed on a total of 93 subjects: 67 renal disease patients and 26 healthy matched subjects. EP prediction was evaluated with an original neural networks model (NN) created in MATLAB. This used all 93 subjects' data as input. The computational experiments for the five years mortality data have used 24 CV risk factors including traditional and noninvasive markers (P1), experiment1, and repeated without carotid plaque/stenosis features (P2), experiment 2. The retraining thru principal component analysis only uses the elements contributing more than 0.01%.

Summary of Results: Mortality after five years was found on about 50% from the ESRD patients with carotid stenosis, plaque, or CIMT over 75 percentile and was computed continuously into the NN model thru an adapting learning process. The neural architectures distributions were: 72:54:6:12 and 21:18:1:2 for the experiment 1 and 72:57:6:9 and 21:15:1:5 for the experiment 2. Success mortality rate prediction was significantly greater utilizing carotid structural markers: P1=0.8571, versus P2=0.5714. Extrapolating only for the renal disease, P1 was 0.833, versus P2: 0.666.

Conclusions: Noninvasive carotid markers highly increase a new CV risk model performance to mortality prediction in renal disease. This NN model has the ability to learn from the previous data and continuously retrain with new information. Optimized on a larger scale, has the potential to help medical decision making in risk stratification and cardiovascular protective renal replacement treatment choice.

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FAMILIES WITH BOTH HODGKIN'S LYMPHOMA AND MYELOMA: ANTICIPATION AND MALE TRANSMISSION

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Purpose of Study: Report an unrecognized relationship between Hodgkin's lymphoma and multiple myeloma

Methods Used: From more than 700 pedigrees of families with multiple hematologic malignancies that we have randomly collected from genetics councilors, physicians and patients we identified 19 with both HL and MM.

Summary of Results: In 11 of the pedigrees a parent and child were affected (8, father-child; 3, mother-child pairs). Six of 19 pedigrees had only 1 affected pair and 13 had multiple affected individuals. Male transmission was evident in 13 pedigrees and female transmission was observed in 6. HL and MM cases had at least 1 generation separating them in 6 pedigrees and the diseases occurred in sequential or identical generations in 13. MM was found in the youngest affected generation in 6 pedigrees, HL in 12 in the youngest generation, and both occurred in the same generation in 1. The median age at diagnosis of HL in these families was 29.5 yrs (range, 17-78 yrs), which is older than expected, and the median age at diagnosis of MM was 64 yrs (range, 31-81) as expected. The presence or absence of anticipation could be assessed in 15 of the 19 pedigrees. Fourteen of those 15 displayed anticipation in terms of succeeding generations developing HL or MM at an earlier age than did previous generations (median, 25 years; range 3-61 years), which is a feature of familial MM that we have previously reported (Deshpande HA, et al: Br J Haematol 1998;103:698). More advanced and aggressive disease at diagnosis in the youngest generation is another feature of anticipation, and this was observed in 12 of 14 pedigrees in which it could be assessed. These pedigrees provide evidence for a previously unrecognized relationship between HL and MM.

Conclusions: Demonstration of anticipation in 14 of 15 evaluable pedigrees suggests a genetic basis for the relationship between these two B-cell disorders. These conclusions are supported by recent reports of HL and MM in the same patient (Kulcsar I, et al: Pathol Oncol Res 2012; 18:733. Molecular studies are planned.

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SENSITIVITY AND SPECIFICITY OF EMPIRIC TREATMENT FOR SEXUALLY TRANSMITTED INFECTIONS IN THE PEDIATRIC EMERGENCY DEPARTMENT

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Purpose of Study: Determine test characteristics of provider judgment to provide empiric antibiotics to adolescent patients who have testing for Neisseria gonorrhea [GC] and Chlamydia trachomatis [CT] sent from the pediatric emergency department [ED].

Methods Used: A retrospective cross-sectional medical record review was conducted on all patients aged 13–19 years who had GC and CT testing sent from an urban, academic pediatric ED in 2012. Abstracted data included patient demographics, chief complaint, disposition, test results, and treatment. We calculated test characteristics comparing clinician judgment to the reference standard of the test result. Clinician decision to treat was considered evidence the clinician considered the patient high risk.

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Summary of Results: Of 1251 patient visits meeting inclusion criteria (15.7% male, mean age 17.0 ±1.5 years), 291 (23.3%; 95% CI 20.9-25.6) had a positive test result (4.3% GC, 16.1% CT, 2.9% co-infection). Empiric treatment was provided in 626 cases (50.5%; 47.7-53.3), including 604 (48.2%) treated for GC and 621 (49.6%) treated for CT. Provider judgment had a sensitivity of 68% (95%CI 62–73) and a specificity of 55% (52–58) to detect any STI. Unnecessary antibiotics were provided to 525 patients (42.0%) without GC and 429 patients (34.3%) without CT. Empiric treatment was more likely with a chief complaint of STI concern or penile/vaginal discharge (OR 2.7; 2.1-3.5). Test characteristics of provider judgment differed by chief complaint (Table 1).

Conclusions: Many high-risk adolescents tested for GC and CT receive empiric treatment. Provider judgment lacked sufficient sensitivity and specificity to identify infected patients, resulting in potential misuse of antibiotics.

Test Characteristics of Provider Judgment by Chief Complaint

Chief Complaint	N	Sensitivity (95% CI)	Specificity (95% CI)
STI concern or discharge	398	83% (74-90)	39% (33-45)
Not STI concern or discharge	853	60% (52-67)	62% (59-66)
Potential STI: STI concern, discharge, dysuria, abdominal /pelvic pain, vaginal bleeding	997	71% (65-77)	52% (48-56)
Not Potential STI	254	55% (42-68)	68% (61-74)
Vaginal bleeding only	47	46% (19-75)	54% (42-65)
Dysuria only	97	86% (64-97)	54% (42-65)

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RACIAL DISPARITIES IN NARCOTIC ADMINISTRATION AMONG PEDIATRIC PATIENTS DIAGNOSED WITH APPENDICITIS IN EMERGENCY DEPARTMENTS

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Purpose of Study: To evaluate racial/ethnic differences in analgesic, and particularly narcotic, administration among children diagnosed with appendicitis in the ED.

Methods Used: We performed a cross-sectional study using the National Hospital Ambulatory Medical Care Survey from 2000-2010 of all ED visits by patients ≤21 years with an ICD 9 diagnosis of appendicitis. We calculated the frequency of analgesia administration (both narcotic and non-narcotic) with complex survey weights using Stata 12.0. We then performed multivariable logistic regression to examine racial/ethnic differences in analgesic and narcotic administration after adjusting for statistically significant demographic and visit covariates on bivariable analysis.

Summary of Results: There were an estimated 1.2 (95% CI 1.0, 1.4) million visits for appendicitis in children. Of those, 51.5% (95% CI 45.6, 57.5) received analgesia of any type and 36.0% (95% CI 29.8, 42.1) received narcotics. 52.5% (95% CI 44.7, 59.7) of non-Hispanic Whites received any analgesic compared to 45.1% (95% CI 24.9, 65.3) of non-Hispanic Black and 50.1% (95% CI 36.0, 65.2) of Hispanics. 38.8% (95% CI 31.0, 46.5) of non-Hispanic Whites compared to 16.2% (95% CI 3.7, 28.6) of non-Hispanic Black and 32.3% (95% CI 19.3, 45.3) of Hispanic patients received narcotics. Multivariable logistic regression revealed no significant racial/ethnic differences in overall analgesic administration. However, non-Hispanic Blacks had significantly lower adjusted odds of narcotic receipt than non-Hispanic Whites (aOR 0.13; 95% CI 0.03; 0.56) after adjusting for age, gender, pain score, ED type, and survey year.

Conclusions: Only one third of children with appendicitis in the ED received narcotic analgesia, with only one half receiving any analgesia. Non-Hispanic Black patients were significantly less likely to receive narcotics than non-Hispanic Whites, even after adjusting for potential confounders. Future studies should seek to understand this disparity, and interventions should be planned to eliminate it.

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IMPACT OF OBESITY ON CLINICAL OUTCOMES IN INNER-CITY CHILDREN HOSPITALIZED FOR ASTHMA EXACERBATION

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Purpose of Study: The prevalence of both childhood asthma and obesity have more than doubled in the past 30 years, disproportionately affecting children in inner-city communities. The relationship between these epidemics is demonstrated by increased asthma risk, severity, and health care utilization in obese patients. While asthma is the third most common cause of pediatric hospitalization, the impact of obesity on hospitalization for asthma exacerbations is not fully understood. We hypothesize that, in a high-risk inner city population, overweight children hospitalized for asthma exacerbations have increased asthma severity and hospital length of stay compared to lean children.

Methods Used: Retrospective chart review of pediatric patients >2 years old admitted to a tertiary children's hospital in Washington, DC for asthma exacerbations over a 12 month period. Data collected included demographics, body mass index (BMI) percentile, asthma severity, and length of hospitalization. T–test, Fischer's exact test, and multivariate regression analyses were used as appropriate (significance $p<0.05$).

Summary of Results: A total of 350 inner-city children were admitted for asthma exacerbations and 335 had data available to calculate BMI percentile. Of those, 128 (38%) were overweight (BMI percentile >85) and 91 (27%) were obese (>95). Average hospitalization length was 1.9 days (SE ±0.08). Obesity was associated with male gender ($p=0.046$) and presence of moderate or severe asthma ($p=0.001$) but not ethnicity. Obese children with moderate or severe asthma were more likely to have a length of stay > 3 days (OR 3.4; 95% CI: 1.2-10.0) compared to non-obese children.

Conclusions: Our results demonstrate that obesity is associated with increased length of stay and the presence of moderate and/or severe asthma in patients admitted for asthma exacerbations. This is the first study to identify associations between obesity and characteristics of asthma admissions for inner-city children. Further studies identifying causal links between obesity and asthma in children and interventions directed towards obese children with asthma will likely decrease adverse outcomes in this high-risk population.

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THE EFFECT OF GLUCOSE AND ALTERNATIVE SUGARS AND SUGAR ALCOHOLS ON THE ANOXIC TOLERANCE OF THE PERIPHERAL NERVE

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Purpose of Study: Diabetic neuropathy can result from altered metabolism, ischemia, or immunologic injury to the peripheral nerve. To better understand how the nerve functions during oxidative stress and subsequent recovery, we determined how different metabolic substrates affect the peripheral nerve during repeated anoxic episodes.

Methods Used: We extracted sciatic nerves from Sprague-Dawley rats and placed them in perfusion chambers containing 1 of 5 metabolic substrates: 5.55 mM glucose, fructose, galactose, sorbitol, and mannitol. The nerve perfusion alternated from an oxygenated- to anoxic-solution every 90 minutes. The nerve was stimulated every 4 seconds and the nerve action potential (NAP) was recorded and digitized. We then increased the concentration of each substrate tenfold and repeated the experiment.

Summary of Results: The NAP disappeared during anoxia and recovered when oxygenated in each condition. After repeated anoxic episodes the NAP amplitude, conduction velocity, and area-under-the-curve decreased while NAP duration increased. The NAP had the highest amplitude when perfused with fructose and the lowest amplitude when given mannitol. A tenfold sorbitol concentration showed a significant increase in amplitude when compared with the original concentration, while a tenfold concentration in the other substrates decreased amplitude. The time (T50) required for the NAP amplitude to reach halfway between its starting and ending values was also determined. With a tenfold substrate concentration, the anoxic and oxygenated phase T50's were highest when given glucose.

Conclusions: The NAP showed signs of progressive damage with repeated anoxic episodes but maintained the highest amplitude when perfused with fructose. The nerve cannot metabolize mannitol, resulting it its poor results. Although the accumulation of intracellular sorbitol is a possible mechanism of diabetic nerve injury, high dose extracellular sorbitol was associated with better recovery from anoxia than glucose. High glucose concentration increases the time for NAP amplitude to disappear during anoxia as well as reappear during re-oxygenation, demonstrating its benefit during stress and its detriment during recovery.

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PRIMARY PAYER STATUS IS ASSOCIATED WITH MORTALITY AND RESOURCE UTILIZATION AMONG LIVER TRANSPLANT RECIPIENTS: A NATIONWIDE STUDY

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Purpose of Study: The efficacy of health insurance is a significant focus of current healthcare reform. We hypothesized that outcomes after liver transplant in the United States is dependent on primary payer status.

Methods Used: From 2003 to 2007, 40,768 isolated liver transplant operations were evaluated using the Nationwide Inpatient Sample (NIS) database. Sample weights were developed to enable nationwide estimates. Patients were stratified by primary payer status: Medicare (26%), Medicaid (15%), private insurance (58%), and uninsured (1%). Multivariable logistic regression models were used to assess the effect of primary payer status on post-operative outcomes.

Summary of Results: Unadjusted mortality for Medicare, Medicaid, uninsured and private insurance payer status were 6.5%, 6.4%, 6.5% and 6.5% respectively. Unadjusted length of stay was longest for Medicaid patients (23 ± 26 days) and shortest for private insurance patients (19 ± 23 days, P<0.001). Medicaid patients accrued the highest unadjusted total costs (361,938 ± 261,551 USD, P<0.001). Importantly, after controlling for patient risk factors, hospital characteristics, Medicare (odds ratio, 1.39; 95% confidence intervals, 1.25-1.55; P<0.001) and uninsured (odds ratio, 1.57; 95% confidence intervals, 1.08-2.27; P<0.001) payer status independently conferred the highest adjusted odds of in-hospital mortality. In addition, Medicaid payer status was associated with the longest adjusted length of stay and highest adjusted total costs (P<0.001).

Conclusions: Medicare and uninsured payer status confers increased risk adjusted in-hospital mortality for liver transplant recipients. Medicaid was further associated with the greatest adjusted length of stay and total costs despite risk factors. Possible explanations include delays in access to care or disparate differences in health maintenance.

Risk-Adjusted Effects of Primary Payer Status on Outcomes After Liver Transplant

Outcomes	Medicare	Medicaid	Uninsured	Private
In-hospital mortality	1.39 (1.25-1.55)	1.36 (1.19-1.55)	1.57 (1.08-2.27)	Ref
Length of stay ≥ 12 days	1.17 (1.11-1.24)	1.33 (1.25-1.43)	0.69 (0.57-0.85)	Ref
Total charge ≥ 250,029 USD	1.05 (0.99-1.10)	1.20 (1.13-1.28)	0.61 (0.49-0.75)	Ref

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DIRECTIONAL IMMUNE RESPONSE AND POLARITY OF VIRAL-INDUCED THYMIC STROMAL LYMPHOPOETIN (TSLP) SECRETION IN HUMAN BRONCHIAL EPITHELIUM(HBE).

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Purpose of Study: Viruses are the most common apical environmental challenge. There is evidence that double stranded (ds)RNA, a viral surrogate, stimulates subepithelial Th2 differentiation via epithelial secretion of the Th2 master cytokine TSLP. It is unclear if this dsRNA-induced TSLP secretion has a specific polarity (apical vs. basolateral) and if there are TSLP-mediated effects occurring at both sides of the bronchial epithelial barrier. This project investigated the directionality of TSLP secretion in HBE cells and characterized its associated effects in apical and basolateral compartments.

Methods Used: Primary HBE cells were differentiated into respiratory tract epithelium under air-liquid interface conditions and then treated apically with dsRNA or TSLP. Apical and basolateral secretions were collected from each compartment at 0-48hrs to generate time response graphs of airway immune polarity. Secretions were analyzed for protein levels of TSLP, IL-1β, IL-12p70, TNF-α, IL-4, IL-5, IL-13, CCL11, CCL17, CCL22, IL-17 and CXCL8 using a multiplex magnetic bead assay. Cytokine levels were compared over time and between compartments.

Summary of Results: Apical dsRNA exposure induced bidirectional secretion of TSLP beginning at both sides of the epithelial barrier at 12h post-exposure. Apical TSLP responses to dsRNA were significantly more pronounced than in the basolateral compartment (p<0.05). Apical TSLP exposure induced unidirectional apical secretion of TNF-α and significant bidirectional secretion of IL-8 and the Th2 chemokine CCL22/MDC. The apical/basal secretion of other Th1/Th2/Th17 cytokines was unchanged.

Conclusions: Apical exposure to dsRNA induces bidirectional epithelial secretion of TSLP, which is more pronounced in the apical side. Apical TSLP induces apical secretion of TNF-α and bidirectional secretion of IL-8 and MDC but not Th2 cytokines directly. These findings suggest a potential TSLP-driven autocrine mechanism occurring at the apical epithelial surface and thereby provide an initial foundation for the generation of aerosolized therapies or airway biomarkers that target apical TSLP secretion during viral infections.

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NURSERY PRODUCT-RELATED INJURIES AMONG CHILDREN TREATED IN UNITED STATES EMERGENCY DEPARTMENTS

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Purpose of Study: To describe the epidemiology of injuries related to nursery products among young children treated in United States emergency departments.

Methods Used: A retrospective cohort study was performed using data from the National Electronic Injury Surveillance System. Records for patients younger than 3 years of age who sustained an injury associated with a nursery product between 1991 and 2011 were analyzed.

Summary of Results: An estimated 1,391,844 nursery product-related injuries in children less than 3 years were treated in U.S. emergency departments during the 21-year study period, averaging 66,278 cases annually or 56.32 injuries per 10,000 children annually. The annual injury rate decreased significantly by 18.4%, from an estimated 70.3 cases to 57.3 cases per 10,000 from 1991 to 2011. Baby walker-related injuries decreased markedly over the study period, but injuries due to baby bouncers and baby carriers experienced significant increases. The most common mechanism of injury was a self-precipitated fall (80.0%), and the most frequently injured body region was the head or neck (47.1%). Cribs and mattresses were 3.12 times more likely to be associated with entrapment compared to other nursery products. Nearly a third of documented product failures (29.9%) and over a quarter of all hospitalizations (25.8%) were associated with baby carriers.

Conclusions: Nursery product-related injuries have declined, due in part to successful injury prevention efforts with baby walkers. However, greater efforts are warranted in preventing injuries with other nursery products, especially injuries associated with baby carriers, cribs, and strollers.

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ASSOCIATION OF SERUM SOLUBLE ST2 AND INTERLEUKIN-33 WITH PRO-INFLAMMATORY CYTOKINES: A LINK BETWEEN ALLERGIC DISEASE AND INFLAMMATION

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Purpose of Study: Interleukin (IL)-33 has been associated with atopic and inflammatory conditions. Previous work by our group supports this dual role of IL-33 in allergic and inflammatory diseases. Serum soluble ST2 (sST2) acts as a decoy receptor that prevents interaction of ST2L with IL-33 and is implicated in the attenuation of Th2-induced inflammatory responses. Recent studies show that the IL-33/sST2 ratio may be a clinical predictor in cardiovascular disease. Here, we examine the possible role of IL-33, sST2 and the IL-33/sST2 ratio in atopic patients (AP) and normal healthy controls (HC).

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Methods Used: 19 AP age 18–55, 25% male, 75% female were enrolled under an IRB approved protocol at WUH. Plasma samples from 8 HC and AP were analyzed for levels of IL-33, IFNγ, TNFα, IL-1β, IL-17α, IL-10, IL-2, IL-5 with MILLIPLEX map Kit (Millipore). sST2 levels were measured with Presage® ST2 Assay (Critical Diagnostics).

Summary of Results: IL-33 level was significantly higher in AP plasma: 85.4±42pg/ml compared to HC (53.4±23pg/ml) ($P<0.05$). IL-33 concentration strongly correlated with levels of IFNγ ($r=0.85$) ($P<.05$), TNFα ($r=0.9$) ($P<0.05$) and IL-17α ($r=0.94$) ($P<0.05$). No significant difference was found in the sST2 levels between HC and AP (22±3 vs.19±5ng/ml). However, the IL-33/sST2 ratio was 2.5 times higher in those with elevated IL-33 levels and correlated with the highest levels of Th1 and Th17 mediated cytokines: IFNγ, TNFα and IL-17α as well as the Th2 mediated cytokine IL-5.

Conclusions: Here we demonstrate that high levels of IL-33 and a high IL 33/sST2 ratio in AP correlates with elevated levels of Th1 and Th17 mediated cytokines: IFNγ, TNFα and IL-17α as well as Th2 mediated cytokine IL-5 demonstrating that IL-33 has pleiotropic effects. The pro-inflammatory nature of IFNγ and TNFα could provide an explanation for pro-atherogenic changes in plasma from AP. Ongoing work by our lab studying alterations in lipid metabolism in this cohort may validate the prognostic value of this ratio in atopic patients.

MP1

SYSTEMIC LUPUS ERYTHEMATOSUS IS AN INDEPENDENT PREDICTOR OF IN-HOSPITAL MORTALITY AMONG PATIENTS WITH ACUTE PANCREATITIS: A US NATIONAL STUDY

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Purpose of Study: Acute pancreatitis is a rare presentation among systemic lupus erythematosus (SLE) patients. However, association of SLE and clinical outcomes among acute pancreatitis has not been studied from a national database.

Methods Used: We used the 2002–2010 Nationwide Inpatient Sample (NIS) databases to evaluate patients who were hospitalized for acute pancreatitis (ICD 9 code 577.0). Discharge weights were used to enable nationwide estimates. Of a total of approximately 80 million hospitalizations in NIS databases, 2.3 million were hospitalized for acute pancreatitis, of which, 14,553 (0.6%) had SLE. Multivariable logistic regression models were used to assess the effect of SLE on in-hospital mortality among these patients.

Summary of Results: Acute pancreatitis patients had a mean age of 53 (±18) years, 49% were women and 50% were whites. In-hospital mortality occurred in 1.5% and 1.2% of patients with and without SLE respectively (unadjusted odds ratios, 1.26; 95% confidence intervals, 1.10-1.44; $P=0.001$). After controlling for patient risk factors, hospital characteristics, SLE patients independently conferred the higher adjusted odds of in-hospital mortality (adjusted odds ratios, 1.86; 95% confidence intervals, 1.62-2.14; $P<0.001$). Acute pancreatitis patients with SLE had a longer mean length of stay (mean stay, 7 vs 5 days, $P<0.001$) and a higher mean hospital charges ($33,984 vs. $27,126 $P<0.001$).

Conclusions: In this nation-wide study, SLE was rare among acute pancreatitis hospitalizations and was independently associated with in-hospital mortality. SLE in acute pancreatitis was also associated with longer length of hospital stay and an increased hospital cost.

MP2

HUMAN METAPNEUMOVIRUS IS ASSOCIATED WITH SEVERE RESPIRATORY DISEASE IN PREMATURE CHILDREN

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Purpose of Study: Human metapneumovirus (HMPV) is a recently discovered respiratory pathogen belongs to the same subfamily as Respiratory Syncytial Virus (RSV). Preterm infants are at increased risk of severe RSV infections that can lead to hospitalization and death. Both HMPV and RSV share the F protein, which is recognized by Palivizumab, a humanized monoclonal antibody that reduces RSV related hospitalizations by 40% to 78%. Disease burden of HMPV in premature babies is not well established. We conducted a project to test the hypothesis that prematurity is a significant risk factor for severe HMPV infection during the first years of life.

Methods Used: We conducted a retrospective cross-sectional analysis of a cohort of young children less than 3 years old admitted with HMPV infection to our institution during 2013 season ($n=26$). Variables included history of severe prematurity (<32 wks gestational age), hospitalization length, ICU admission, oxygenation parameters and clinical variables upon admission. Multivariate models examined the joint effect of HMPV-induced hypoxemia and other clinical variables controlling for potential confounders. Significance was taken at $p<0.05$.

Summary of Results: Our data demonstrated that 34% of young children admitted with HMPV had history of prematurity. Relative to full term children, these premature babies and infants had more severe HMPV disease illustrated by new or increased need for supplemental O2, longer hospitalizations and greater need for mechanical support in PICU ($p<0.05$). Clinically, they also had more hypoxemia and retractions ($p<0.05$), although wheezing was equally frequent in premature and full term babies. Multivariate linear models showed that the degree of HMPV-induced hypoxemia was independent of age, ethnicity and history of asthma.

Conclusions: HMPV infection causes significant disease burden in premature children characterized by hypoxemia and respiratory compromise. This translates into increased health care resource utilization with prolonged hospitalizations and increased rate of ICU admissions. Accordingly, this data suggests that new strategies are needed to prevent severe respiratory HMPV infections in premature babies during the first years of life.

MP3

SERUM STARVATION REGULATES E-CADHERIN EXPRESSION THROUGH ACTIVATION OF C-SRC IN LUNG EPITHELIAL CELLS

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Purpose of Study: E-cadherin plays a central role in the regulation of lung epithelial barrier integrity. The loss of E-cadherin diminishes cell adherence junctions and promotes cell permeability. The down-regulation of E-cadherin has been well studied, while few studies have focused on its up-regulation. Here, we show that starvation increases E-cadherin expression through the activation of c-Src. Further, TGFβ attenuates starvation-induced E-cadherin expression as well as activation of c-Src.

Methods Used: Lung type II epithelial cell line A549 was cultured in RPMI 1640 medium. Immunoblotting was performed to examine the changes of protein levels. Super transfection reagents were used to transfect plasmids to A549 cells.

Summary of Results: Serum-free medium treatment increased E-cadherin expression in lung epithelial cell line A549 at 6, 24, and 48 h. The effect was attenuated by FBS in a dose-dependent manner. Further, we found that starvation has no effect on E-cadherin mRNA expression, while protein translation inhibitor, cycloheximide, blocked the starvation-induced E-cadherin expression, suggesting that starvation induced E-adherin translation in A549 cells. The c-Src kinase is known to be involved in protein translation process. We found that starvation induced activation of c-Src, which was attenuated by FBS in a dose-dependent manner. To investigate if c-Src mediates starvation-induced E-cadherin expression, we inhibited c-Src activity through the over-expression of kinase dead c-Src mutant (dn-c-Src). Dn-c-Src reduced E-cadherin levels and attenuated starvation-induced E-cadherin expression. TGFβ has been known to reduce E-cadherin expression in A549 cells. Here, we found that TGFβ attenuated starvation-induced E-cadherin expression, as well as activation of c-Src.

Conclusions: Starvation induces E-cadherin expression through activation of c-src kinase. TGFβ attenuates starvation-induced E-cadherin expression as well as activation of c-Src. This study is the first report to demonstrate the effect of starvation on E-cadherin expression. The data provide a molecular basis for the of E-cadherin expression regulation.

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MP4

LARGER NECK CIRCUMFERENCE IS ASSOCIATED WITH POOR ASTHMA CONTROL IN OBESE YOUTH

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Purpose of Study: The incidence of obesity is significantly higher in children with asthma, but current standard indices of adiposity, mainly BMI, have not been shown to correlate with asthma morbidity. Research has established neck circumference as a reliable proxy and regionally specific index of adiposity. Our objective was to demonstrate that a previously established neck circumference cutoff value is associated with adverse outcomes in obese children with asthma.

Methods Used: A cross-sectional analysis was performed on our AsthMaP2 cohort of children age 6–20 years, inclusive with physician diagnosed asthma for >1 yr. Anthropometric and clinical data collected at the baseline visits included age, gender, neck circumference, asthma severity, and indices of asthma symptoms (Integrated Therapeutics Groups Short Form; ITG) and control (Asthma Control Test; ACT). Patients were stratified based a neck circumference measurement cutoff value previously associated with age and gender corrected BMI percentile>85. Statistical analyses include linear regression (ITG score, ACT) and logistic regression (asthma severity) analyses.

Summary of Results: Of the 72 subjects enrolled in AsthMap2 with recorded neck circumference measurements, 57 (79%) were below and 15 (21%) were above the cut off value. The group above the cutoff value had significantly lower ITG functional (p=0.048) and ACT (p=0.022) scores compared to the group below the cutoff value. No association between neck circumference cutoff and asthma severity was identified.

Conclusions: This is the first study in children with asthma demonstrating that increased neck circumference is associated with increased symptoms and decreased asthma control and suggests that neck circumference should be considered as an obesity measure in asthma studies. Future studies comparing neck circumference to other traditional markers of obesity, including BMI and BMI percentile, as well as other asthma outcomes, including pulmonary function testing, may prove that neck circumference is a more sensitive measure to demonstrate the impact of obesity on childhood asthma.

MP5

SPATIAL DISTRIBUTION OF ADOLESCENTS WITH SEXUALLY TRANSMITTED INFECTIONS DIAGNOSED IN THE PEDIATRIC EMERGENCY DEPARTMENTS OF WASHINGTON, DC

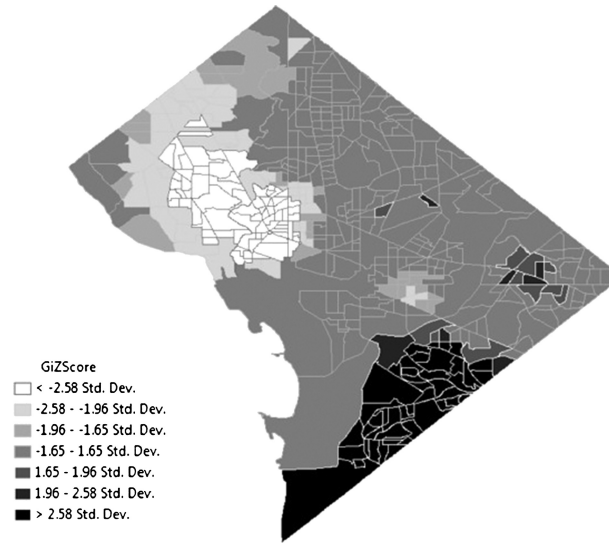
Shilpa Patel[1], Lisa Tuchman[2], Katie L. Hayes[3], Gia Badolato[1], Stephen J. Teach[1], Monika K. Goyal[1]. *[1]Division of Emergency Medicine, Children's National Medical Center, Washington, DC, United States. [2]Division of Adolescent Medicine, Children's National Medical Center, Washington, DC, United States. [3]Division of Emergency Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, United States.*

Purpose of Study: (1) To describe the spatial distribution of adolescents with ED-diagnosed STIs in a large urban area; and (2) to compare census block groups and identify "hot spots."

Methods Used: We performed a retrospective cross-sectional medical record review of all visits to the two large urban pediatric EDs in Washington, DC made by District residents aged 13–19 years old in 2012 and abstracted demographic and visit data, including STI testing results for gonorrhea(GC) and chlamydia(CT). Geospatial statistical analyses were performed using ArcMap 10.1.

Summary of Results: Of 1002 adolescents tested for STIs, 6.8% tested positive for GC, 18.6% tested positive for CT, 22.7% tested positive for either GC or CT and 2.9% tested positive for co-infection. The mean age of patients with STIs was 16.9 years (SD 1.5); 78.4% were female. Of the 227 patients with ≥1 positive test, 95% of their addresses were successfully geocoded. Hot Spot Analysis indicated statistically significant clusters of STI cases (Figure 1). Spatial autocorrelation (Moran's I) demonstrated that the distribution of cases was not random (z- score 13.3, $p < 0.05$). The odds of adolescent patients from DC Ward 6 testing positive for CT was twice that of DC Ward 7(aOR 2.07; 95% CI 1.07 – 3.98).

Conclusions: Geographic analyses identified areas with significantly higher cases of ED-diagnosed STIs. Geographic data in conjunction with other clinical variables may improve prediction of STIs in adolescents presenting to the ED, decrease empiric treatment, and allow targeted public health prevention.



MP6

CUTANEOUS METASTASIS OF PROSTATE CANCER: A CASE REPORT AND BIOINFORMATICS ANALYSIS OF MULTIPLE HEALTHCARE DELIVERY NETWORKS

G. T. Brown[1], Chyi-chia Lee[1]. *[1]Laboratory of Pathology, NIH, NCI, Bethesda, MD, United States.*

Purpose of Study: To characterize cutaneous metastasis of prostate carcinomas, a very prevalent carcinoma with seemingly low rates of cutaneous metastasis.

Methods Used: The Explorys database aggregates EHR data across multiple healthcare institutions, and de-identified data was obtained using the Explore application, which places a health data gateway (HDG) server behind the firewall of each healthcare organization. After collecting data from a variety of health information systems the HDG maps the data to informatics ontologies (i.e. SNOMED, LOINC, RxNorm, ICD), standardizing and normalizing any measurements. Next, the data from each participating healthcare organization is passed into a data grid. The HIPAA-compliant Explore application allows each healthcare organization to search and analyze the aggregated, standardized, normalized, and de-identified population level data. NIH has developed its own tool that brings together clinical research data from the NIH Clinical Center and other NIH Institutes and Centers. The Biomedical Translational Research Information System (BTRIS) database aggregates EHR data across multiple clinical trials, and de-identified data was obtained using the BTRIS web-based application. The BTRIS application is also HIPAA-compliant, drawing data from a database of more than 300,000 patient records.

Summary of Results: Using the Explorys Explore application yielded 166,450 patients with prostate cancer and of those, 100 had a diagnosis of cutaneous metastasis representing 0.06% of cases. In BTRIS we found 4,558 distinct patients with prostatic carcinoma and of those, 5 patients had secondary cutaneous neoplasms representing 0.11% of cases. Combining case reports, meta-analyses, and our two bioinformatics approaches results in an overall rate of 0.09% cutaneous metastases out of 174,836 patients with prostate carcinomas.

Conclusions: While cutaneous metastasis usually implies a poor prognosis there are reports of relatively long survival after cutaneous metastasis. Although we have demonstrated that the overall rate of cutaneous metastases is low, there exists the possibility that a skin lesion may represent an undiagnosed metastasis. Careful consideration must be employed when examining rashes or nodules in patients with a prior history of prostate carcinoma to avoid delayed diagnosis or misdiagnosis.

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MP7

GENETIC VARIANTS ASSOCIATED WITH BODY COMPOSITION AND PHYSICAL ACTIVITY IN A PEDIATRIC AFRICAN AMERICAN COHORT

Trevor Slezak[1], Courtney Sprouse[2], Alexandra D'Agostini[1], Fady Hijji[1], Chika Okafor[3], Leticia M. Ryan[4], Eric Hoffman[5], Heather Gordish-Dressman[5], Joseph M. Devaney[5], Laura L. Tosi[5]. *[1]The George Washington University School of Medicine and Health Sciences, Washington, DC, United States. [2]Children's National Medical Center, Washington, DC, United States. [3]Howard University College of Medicine, Washington, DC, United States. [4]Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, United States. 5. Children's Research Institute, Washington, DC, United States.*

Purpose of Study: The purpose of this study was to determine whether six single nucleotide polymorphisms (SNPs) were associated with physical activity levels and body composition in a young African American cohort. Rs12405556 in the LEPR gene, rs10946904 in the PRSS16 gene, rs1766581 in the SIPA1L2 gene, rs2762527 in the PAPSS2 gene, rs9633417 in the SGIP1 gene, and rs667923 in the DNASE2 gene.

Methods Used: Our cohort consisted of 142 African American children, aged 5 to 9 years. We looked for associations between the SNPs and total body bone mineral density (BMD), total body fat, total body lean mass, total percent body fat, total body BMD z-score, body mass index, calcium level, phosphorous level, vitamin D level, and outdoor playtime. The SNPs were genotyped using Taqman allelic discrimination assays and associations between SNPs and phenotypes were tested using a one-way ANOVA. All analyses used a dominant genetic model to compare homozygous common allele individuals to heterozygotes and homozygous rare allele individuals combined.

Summary of Results: Rs10946904 was associated with total body fat and total body percent fat. Rs12405556 was associated with total body BMD z-score. Rs9633417 and rs1766581 were associated with blood calcium levels. Rs9633417 was associated with outdoor playtime on weekdays.

Conclusions: This is the first study to look at SNPs associated with physical activity in a young African American cohort. Many SNPs associated with physical activity in Caucasians are also associated with physical activity or measures of body composition in our cohort. The results suggest that only one of the six SNPs determined by GWAS to be associated with physical activity in Caucasian adults is associated with physical activity in African American children. Further study in a larger sample size is needed to confirm this finding and better understand the implications of genetic variation in the development of exercise intervention.

MP8

CALCIUM INTAKE MODULATES OBESITY PHENOTYPES IN AFRICAN AMERICAN CHILDREN POSSESSING RISK ALLELES FOR DEVELOPMENT OF TYPE 2 DIABETES

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Purpose of Study: Explore whether total calcium consumption modulates obesity phenotypes in African American children (AA) possessing risk alleles for development of type 2 diabetes (T2D).

Methods Used: 142 AA children (5 to 9 yrs) were genotyped for alleles associated with increased risk of developing T2D. 67 single nucleotide polymorphisms (SNPs) were chosen from published GWAS to identify T2D risk loci. We evaluated three obesity phenotypes; body mass index percentile and, using DXA, percent fat, and total body fat/height. Assessments of nutritional intake (milk, dairy, and total calcium) were measured using a validated food frequency questionnaire, and then evaluated to assess their effect on the significant outcome/SNP relationships. All analyses used linear or quantile regression models.

Summary of Results: We found significant relationships between body fat outcomes and 5 SNPs (ADAMTS9-AS2, CDC123, PRC1, ZMIZ1, and rs7560163). Assessment of the effect of nutritional intake showed that total calcium intake normalized for body weight was a highly significant predictor of body fat and a significant modifier of the outcome/SNP effect.

Conclusions: In AA children, calcium intake modulates obesity phenotypes in individuals possessing risk alleles associated with development of T2D. Expansion of this research may help identify individuals for whom increased calcium intake will have the most beneficial effect.

MP9

F-BOX PROTEIN FBXL19 MEDIATES RAC3 UBIQUITINATION AND DEGRADATION IN ESOPHAGEAL CANCER CELLS

Jianxin Wei[1], Su Dong[1], Rachel K. Bowser[1], Jing Zhao[1], Yutong Zhao[1]. *[1]University of Pittsburgh, Pittsburgh, PA, United States.*

Purpose of Study: Rac3 is a small GTPase multifunctional protein that regulates cell adhesion, migration, and differentiation. It has been considered as an oncogene in breast cancer; however, its role in esophageal cancer and the regulation of its stability have not been studied. Recently, we have shown that FBXL19 targets Rac1 and RhoA, which results in their ubiquitination and degradation. Here, we demonstrate the role of FBXL19 in the regulation of Rac3 site-specific ubiquitination and stability. Expression of TGFβ1 is associated with poor prognosis of esophageal cancer. TGFβ1 has been known to reduce E-cadherin expression in various epithelial-derived cancers. In this study, we investigate the role of FBXL19-mediated Rac3 degradation in TGFβ1-induced E-cadherin down-regulation in esophageal cancer cells.

Methods Used: HEK293 and OE19 cell lines were cultured in RPMI 1640 medium with 10% FBS. Immunoblotting and immunoprecipitation were performed to examine the changes of protein levels and protein-protein interaction.

Summary of Results: Overexpression of FBXL19 decreased endogenous and over-expressed Rac3 expression by interacting and polyubiquitinating Rac3, while down-regulation of FBXL19 suppressed Rac3 degradation. Lysine166 within Rac3 was identified as an ubiquitination acceptor site. The FBXL19 variant with truncation at the N-terminus resulted in an increase in Rac3 degradation; however, the FBXL19 variant with truncation at the C-terminus lost its ability to interact with ubiquitinate Rac3 protein. Further, we found that Rac3 plays a critical role in TGFβ1-induced E-cadherin down-regulation in OE19 esophageal cancer cells. Over-expression of FBXL19 attenuated TGFβ1-induced E-cadherin down-regulation and elongation of OE19 cells.

Conclusions: FBXL19 functions as an antagonist of Rac3 by mediating its stability and regulating the TGFβ1-induced E-cadherin down-regulation. This study will provide a new potential therapeutic strategy to regulate TGFβ1 signaling, thereby suppressing esophageal tumorgenesis.

MP10

MUTATIONS IN WERNER AND FANCD2 GENES ARE ASSOCIATED WITH POOR PROGNOSIS IN OVARIAN CANCER PATIENTS.

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Purpose of Study: To determine if specific gene mutations in the genomic DNA correlate with outcome from ovarian cancer and asses differences in DNA mutations between ovarian cancer patients and those with benign masses.

Methods Used: DNA samples were obtained from the Breast and Ovarian Tissue Bank for 24 patients with ovarian cancer and 20 patients with benign pelvic masses. The ovarian patients were grouped into long term survivors >4 yrs and short term survivors<2yrs. Using the True Sight Cancer Panel, we looked for the most frequent of ninety-four genes in two thousand exomes to determine if specific gene mutations were correlated with outcome. Statistical analysis was performed for each group of samples using Normal method with standard error of proportion of 0.261 for 95% confidence interval (normal value 1.96)

Summary of Results: On the other hand, a few gene mutations were abundant in the ovarian samples and not the controls, such as the gene for Werner protein (WRN), which provides instructions for producing the Werner protein. This mutation occurred in half of the ovarian samples 0.5 and in only one-sixth of the controls 0.33. Additionally, 10 out of the 12 samples with this mutation were dead within 2 years 0.833. Furthermore, another gene that had a high mutation count was FANCD2. FANCD2 plays a role in chromosomal stability. It promotes accurate and efficient pairing of homolog during meiosis. In this gene

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variations at two different locations were highly prevalent. Eight out of the 11 samples with this mutation died within 2 years 0.72. If bi-allelic mutations were present in the FANCD2 gene 9 out of 11 of the samples died after 2 years 0.81.
Conclusions: FANCD2 interacts with BRCA2 in homologous repair process. Defects in repair of double stranded DNA breaks may herald propensity for ovarian cancer. One third of patients with complex pelvic masses and half of the ovarian cancer patients had mutations in WRN gene. DNA repair may not be functional in patients progressing from complex pelvic masses to frank ovarian malignancies. If our pilot results are replicated in a larger sample size these findings will improve methods of ovarian cancer detection.

MP11

CHANGES IN MODIFYING GENES XPC AND RAD51 INCREASE BREAST CANCER SUSCEPTIBILITY IN PATIENTS WITH BRCA MUTATIONS

Iuliana Shapira[1], **Elizabeth Arenare[2]**, Andrew Shih[3], Michaela Oswald[3], Cathleen Mason[3], Mary Keogh[3], Annette Lee[3]. *[1]Monter Cancer Center, Hofstra North Shore LIJ School of Medicine, Lake Success, NY, United States. [2]Manhasset High School, Manhasset, NY, United States. [3]Feinstein Institute for Medical Research, Manhasset, NY, United States.*

Purpose of Study: To identify additional gene changes in breast cancer patients with or without BRCA mutations that may be associated with the development of malignancies.
Methods Used: 24 DNA samples were obtained from the Breast and Ovarian Tissue Bank. 20 patients had breast cancer 4 patients were carriers of BRCA and 24 individuals were cancer free age-race matched controls. The subjects were chosen based on diagnosis and BRCA status. For this experiment, we followed the Nextera Rapid Culture Enrichment protocol provided by Illumina. This study investigated 94 genes associated with Breast Cancer by using the TruSight Cancer Panel which features a highly optimized probe set of genes associated with common cancers. The TruSight Cancer content set provides custom oligos targeting identified regions of interest. It includes 4,000 80-mer probes, each constructed against the human reference genome.
Summary of Results: RAD51C mutations on chromosome 17 in positions 56774124 and 56774128 were present in 20 of the 24 patients who developed breast cancer and zero of the 24 patients who were breast-cancer free. There was no relationship between these gene mutations and BRCA gene mutations. XPC mutations on chromosome 3 in positions 14200104, 14200112 and 1400109 were present in 15 patients with breast cancer, 13 patients with breast cancer and 12 patients with breast cancer respectively. There was no relationship between either of these gene mutations and BRCA gene mutations
Conclusions: CIMBA consortium reported an association between RAD51 mutations and breast cancer in BRCA carriers. More research needs to be done to further investigate the role of RAD51C and XPC gene mutations detected in this study as it relates to Breast Cancer. This study needs to be repeated with a much greater sample size to confirm my results and to investigate what percentage of RAD51C or XPC mutation carriers develop also breast cancer. The major limitation of this study was the small sample size. In regard to RAD51 our results mirror those seen by CIMBA investigators.

MP12

TRAVEL RELATED STROKE DISPARITY IN PATENT FORAMEN OVALE PATIENTS AND PLANS FOR A TRIAL FOR INTERVENTION

T. Wickham[1], K. Feeney[1], W. Deng[1], L. Chen[1], I. Inglessis[1], I. Palacios[1], D. McMullin[1], E. H. Lo[1], F. Buonanno[1], MingMing Ning[1]. *[1]Massachusetts General Hospital, Boston, MA, United States.*

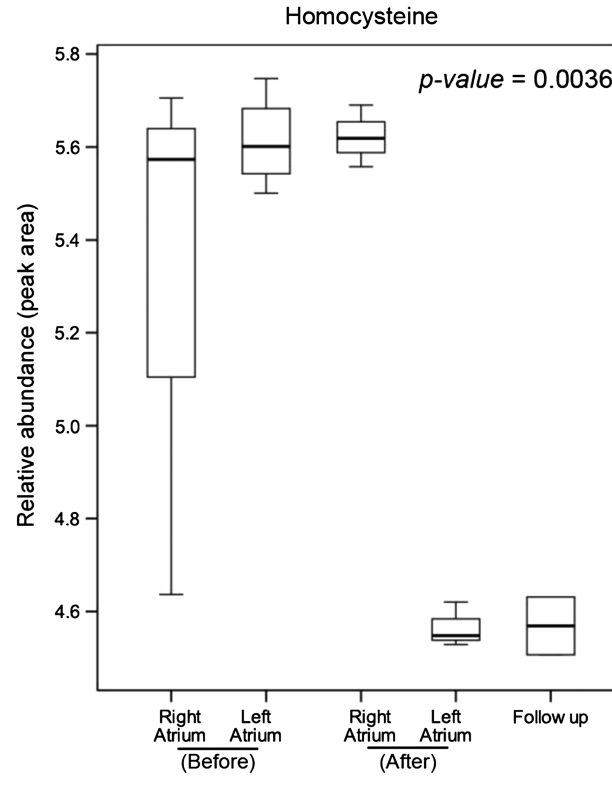
Purpose of Study: Background: Patent Foramen Ovale (PFO) is a congenital communication in the heart causing shunting between the right and left atria found in one quarter of the general population. This enables clots and debris to pass through the heart to the brain leading to a potential ischemic stroke. PFO patients are approximately ten years younger than the general stroke community, but contribute disproportionately to stroke cases related to travel.Those suffering cardioembolic strokes with recent travel history show an almost 17% increase in strokes over those without travel history. African-Americans experience a 41% increase in stroke deaths compared to Caucasians. There is currently little research on PFO travel education, especially in high-risk communities such as young patients and African-Americans.
Methods Used: To reduce implications of stroke in the aging population, Mass Approach and High-Risk Approach strategies must be developed. With the advent of the Affordable Care Act, access to primary preventative measures is expected to increase as an attempt to reduce upstream risks for stroke. There is a need to educate PFO patients about their increased risk for stroke during long periods of travel because of a multitude of clotting risk factors including sedentary state, lack of hydration, and pressurization of airplane cabins.
Summary of Results: Interventions: We propose a prospective study, utilizing questionnaires regarding stroke risks such as sedentary lifestyle, smoking status, clotting state, frequency of travel, presence of a PFO, and migraine history to identify high-risk patients. Potential areas for public health intervention include collaboration with the African American Health Coalition to include PFO and travel precaution education in community outreach programs regarding stroke.
Conclusions: Dialogue and resources provided during inpatient and outpatient stroke care will engage patients in the topic, while cooperation with community health workers continues the discussion outside the clinic. This is especially important in patients marked as high-risk, such as frequent flyers. The current paradoxical contribution of the PFO subgroup to travel-related stroke requires attention.

MP13

METABOLOMIC ANALYSIS REVEALS LONG-TERM DECREASE OF HOMOCYSTEINE POST PFO CLOSURE

Wenjun Deng[1], Ferdinando S. Buonanno[1], Mary Lopez[1], Christopher Beecher[1], Charles Burant[1], Frank De Jong[1], Igor Palacios[1], Ignacio Inglessis[1], Scott Silverman[1], Kathleen Feeney[1], Mikaela Elia[1], Thomas R. Wickham[1], David McMullin[1], William Dec[1], Eng H. Lo[1], Mingming Ning[1]. *[1]Massachusetts General Hospital, Boston, MA, United States.*

Purpose of Study: PFO can increase the risk of stroke by enabling direct mixing of venous and arterial circulation and serving as a conduit for venous clots. Our previous study found that PFO disturbs pulmonary filtration of harmful factor, serotonin (5HT), which stays high in circulation and creates a prothrombotic state. In the context of endovascular PFO closure, a bedside model to understand PFO circulatory signaling, we performed a full metabolomic profile of other mediators that may respond to PFO closure.



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Methods Used: Patients were recruited in accordance with IRB approval. Plasma was sampled from left (LA) and right (RA) atria pre and post PFO closure and also from venous 3 months post closure. A discovery metabolite screening was performed in 14 patients and analysis was performed with one-way ANOVA.

Summary of Results: With strict analysis (537 metabolites, one-way ANOVA, $p<0.01$), we identified homocysteine (HCY) with the most prominent change after PFO closure. While HCY levels in the left atrium (LA) and right atrium (RA) were comparable pre-closure (pre-LA: 5.61±0.09; pre-RA: 5.30±0.48), HCY immediately decreased in LA post closure (post-LA: 4.56±0.04) and remained low in peripheral venous blood at 3-month follow-up (4.57± 0.06; $p=0.0036$).

Conclusions: We found PFO closure immediately reduces HYC in left atrial (arterial) blood, and this effect persists in peripheral venous circulation at 3 months post closure. Since high HCY level is independently related to stroke and heart disease, our results suggest that mechanical PFO repair may improve circulatory profile of PFO stroke patients. Studies in a larger patient cohort and validation of other important metabolites are ongoing.

MP14

PERSONALIZED METABOLOMICS OF IDENTICAL TWINS VS GENERAL STROKE POPULATION

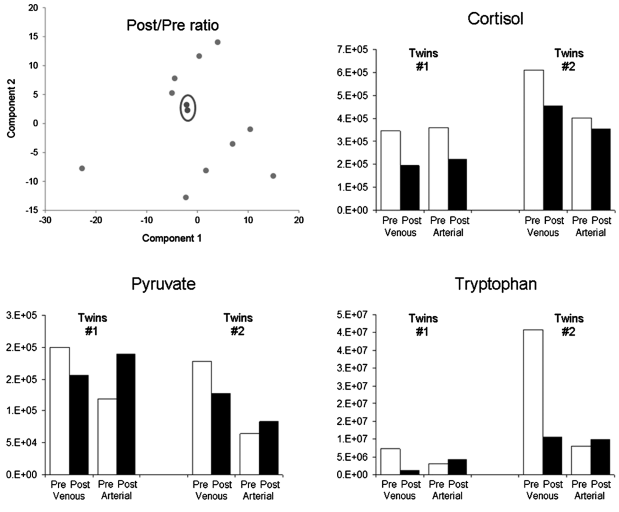
Wenjun Deng[1], Christopher Beecher[1], Mary Lopez[1], Frank De Jong[1], Igor Palacios[1], Ignacio Inglessis[1], Kathleen Feeney[1], Mikaela Elia[1], David McMullin[1], William Dec[1], Charles Burant[1], Eng H. Lo[1], Ferdinando S. Buonanno[1], Mingming Ning[1]. [1]*Massachusetts General Hospital, Boston, MA, United States.*

Purpose of Study: It is often challenging to disentangle genetic from environmental factors that influence proteomic and metabolic profiles. While there is strong genetic contribution to the metabolic profile of a newborn at birth, in adulthood the balance of these changes in the context of stroke or therapeutic response are not well understood. To probe this intricate balance, we study a pair of rare identical twins who both had PFO-related strokes at age 45, and compare their metabolomic profiles to age/risk factor matched PFO stroke patients.

Methods Used: We investigate changes in the venous and arterial metabolomic profiles between PFO stroke twins and general PFO stroke patients pre and post PFO closure. In accordance with IRB, plasma was sampled from left (LA) and right (RA) atria pre and post closure.

Summary of Results: PCA analysis shows that at baseline pre closure, the profiles of the twins were indistinguishable from age/risk factor matched unrelated PFO strokes patients. However, when analysis was adjusted for PFO closure, the ratio of changes pre vs post closure clustered twin patients very closely in PCA analysis(red dots). Thus at a cutoff of >1.2-fold change, we found that most of the closure-related changes are consistent between twin patients in both venous (22 out of 29, 75.86%) and arterial (23 out of 37, 62.16%) plasma.

Conclusions: We found that while at baseline the metabolomic profiles of the adult PFO stroke twins have little in common, they respond very similarly to endovascular PFO treatment, compared to non-related stroke patients. Our data suggest that genetic influence may be more prominent in response to a specific treatment such as PFO closure. Larger studies are needed to understand these important changes in PFO related stroke to individualize treatment better.



12

ADIPOCYTE EXOSOMAL MIRNA REGULATE A549 LUNG EPITHELIAL GENE EXPRESSION IN A DOSE-DEPENDENT MANNER

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Purpose of Study: Childhood asthma and obesity epidemics appear connected as obesity is associated with increased asthma severity and poor response to therapy. Despite this, there are no studies identifying a mechanistic link. We have shown that adipocytes from obese patients produce mediators, including TGFβ, which are central to asthma pathobiology. Adipocytes secrete exosomes containing mRNAs and/or miRNAs that may influence distant cells. We hypothesized that adipocyte-derived exosomes contain mediators capable of activating TGFβ signaling in airway epithelium.

Methods Used: We isolated exosomes from lean (L) and obese (Ob), paired visceral (v) and subcutaneous (sq) adipose depots (n=3L/5Ob) using a novel bead-based flow cytometry assay. Exosomal miRNA expression was measured using Affymetrix GeneChip miRNA 3.0 arrays. Data were analyzed in Partek Genomics Suite and Ingenuity Pathways Analysis. T-test was used to compare miRNA expression between L and Ob groups, using $p \leq 0.1$ and fold change $\geq |1.2|$. Candidate miRNA were confirmed by qRT-PCR. Exosomes at varying concentrations (0.03 to 10 μg/ml) were incubated with proliferating A549 lung epithelial cells for 24h to identify optimal dose response using Illumina BeadArray gene expression.

Summary of Results: Biological pathway analysis of the 7,789 mRNA targets of the 55 differentially expressed miRNAs highlighted TGF-β ($p = 8.3 \times 10–10$) and Wnt/ β-catenin ($p = 4.6 \times 10–10$) signaling as the top canonical pathways expected to be altered with visceral adiposity. A549 results demonstrated a 67% increase in number of genes differentially expressed when comparing 0.03 μg/ml to an average dose of 1.35 μg/ml with no significant change in successive doses. A total of 208 mRNA, including validated mRNA targets of miR23b and miR148b, were found in the four highest concentrations with TGFβ signaling as a top canonical pathway.

Conclusions: Obese visceral adipocyte exosomal miRNA are capable of regulating TGFβ signaling in A549 lung epithelial cells. Applying these methods to primary cells in asthma will elucidate a mechanistic link for adipose exosome-derived stimulation of TGFβ signaling in asthma that may lead to novel therapeutic targets.

13

SCF E3 LIGASE REGULATES HISTONE ACETYLATION AND CYTOKINE RELEASE THROUGH TARGETING CBP

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Purpose of Study: The CREB-binding protein (CBP) regulates proinflammatory gene expression via acetylation of histones. However, molecular regulation of CBP at the level of protein stability has not been well studied. Here, we investigate the role of F-box protein, FBXL19, in the regulation of CBP ubiquitination and degradation.

Methods Used: Mouse lung epithelial cell line (MLE12) and human bronchial epithelial cells (HBEpCs) were used to investigate the mechanisms by which FBXL19 regulates CBP expression and cytokine release. Plasmid transfection was used to over-express target proteins. The changes of protein expression and modification were determined by immunoblotting. Elisa kits were used to measure cytokine release.

Summary of Results: We transfected mouse lung epithelial cells (MLE12) with a FBXL19-V5 plasmid and found that FBXL19-V5 over-expression reduced both endogenous and over-expressed CBP, without altering p300 expression. Further, over-expression of FBXL19 induced CBP ubiquitination, which

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was attenuated in the FBXL19 shRNA transfected cells. Co-immunoprecipitation and co-immunostaining studies indicated that FBXL19 is associated with CBP. Next, we investigated the role of FBXL19 in CBP-mediated histone acetylation and proinflammatory gene expression. Human lung epithelial cells were transfected with FBXL19-V5 plasmid prior to bacterial endotoxin treatment. FBXL19-V5 overexpression attenuated LPS-induced histone H4 acetylation at lysine residue 8 (H4K8) and IL-8 release. Over-expression of FBXL19 in mouse lungs by intratracheal lentiviral vector gene delivery system dimished intratracheal LPS-induced acetylation of H4K8 in mouse lung tissues and IL-6 in bronchoalveolar lavage fluids.

Conclusions: FBXL19 regulates CBP stability by inducing its ubiquitination. FBXL19 reduces CBP-mediated histone acetylation and cytokine release. FBXL19 protects against bacterial endotoxin-induced lung inflammation in murine model of acute lung injury. These data may provide a potential therapeutic strategy to target the FBXL19 / CBP pathway, thereby lessening the severity of lung inflammatory diseases.

14

EFFECT OF ANTIRHEUMATIC DRUGS ON CHOLESTEROL EFFLUX PROTEIN EXPRESSION IN THP-1 HUMAN MACROPHAGES

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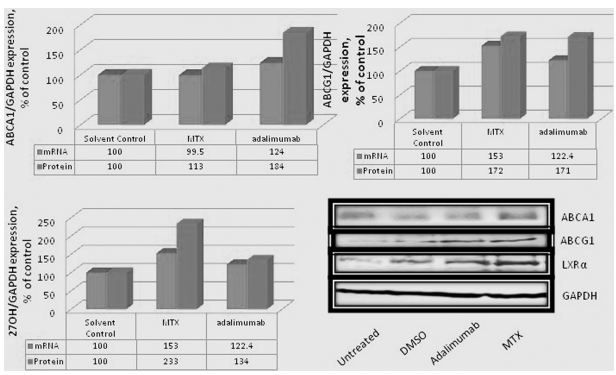
Purpose of Study: Premature atherosclerotic cardiovascular disease (CVD) is a significant cause of early morbidity and mortality in patients with rheumatoid arthritis (RA). Methotrexate (MTX), a mainstay in the treatment of RA, is a disease modifying anti-rheumatic drug (DMARD) that reduces death rates due to CVD in RA patients. The potential atheroprotective benefits of newer DMARDs, including the biologic agent adalimumab (an anti-tumor necrosis factor antibody), have yet to be investigated. This study compares anti-atherosclerotic properties of MTX and adalimumab.

Methods Used: THP-1 human macrophages were incubated for 18h in medium alone or containing MTX (5μM) or adalimumab (50μg/ml). Following incubation, mRNA was isolated and reverse transcribed. The resulting cDNA was subjected to quantitative real-time PCR using specific primers for the cholesterol efflux genes 27-hydroxylase, ATP binding cassette transporter (ABC) A1, ABCG1, and liver X receptor. Protein levels were measured in cell extracts by Western blot.

Summary of Results: MTX and adalimumab each upregulated cholesterol efflux proteins and the pattern of enhancement was distinct for each drug. Compared to solvent controls, MTX significantly upregulated expression of ABCG1 and 27-hydroxylase both by 53% (n=3, P<0.05), while adalimumab upregulated expression of ABCG1 by 22.4% and ABCA1 by 12.4% (n=3, P<0.05) and did not change expression of 27-hydroxylase. Alterations in cholesterol efflux, observed on mRNA level were confirmed by Western blot (Figure 1).

Conclusions: This study supports the anti-atherosclerotic role that MTX plays in RA. It further suggests that adalimumab may have atheroprotective properties. These DMARDs differed in their influence on individual genes, suggesting that separate pathways are involved in mediating their effects.



Cholesterol Efflux Protein Expression in THP-1 Human Macrophages

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15

MITOTIC ASYNCHRONY INDUCES A PRO-INFLAMMATORY STATE IN AIRWAY EPITHELIUM

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Purpose of Study: Mitotic behaviors are likely important for maintaining and restoring homeostasis in diseases with epithelial injury. We proposed that regenerative asynchrony in repairing tissue may underlie chronic inflammation, where immune infiltration is secondary to pro-inflammatory cross-talk among asynchronously repairing tissues.

Methods Used: In vitro experiments were performed wherein airway epithelial cells were mitotically asynchronous due to asthma and then resynchronized by capture of the G1/S checkpoint via two-hour pulse exposure to dexamethasone, simvastatin, or aphidicolin. Further experiments utilized a novel method of inducing asynchrony in normal progenitors.

Summary of Results: Upon injury, human asthmatic ALI airway epithelial mitosis was asynchronous(G1[mean±SEM],S,G2/M: 47±4,24±6,29±5%) relative to normal epithelia(71±1,12±2,17±2%). Mitotic capture increased the percentage of cells in G1. Capture in the asthmatic epithelia reduced TGF-β1 secretion, in particular at the 24-hour peak (TGF-β1PBS=285±74ρg/mL) but decreased to 45±17ρg/mL with dex, 81±26ρg/mL with sim, and 77±50ρg/mL with aph. If inflammation is downstream of abnormal mitotic behavior, conditioned media would not alter the synchrony of co-cultured airway epithelial cells. Mitotic synchrony of these progenitor cells did not change. Mitotic asynchrony was induced in parallel cultures of normal proliferating epithelial cells via serum starvation. The mixed samples showed asynchrony at 6 and 12 hours that resolved by 24 hours. Mixed conditions showed elevated TGF-β1 secretion at 12 hours. In the induced asynchronous cells, cells that were in contact resynchronized by 18 hours; however cells not in contact, did not resynchronize until 24 hours.

Conclusions: We used a series of mitotic experiments wherein airway epithelial mitosis was desynchronized and resynchronized via G1/S checkpoint manipulation. Analysis shows synchrony is the homeostatic state in airway epithelial populations and poorly-synchronized mitosis induces TGF-β1 secretion and a pro-inflammatory/pro-fibrotic airway. This finding establishes rationale for targeting progenitor cell mitotic behavior rather than immune-mediated inflammation in fibrotic disease.

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REGENERATIVE ASYNCHRONY IS A DRIVER IN CHRONIC INFLAMMATION IN AGING

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Purpose of Study: Age-associated chronic diseases are associated with a pro-inflammatory state. However, it has been challenging to determine cause and effect – do age-associated pathologies increase inflammation or does inflammation induce age-associated pathologies, or both? We recently showed that disease-related regenerative asynchrony in repairing lung is the cause of chronic inflammation and fibrosis. Given this, we hypothesized that the aged lung is itself asynchronously regenerating leading to a pro-inflammatory and pro-fibrotic pulmonary milieu.

Methods Used: Tracheas were harvested from healthy C57BL6 mice in two age groups of both genders. Young mice were between 8 and 20 weeks of age. Aged mice were between 23 and 33 months of age. Tracheal epithelial progenitor cells were isolated and cultured on collagen-coated membranes for 6 days. Cultures were exposed continuously to BrdU. Cellular regeneration was analyzed by flow cytometry for 7-AAD DNA staining in BrdU+ cells. Concentrations of an initial screening set of cytokines (IL-1β, IL-6, and TNFα) in cell culture supernatants were measured on days 2 and 6 using magnetic bead-based assays.

Summary of Results: Primary airway epithelial progenitor cell populations from young mice undergo mitosis frequently and synchronously. However, fewer airway epithelial progenitors underwent mitosis from the aged mice than

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from the young mice. Additionally, the tracheal epithelial progenitors from aged mice were asynchronously distributed along the cell cycle (G1, S, G2/M: 44, 25, and 31%) compared to those from young mice (62, 14, and 24%). Concentrations of IL-6 were not significantly different between age groups in supernatant from day 2 of culture (young=328±118pg/mL, aged=228±55pg/mL; p=NS) but remained higher in young compared to aged progenitors on day 6 (young: 291±165pg/mL, aged: 50±16pg/mL; $p<0.05$). Finally, IL-1β and TNFα were not detected in either group and either time point.

Conclusions: Our data support the concept that aging induces progenitor cell mitotic asynchrony. It is possible that this epithelial mitotic asynchrony would then contribute to the pro-inflammatory state associated with aging, as seen in other chronic inflammatory states.

17

CLINICAL FACTORS ASSOCIATED WITH VITAMIN D DEFICIENCY IN AFRICAN AMERICAN CHILDREN WITH FOREARM FRACTURES

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Purpose of Study: Vitamin D deficiency (serum 25-hydroxyvitamin D concentration < 20 ng/mL) is a significant public health issue affecting > 50% of African American (AA) children. Vitamin D deficiency is associated with deficits in bone mineral density (BMD) and increased risk for forearm fracture, an injury that is increasing in incidence. It is unknown which children with fractures are most likely to have vitamin D deficiency. Our objective is to identify clinical factors associated with vitamin D deficiency in children with fractures, which may facilitate screening and subsequent treatment.

Methods Used: This case–control study in healthy AA children, aged 5–9 years, prospectively enrolled 150 children with and without forearm fracture at Children's National Medical Center in Washington, DC. Measurements included body mass index (BMI), dietary intake (BLOCK Kids 8–17 Food Frequency Questionnaire), outdoor play time, BMD and serum 25-hydroxyvitamin D level. Data analysis focused on the case patients with fractures. Multivariable logistic regression analyses were used to test for associations between vitamin D deficiency and relevant clinical factors amenable to screening in the emergency department setting, with control for potential confounders.

Summary of Results: The analysis included 70 children with fractures; of these, 30 (43%) had vitamin D deficiency. There were no statistically significant associations between vitamin D deficiency and age, gender, parental education, BMI, presence of asthma, or bone(s) fractured. However, injury during the winter/spring seasons [adj OR 5.1 (95%CI 1.1-23.3)], self-reported outdoor play ≤ 1 hour daily [adj OR 6.9 (1.1-42.9)] and self-reported milk intake ≤ 1 serving per day [adj OR 6.1 (1.2-30.5)] were significantly associated with increased adjusted odds of vitamin D deficiency.

Conclusions: Easily obtained clinical factors are associated with significantly increased adjusted odds of vitamin D deficiency in this sample of AA children with forearm fractures. Because treatment of vitamin D deficiency may potentially improve bone health and decrease fracture morbidity in both childhood and adulthood, further consideration should be given to screening high risk populations who may benefit from intervention.

18

CENTRAL KATP CHANNELS CONTRIBUTE TO THE REGULATION OF ENDOGENOUS GLUCOSE PRODUCTION BY HYPERGLYCEMIA IN HUMANS

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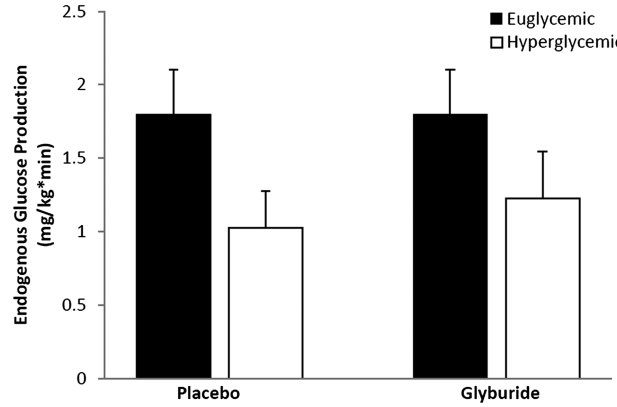
Purpose of Study: Endogenous glucose production (EGP) is a critical process that maintains plasma glucose during fasting, and is the major cause of hyperglycemia in type 2 diabetes mellitus (T2DM). In non-diabetic humans, hyperglycemia has marked inhibitory effects on EGP. Rodent studies suggest these effects are partly mediated via ATP-sensitive potassium (KATP) channels in the hypothalamus, since central administration of the KATP channel inhibitor glyburide blocks the suppressive effects of hyperglycemia on EGP (Science 309: 5736, 2005). Since it is known that glyburide crosses the blood brain barrier, we examined the effect of inhibiting KATP channels with glyburide on hyperglycemia's ability to suppress EGP in humans.

Methods Used: We performed paired 4-hour clamp studies in n=7 non-diabetic subjects (4M, age=38±5 yr, BMI=24±1 kg/m2) following glyburide 10 mg vs. placebo. EGP (6,6-D-glucose) was compared during euglycemia (5 mM) vs. hyperglycemia (10 mM). To exclude effects on pancreatic KATP channels, insulin secretion was suppressed with somatostatin, and insulin, growth hormone and glucagon infused to maintain comparable, basal hormone concentrations (insulin levels: placebo = 25+4 and glyburide = 24+4 μU/ml, p=0.83).

Summary of Results: Glyburide impaired the ability of hyperglycemia to suppress EGP (% suppression of EGP by hyperglycemia with glyburide = 26% vs. placebo = 47%, p=0.03), supporting our hypothesis that hyperglycemia regulates EGP in humans at least in part via central KATP channels (Figure).

Conclusions: Demonstrating the role of central KATP channels in the regulation of EGP provides a rationale for new pharmacologic approaches for T2DM.



Effect of glyburide on suppression of EGP by hyperglycemia.

19

CIRCULATING LEVELS OF MICRORNAS DERIVED FROM MIR-30 POLYCISTRON ARE DIFFERENTIALLY EXPRESSED BEFORE AND AFTER SURGERY IN SUBTYPES OF BREAST CANCER PATIENTS.

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Purpose of Study: We compared microRNA data on miR-30 family from microRNA array expression in pre-surgical with post-surgical and post-chemotherapy in AA and C plasma and compared them with race and age matched controls to analyze differences in plasma and tumor microRNA that may explain the survival disparity.

Methods Used: Between 2004 and 2012 we investigated patterns of plasma miRNAs collected before, after surgery, during and after chemotherapy in 18 patients presenting for surgery for breast cancer and 10 age and race matched normal controls. We analyzed the changes plasma microRNA from miR-30 family of Caucasian (C) and African American (AA) women with triple negative (TNBC) or Estrogen positive breast cancer (ER+) BrCa enrolled in our breast ovarian tissue bank between 2004 and 2012. miRNAs expression cancer vs benign done in 5 specimens. Two-sample t-test was used for all 2-sample comparison and ANOVA followed by Benjamin Hochberg post-hoc test to compare the mean response between subject factors of interest ($p<0.05$)

Summary of Results: High levels of miR-30 were detected in healthy C compared to AA controls.

Both ER positive and TNBC AA patients had very low levels of circulating miR-30 polycystron and miR-30 family pre-operative, post-operative after chemotherapy and at relapse. None of C BrCa in our small samples had decreased presurgical miR-30.

Hsa-miR-30c was1100 fold lower in ER+ AA pre-op versus control $p<0.0000026$.

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Conclusions: MiR-30 family is polycystronically transcribed and down-regulated in metastatic disease in variety of cancer. High levels of miR-30 were detected in healthy C compared to AA controls.

Both ER positive and TNBC AA patients had very low levels of circulating miR-30 polycystron and miR-30. None of C BrCa in our small samples had decreased presurgical miR-30. Low miR-30 family increases tumorigenesis and metastasis in animals. MiR-30 levels were low only in AA patients with BrCa, this finding if reproduced in larger cohorts may in part explain the lower survival of AA breast cancer patients.

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MALE BREAST CANCER, IS THERE A CORRELATION BETWEEN PROGNOSTIC FACTORS AND MOLECULAR ANALYSIS?

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Purpose of Study: Male breast cancer (MBC) is rare with about 2,140 new cases and 500 deaths per year. MBC shares morphological characteristics with its female counterpart, but, male tumors are less common, present at later onset, and have overall poor prognosis. MBC has a high rate of hormone receptor expression (ER+/PR+), whereas most tumors do not show HER2 amplification. We investigated the risk factor profile, histological features and microRNA (miRNA) molecular profile in MBC and investigated whether they have correlation with clinico-pathologic parameters and a possible role in therapy

Methods Used: Forty-two cases of MBC were studied and their clinicopathological features reviewed. In 12 cases, normal and tumor tissues were microdissected for RNA extraction. miRNA quantitative assays for miR-10, miR106a, miR-181c, miR-183, miR-17 and miR-21 were used to evaluate mature miRNA expression using the TaqMan® approach

Summary of Results: Patients age range was 36–85 (m 61). Tumor size varied from 0.5 to 5cm. Histologically, 30 cases were invasive ductal cancers, 4 were papillary, 1 micropapillary, 1 was mucinous and 6 were DCIS. Fifty-five percent were grade II and 45% Grade III; lymph node (LN) status was known in 68% of the cases, of these, 74% had LN metastasis. Prognostic factors were known in 28 cases; 25 were ER+ and 22 PR+, 2 were ER+/PR-, 3 showed Her2 amplification, 6 were 2+ and the rest were negative. P53 was positive in 8 cases. AR was heterogeneous and was strongly + in DCIS. There was down regulation of miR-10a, miR-181c, miR-106a and miR-17. miR-183 was up-regulated. All the cases that showed miR-183 up-regulation were ER+/PR+ and were either moderate or high grade tumors. Although correlation between down-regulation of miR-10a, miR-181c, miR-106a and miR-17 and prognostic factors presented more variability among the cases, the tendency was towards a majority of ER and PR positivity and moderate grade tumors

Conclusions: Our study suggests that male breast cancer has specific miRNAs implicated in the development and progression of MBC. The presence of these miRNAs and their correlation with prognostic factors may identify tumors with aggressive behavior and makes them good candidates as possible molecular targets.

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VITAMIN D AND GLUCOCORTICOIDS INTERACT TO REDUCE UBIQUITIN C IN ASTHMATIC AIRWAY EPITHELIUM

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Purpose of Study: Current research show that vitamin D insufficiency (25 (OH)D levels in serum) contributes to more severe asthma through decreased sensitivity to glucocorticoids. We previously showed a strong association between low 25(OH)D levels and asthma in urban youth. Here, we proposed a synergism between 25(OH)D and glucocorticoid signaling pathways as a potential explanatory mechanism.

Methods Used: Nasal epithelial cells were collected from urban youth between ages 6 and 20, 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.

Summary of 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.

Conclusions: 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, in turn, may improve barrier function and inflammation. Although, the role of vitamin D in airway inflammation remains unclear, altered sensitivity to glucocorticoids may be a mechanism by which vitamin D supplementation could improve asthma.

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EPITHELIAL-MESENCHYMAL CROSS TALK: IN VIVO XENOGRAFT MODEL OF ASTHMATIC AIRWAY EPITHELIUM PROMOTES AIRWAY REMODELING

Sarah Ferrante[1], Tillie L. Hackett[2], Furquan Shaheen[2], Sarah E. Alcala[1], John Engelhardt[3], Claire E. Hoptay[1], Dinesh K. Pillai[1], Mary Rose[1], Robert J. Freishtat[1]. [1]*Children's National Medical Center, Washington, DC, United States.* [2]*UBC James Hogg Research Centre, Vancouver, BC, Canada.* [3]*The University of Iowa, Iowa City, IA, United States.*

Purpose of Study: We recently made progress in mechanistically dissecting the cause/effect relationship between inflammation and airway remodeling in the lung. Our initial observations using in vitro normal airway epithelium demonstrated that wound repair is associated with mitotic synchrony and lack of an inflammatory response, whereas wound repair in asthmatic epithelium is associated with poorly synchronized mitosis and a pro-inflammatory/fibrogenic response. We hypothesized that poorly synchronized epithelial mitotic regeneration induces fibroproliferation and matrix deposition.

Methods Used: Human normal and asthmatic airway epithelial cells (n=5) were seeded into freeze-thaw denuded rat tracheas harvested from Fisher 344 rats. Tracheas were ligated to tubing at both ends and implanted subcutaneously in the flanks of nude BALB/c mice. Grafts were flushed weekly to remove excess mucus and maintain a patent lumen. We harvested grafts at 2, 4, and 6 weeks.

Summary of Results: Xenografts were compared between asthmatic and normal epithelia for evidence of fibroproliferation. Grafted epithelial cells generated a differentiated epithelium containing basal, ciliated, and mucus expressing cells. Compared to non-asthmatic and acellular control grafts, asthmatic xenografts showed limited ciliated and goblet cells by Masson's trichrome and PAS staining. The non-asthmatic epithelium was more differentiated at 6 weeks compared to asthmatic cells (1,982 vs. 963 pixel area/unit length of basement membrane). The mean number of mucus cells within the asthmatic airway epithelium compared to non-asthmatic epithelium was increased (27 vs. 15 PAS+ cells/unit length of basement membrane). Collagen analysis using Masson's trichrome and Picrosirius Red showed more abundant and dense accumulation of collagen in asthmatic xenograft matrix. Multiphoton fluorescence microscopy using second-harmonic generation showed accumulation of fibrillar collagen in asthmatic xenograft matrix.

Conclusions: These findings are consistent with our hypothesis that the mitotic asynchrony of asthmatic epithelium alters the epithelial morphology and induces underlying fibroproliferation and matrix deposition.

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VITAMIN D ADMINISTRATION IMPROVES HEPATIC INSULIN SENSITIVITY AND ADIPOSE TISSUE INFLAMMATION IN OBESE, INSULIN RESISTANT HUMANS.

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Purpose of Study: Vitamin D (VitD) deficiency has increased dramatically in prevalence due to avoidance of sun exposure. Epidemiological studies have shown that low VitD levels increase the risk of Type 2 diabetes, and are inversely correlated with insulin resistance. Therefore, we hypothesized that insulin sensitivity as assessed by hyperinsulinemic clamps would improve upon correcting 25(OH) VitD levels in deficient (<20 ng/ml), obese insulin resistant subjects. We also hypothesized that VitD deficiency predisposes to adipose tissue inflammation and insulin resistance by activating adipose tissue macrophages (ATMs).

Methods Used: Euglycemic, hyperinsulinemic pancreatic clamp studies were performed in 9 obese, insulin resistant subjects (age 42.7±3.7 yrs, BMI=33.6±1.4 kg/m2, HOMA-IR=5.14±0.67) at baseline, and following oral vitamin D3 supplementation to normalize VitD levels (LoD; >30ng.ml) for 2 months, then raise to higher VitD levels (HiD; ~50ng/ml). 6-6D-glucose was utilized to examine hepatic (EGP) and peripheral insulin sensitivity (Rd) at insulin infusion rates of 30 and 80 mU/m2/min.

Summary of Results: The 25(OH)D levels of 14.5±1.1 ng/ml at baseline increased to 38.9±4.6 ng/ml over the first 2 months and to 51.6±2.4 ng/ml over the subsequent 2 months. EGP decreased by 27% with LoD and by 38% with HiD (baseline=1.43±0.21, LoD=1.04±0.11 and HiD=0.88±0.18 mg/kg/min, $p<0.05$). Rd remained unchanged at both HiD and LoD levels.

The effects of VitD repletion on adipose tissue inflammation were studied in a subgroup of 6 subjects. Adipose tissue biopsies were obtained from lower abdominal subcutaneous adipose tissue. Gene expression of the pro-inflammatory markers IL-6, iNOS and PAI-1 in isolated ATMs was significantly decreased after VitD repletion to low normal levels (0.5, 0.73 and 0.57 fold change respectively; all $p< 0.05$). No significant changes were seen in ATM gene expression between low normal vs. high normal vitamin D levels.

Conclusions: These findings suggest that VitD deficiency induces insulin resistance and adipose tissue macrophage activation in humans, and that these effects are reversible upon VitD repletion. There appears to be no further metabolic benefit to raising 25(OH)D levels beyond those required to correct deficiency.

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IMPACT OF LUPUS PLASMA ON LIPID ACCUMULATION IN THP-1 HUMAN MACROPHAGES

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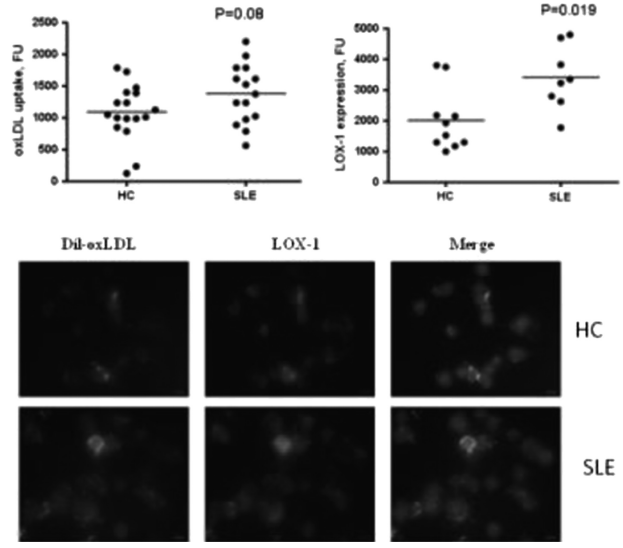
Purpose of Study: Atherosclerotic cardiovascular disease (ASCVD) is a characteristic feature of systemic lupus erythematosus (SLE), resulting in severe complications such as myocardial infarction and stroke. Framingham risk factors or disease activity markers cannot predict CVD susceptibility. This study examines whether plasma from SLE patients modulates lipid uptake and processing in human monocytes/macrophages.

Methods Used: In an IRB approved study, cultured naïve THP-1 macrophages were exposed to 10% plasma from each of 21 healthy controls (HC) and 12 SLE patient ± 5 μg/ml (Dil)-oxLDL. OxLDL accumulation was determined by fluorescent intensity. Following 18h incubation, RNA and protein were isolated. QRT-PCR and Western blotting techniques measured expression of scavenger receptors: CD36, SR-A1 and lectin-like oxidized low density lipoprotein receptor (LOX-1).

Summary of Results: Our results demonstrate that 10% SLE plasma elevates cholesterol influx proteins in THP-1 human macrophages, increasing CD36 mRNA to 189.4±6.9%, SR-A1 to 195.8±5.8% and LOX-1 to 180.1±3.0% compared to HC (n=3, $P<0.01$). Protein expression of SR-A1 was upregulated to 285.4±69.5%,CD36 to 170.0±42.3% and LOX-1 to 271.4±69.5% of control. Macrophage oxLDL uptake in the presence of SLE plasma increased to 1608±108.7 fluorescent units [FU] (n=15) versus HC (1049±83.3FU, n=17, not statistically significant, $p=0.08$).

Conclusions: SLE plasma is atherogenic and promotes lipid uptake in human macrophages via upregulation of scavenger receptors CD36, SR-A1 and LOX1. These results may have predictive value for CV risk in this susceptible population. However, future investigations based on a larger cohort of SLE subjects is indicated to determine whether our preliminary finding of an upward trend is significant.



OxLDL uptake and LOX1 expression in THP-1 macrophages in the presence of HC and SLE plasma.

25

UNABLE TO BE PUBLISHED

26

RHINOVIRUS INFECTION IN EARLY CHILDHOOD IS ASSOCIATED WITH ELEVATED AIRWAY THYMIC STROMAL LYMPHOPOETIN LEVELS AND A TH2 BIAS IN AIRWAY IMMUNE RESPONSE

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Purpose of Study: Thymic stromal lympoietin (TSLP) is an airway epithelial cytokine responsible for priming Th0 cells into Th2 cells. Rhinovirus (RV) causes the majority of asthma exacerbations in children and has been shown to increase TSLP levels in airway epithelial cells. This suggests that TSLP may be the missing link between antiviral and Th2 pro-asthmatic immune responses. Given that RV infections in early life are a risk factor for persistence of asthma beyond childhood, we postulated that RV infections in young children are associated with elevated airway TSLP levels and enhanced Th2 responses.

Methods Used: Nasal airway secretions were obtained from children <3 y/o during acute respiratory illnesses using standard nasal lavage technique. Samples were analyzed by PCR to identify RV and other respiratory viruses and then for protein levels of TSLP, IL1β, IL12, IFNγ, TNFα, IL4, IL13, eotaxin-1, TARC, MDC and IL17 using a magnetic bead assay. Multivariate regression models were built to study the link between RV infection and TSLP/Th2 levels adjusted by clinical variables.

Summary of Results: 111 children (age 10+/−7 months) were included in the study. 58 subjects had RV and 53 had negative viral PCR. Children with RV had higher nasal TSLP levels compared with those with negative PCR (mean +/− SE 5.5+/− 0.9 pg/mL vs. 14.27+/−1.2 pg/mL; $p<0.001$). Increased TSLP levels correlated positively with a Th2 biased response in children with RV infection, according to Th2/Th1 ratio (IL4/IL12;$p<0.05$).

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Conclusions: Our data indicates that acute RV infection in young children is associated with elevated airway levels of TSLP/Th2 cytokines. This new information suggests a novel mechanism by which RV can shift immune responses toward Th2 in early life, which may facilitate the development of asthma during early childhood. Further characterization of the developmental aspects of TSLP biology will enhance our knowledge about the origins of viral-induced asthma and may identify new strategies to prevent the generation of the asthmatic and atopic state during early life.

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INTERACTION BETWEEN GENETIC VARIANTS RELATED TO TYPE 2 DIABETES AND BONE PHENOTYPES IN YOUNG AFRICAN AMERICANS

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Purpose of Study: Determine if single nucleotide polymorphisms (SNPs) previously associated with increased risk of developing type 2 diabetes (T2D) are also associated with increased likelihood of fracture or decreased bone mineral density (BMD).

Methods Used: Sixty-six SNPs, previously found to be highly associated with pre-diabetic phenotypes or increased risk of developing T2D, were chosen from genome wide association studies (GWAS). The 66 SNPs were then genotyped using Taqman allelic discrimination assays. DNA was isolated from whole blood in a population of 142 African American children, aged 5 to 9 years. SNPs were analyzed for associations with Total BMD and Lumbar Spine BMD obtained from dual energy x-ray absorptiometry (DXA). Mean continuous phenotypes were compared among genotypes from each SNP using analysis of covariance models adjusted for gender and age. Associations between SNPs and fracture status were tested using logistic regression adjusted for gender. All regression models used a dominant genetic model comparing homozygous common allele individuals to heterozygotes and homozygous rare allele individuals.

Summary of Results: Significant associations with fracture status were found with rs17036101 located in the SYN2 gene (OR= 3.54; 95% CI=1.21-10.34; p=0.021), rs896854 located in the TP53INP1 gene (OR= 1.98; 95% CI= 1.02-3.86; p=0.045), and rs11634397 located in the ZFAND6 gene (OR= 0.40; 95% CI=0.19-0.85; p=0.018). Furthermore, significant associations were found between rs13266634 located in the SLC30A8 gene and total body bone mineral density (BMD) [CC: 0.673 ± 0.015 g/cm3; CT/TT: 0.711 ± 0.021 g/cm3; p=0.020] and lumbar BMD [CC: 0.549 ± 0.018 g/cm3; CT/TT: 0.593 ± 0.025 g/cm3; p=0.020]; and rs7542900 located in the SYN2 gene with both total BMD [CC: 0.651 ± 0.018 g/cm3; CT/TT: 0.681 ± 0.014 g/cm3; p=0.019] and lumbar BMD [CC: 0.549 ± 0.018 g/cm3 CT/TT: 0.518 ± 0.022 g/cm3; p= 0.006].

Conclusions: In our study population, children possessing alleles associated with increased risk of developing T2D in adulthood also have lower BMD and increased risk of fracture in childhood.

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DO MALE AND FEMALE BREAST CANCER SHARE SIMILAR MICRORNA EXPRESSION PATTERNS?

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Purpose of Study: Mature microRNAs are small non-protein coding RNAs which modulate gene expression by acting post-transcriptionally. There are only few studies suggesting that male breast cancer (MBC) displays distinctive miRNAs patterns. We performed a comprehensive profiling of 800 miRNAs in MBC samples to further elucidate their role in the development and treatment of these tumors

Methods Used: Forty-two cases of MBC were retrieved and their clinicopathological features were reviewed. After manual microdissection, miRNA was extracted from tumor and normal epithelium for profiling using NanoString approach. Differentially expressed miRNAs were obtained comparing tumor vs. normal epithelium

Summary of Results: The profiling of 800 miRNAs showed different miRNA expression between tumor and normal tissues, suggesting a cancer-specific miRNA expression profile. Forty-nine miRNAs showed increased expressions while 26 miRNAs were down-regulated in the MBC when compared with their normal component. The miRNA profile found in our study also showed to be different from previously published miRNA profiles in female BC. For instance, expression of miR-222 and miR-296-5p have shown no significant difference between the breast cancer and normal tissue in females, while in our study both showed to be up-regulated in the male tumors. miR-135b-5p, miR-1180, miR-503, miR-34a-5p, miR-362-5p, miR-424-5p and miR-194-5p showed to be significantly up-regulated in our cohort while in female breast cancer these miRNAs have shown to be down-regulated. Among the most down-regulated miRNAs found in the present study, miR-155-5p and miR-203 have shown to be up-regulated in female breast tumors. Relationships between the expression of the most deregulated miRNAs and the pathologic features showed a statistically significant association between tumor size and miR-125b ($P < 0.05$)

Conclusions: The results presented in this study further support the fact that MBC have a unique expression profile in comparison with normal mammary tissue and to that presented in female breast cancer. The differentially expressed miRNAs may provide insights into the understanding of this highly aggressive cancer, and provide new tools for the development of new molecular targets

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EFFECT OF ENDOVASCULAR CLOSURE PROCEDURE ON THE QUALITY OF LIFE IN STROKE PATIENTS WITH PATENT FORAMEN OVALE

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Purpose of Study: Patent foramen ovale (PFO), an opening between the left and right atrium, is an independent stroke risk factor associated with more than 150,000 strokes per year in the United States. PFO stroke patients tend to be younger – most are of child-bearing age, enjoy an active lifestyle and are a major component of the work force, who are not long-term anticoagulant candidates. While trials are ongoing to compare closure versus medical treatment, younger stroke patients tend to prefer endovascular closure rather than long term anticoagulation. Here we investigate the effect of PFO closure for stroke prevention on patient's quality of life.

Methods Used: Patients were recruited per IRB-approved protocol from the MGH Cardio-Neurology Clinic. To quantify the effect of PFO closure on depression and anxiety, validated Becks Depression and Anxiety Inventory questionnaires were performed by trained research nurse at 3 months before and 3–6 months after PFO closure. Clinical data on stroke severity, clinical outcome and blood samples were collected.

Summary of Results: 32 consecutive PFO stroke patients, adjudicated by two vascular neurologists (average age 50.75; 56% male r, stroke severity Y,) were enrolled. No new treatment (i.e. anti-depressant/anti-anxiety meds) were initiated during the study. After successful PFO closure, patients had significantly improved anxiety scores (3 vs 5.75, p= 0.043) and depression score (2.58+/– vs3, p= 0.05) (Figure). Patients also had lower cortisol level post PFO closure (data not shown due to space).

Conclusions: PFO stroke patients have improved quality of life after endovascular closure as measured by validated quantitative anxiety and depression scales under the care of a team composed of nurses, physicians and neuropsychologists. These findings demonstrate the importance of a multi-disciplinary approach to stroke patient care and also the effect of endovascular closure treatment in improving the quality of life in younger stroke patients. Future studies are needed in a larger cohort with long term follow-up to validate these results.

DISPLAY POSTERS

P1

MANAGEMENT OF ASTHMA EXACERBATIONS IN CHILDREN AND ADOLESCENTS: DIFFERENCES BETWEEN PEDIATRIC AND GENERAL EMERGENCY DEPARTMENTS

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Purpose of Study: To evaluate differences in management of pediatric asthma exacerbations between pediatric and general EDs.

Methods Used: e performed a repeated cross-sectional study using the National Hospital Ambulatory Medical Care Survey from 2000-2010 of ED visits with ICD9 diagnoses of asthma (493.XX) among patients ≤21 years. Visits with co-diagnoses of pneumonia were excluded.We calculated frequencies of CXRs, CBCs, and antibiotic usage. Bivariable logistic regression was performed to identify demographic differences in diagnostic testing and antibiotic prescription. Multivariable logistic regression was then performed to identify differences in asthma management by ED type (pediatric vs. general) after adjusting for statistically significant demographic covariates. A Pediatric ED was defined as an ED with >75% of visits made by patients ≤ 21 years old.

Summary of Results: Over the study period, there were 3,854 observations, representing an estimated 13.3 (95% CI 11.8, 14.7) million ED visits for asthma in children aged ≤ 21 years (mean age 8.0 years; 57.6% male). Asthma comprised 3.5% (95% CI 3.3, 3.8) of all ED visits by children. Of these, 20% (95% CI 14.6, 25.4) occurred in pediatric EDs. A total of 5.8% (95% CI 4.7, 6.9) had a co-diagnosis of pneumonia with no difference by ED type (p=0.97). Multivariable logistic regression revealed that visits to pediatric EDs were significantly less likely to include CXRs (aOR 0.43; 95% CI 0.28, 0.66); or CBCs (aOR 0.38; 95% CI 0.20, 0.70); and antibiotic use (aOR 0.62, 95% CI 0.44, 0.87) after adjusting for survey year, age, racial/ethnic group, insurance status, triage level, metropolitan statistical area, and geographic region.

Conclusions: There are substantial differences in use of diagnostic testing and antibiotics among pediatric patients with asthma by ED type, suggesting potential resource overuse in general EDs. Future studies should focus on evaluating the impact of quality improvement efforts for ED asthma management.

P2

COMPARING VITAMIN D LEVELS AMONG ANOREXIC AND OBESE ADOLESCENT POPULATIONS

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Purpose of Study: To examine if vitamin D levels in anorexic and obese young females are different due to differences in adipose tissue mass.

Methods Used: Nine patients were identified in the anorexic group and 9 patients in the obese cohort. Subjects were initially identified using the ICD 9 codes 263.9 for malnutrition, 272.4 for hyperlipidemia, and 783.1 for abnormal weight gain. Mean age 16 (range 11 – 19) and only included female patients due to the fact that the vast majority of anorexic patients were of that gender. The data that was recorded included the age, weight, height, BMI, percentile for age and gender, date of vitamin D testing, serum 25OH-vitamin D level (vitamin D level), serum Calcium level, and patient co-morbidities. The data analysis was performed using IBM SPSS 19. Descriptive statistics was performed on each data element. Comparisons between the two patient groups was performed using Fisher's Exact tests for categorical variables and t-tests/Wilcoxon Rank-Sum test for continuous variables to determine statistically significant differences. Statistical significance was defined as $p < 0.05$.

Summary of Results: There were more obese than anorexic patients meeting inclusion criteria, therefore obese patients were matched 1:1 to anorexia nervosa patients based on age and race. The patients BMI percentages for age and weight were a mean of 22.0 ± 25.8 for the anorexic group and 97.8 ± 2.3 for the obese group with a t-test showing a p value of <0.0001. The mean serum vitamin D level in the anorexic group was 48.3 ± 15.1 ng/ml and for the obese group 17.6 ± 5.7 ng/ml. The t-test showed a p value of <0.0002 and a two tailed P value less than 0.0001.

Conclusions: A statistically significant difference in vitamin D levels was seen with excessive adiposity versus the group minimal body fat. We compared two groups of female patients living in the same region and took care to decrease the influence of co-variants such as race, age, geographical location, diet, and culture. If replicated in a larger cohort our study may provide a better understanding of supplementation in Vitamin D deficiency.

P3

ASTHMA SPECIALTY CLINICS DECREASE EMERGENCY DEPARTMENT VISITS IN INNER-CITY CHILDREN HOSPITALIZED FOR ASTHMA EXACERBATION

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Purpose of Study: Pediatric asthma exacerbations lead to 750,000 emergency department (ED) visits and 198,000 hospitalizations annually. Urban children disproportionately utilize ED services and also have a high rate of ED recidivism. The National Asthma Education and Prevention Program (NAEPP) expert guidelines recommend all children hospitalized for asthma exacerbations be seen by asthma specialists. The impact of specialist intervention remains unclear. We hypothesize that inner-city children admitted for asthma exacerbation that follow-up at specialty clinics will have decreased asthma-related ED visits.

Methods Used: Retrospective chart review performed of all children >2yrs admitted for asthma exacerbations over a 12-month period to an inner-city tertiary children's hospital. Data collected included demographics, asthma severity, subspecialty referrals, and healthcare utilization 1 year before and after admission. Specialty clinics included an ED based asthma clinic, pulmonary clinic, and allergy clinic. T-test, chi-square test and multivariate regression models were used when appropriate (significance $p<0.05$).

Summary of Results: During the 12 month period, 350 inner-city children were admitted for asthma exacerbations. Of those, 263 (75%) were referred and 154 (44%) went to at least one asthma specialist within 1 year after discharge. Only 117 (33%) were seen by an asthma specialist within 3 months. Children with moderate or severe asthma and >1 ED visit prior to admission had an increased risk of having a new asthma-related ED re-visit (RR 6.2; p=0.017) if they did not see an asthma specialist within 3 months of discharge compared to those who did follow up with an asthma specialist.

Conclusions: Although NAEPP guidelines recommend that all children admitted for asthma should see a specialist, only 33% of our urban population followed with a specialist within 3 months. Inner city patients admitted with moderate or severe asthma represent a high risk population. Our data suggest that improving referral and attendance to asthma specialty clinics for these patients has the potential to improve outcomes and healthcare utilization.

P4

THE DIFFERENTIAL SECRETOME OF FIBROBLASTS ISOLATED FROM PEDIATRIC PATIENTS WITH CHRONIC RHINOSINUSITIS

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Purpose of Study: Submucosal glandular hyperplasia/hypertrophy (SMGHH) is the primary histopathologic feature seen in chronic rhinosinusitis (CRS). Several investigators have shown that fibroblast growth factors mediate epithelial proliferation and differentiation to promote SMGHH. We hypothesized that in CRS, fibroblasts and their secretions not only play a key role in epithelial proliferation and differentiation, but also promote targeted movement and organization of epithelial cells into glandular structures facilitating SMGHH. To begin investigating our hypothesis, we analyzed the secretomes of primary fibroblasts isolated from sinus tissue from CRS pediatric patients and non-diseased controls.

Methods Used: Sinus fibroblasts from patients with CRS (n=2) and controls (n=2) were grown to confluence and placed in serum free media for 24 hours. The secretions were resolved by electrophoresis before being in-gel digested with trypsin. The peptides were then analyzed using mass spectrometry. Protein identification and quantification was performed using Integrated Proteomics Pipeline. Ingenuity Pathway Analysis (IPA) software was used to identify the most relevant signaling pathways and biological functions of differentially regulated proteins.

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Summary of Results: CRS and control sinus fibroblasts have distinct secretomes under homeostatic conditions. 171 peptides had a spectral count >20 and a fold change more than +/− 1.5; 166 were fit into IPA networks. The top functional network identified by IPA was cellular movement. Proteins differentially secreted by CRS fibroblasts were involved with increased movement and adhesion of epithelial cells (CLIC4, IGFBP5, POSTN, CDH11), fibroblasts (POSTN, FLNB, ENPP2, TIMP2), and immune cells (C4A/C4B, C3 THBS2, MMP1).
Conclusions: (1) Sinus fibroblasts derived from patients with CRS have different secretomes than those of fibroblasts from healthy patients; and (2) The CRS secretome is comprised mostly of proteins involved with tissue remodeling, especially cellular movement, many of which would be expected to play a role in SMGHH.

P5

CARDIAC MRI IN PATIENTS WITH VALVULAR HEART DISEASE TO EVALUATE CARDIAC FUNCTION AND PREDICT OUTCOMES

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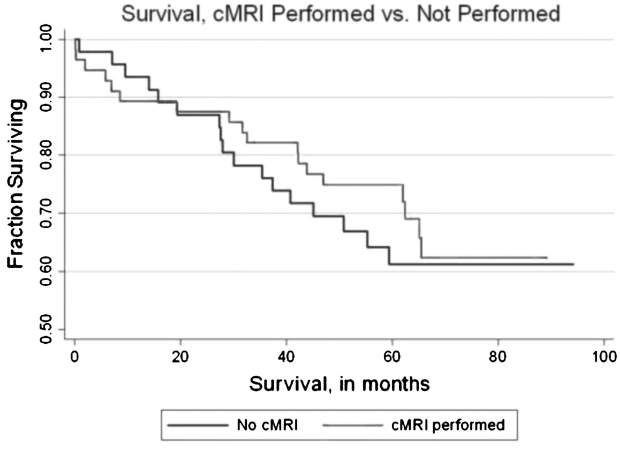
Purpose of Study: Patients with valvular heart disease have elevated left atrial and pulmonary pressures that can lead to right ventricular strain and right heart failure. Pulmonary artery (PAP) and left ventricular end diastolic (LVEDP) pressures have been used as markers of right heart dysfunction and correlate with poor outcomes. With cardiac MRI (cMRI), it is possible to directly quantify both left and right ventricular function (LVEF and RVEF). We compared cMRI to traditional markers as outcome predictors.
Methods Used: A review of prospectively collected data was performed on 103 consecutive patients having valve surgery over a 4 yr period. All patients had preoperative cardiac catheterization, with 56 receiving cMRI. Patients were divided into two cohorts; cMRI compared to only catheterization. Logistic regression were applied to determine predictors of mortality. Predictive models for mortality using preoperative PAP, mean PAP (MPAPA), and LVEDP were compared to models using LVEF and RVEF obtained from cMRI.
Summary of Results: Overall, the two groups were similar. Of the risk factors analyzed, only age emerged a predictor of mortality (p=0.01) by univariate models. Step-wise regression models comparing catheterization to cMRI groups, showed the cMRI model has a slightly better R^2, c (prediction accuracy), and sensitivity/specificity (0.22 v 0.28; 0.77 v 0.82; and 0.63/0.62 v 0.69/0.64, respectively).
Conclusions: In patients selected for valvular heart surgery, cMRI can accurately assess LV and RV function and morphology, and LVEF and RVEF were maintained and served as better predictors of mortality than PAP. Additionally, cMRI allows stratification of elevated PAPs into those caused by right heart dysfunction, and those due to other causes , allowing for risk factor modification preoperatively.



P6

OBJECT PRESENCE IN THE SLEEP ENVIRONMENT: ASSOCIATIONS WITH INFANT MORTALITY

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Purpose of Study: To describe the circumstances of death and the objects present in the sleeping environment upon death in a cohort of infants who sustained fatal suffocation or strangulation injuries.
Methods Used: 1,736 cases of accidental suffocation and strangulation in bed (ASSB) between 2000 and 2012 were retrospectively reviewed from four unique databases administered by the Consumer Product Safety Commission.
Summary of Results: The mean age of death for infants was 3.76 months (SD: 2.51), and over two-thirds of all fatalities occurred in infants less than five months of age (67.3%). Infants were found in a crib or bassinet less than a third (30.6%) of the time. When documented, the prone sleep position was most common (84.9%). Wedging (43.3%) followed by a position on top of and face down or prone on an object (25.9%) were the most common positions relevant to death. Pillows were associated with death in 425 cases and were present but unrelated to death in an additional 140 cases, thus present at the death scene in nearly a third of all fatalities (32.5%). Other common objects associated with death included mattresses (364 cases), blankets (228 cases), and walls (199 cases). Co-sleeping was documented in 20.2% of all deaths and was associated with ASSB in 112 cases.
Conclusions: Both caregivers and healthcare providers should be aware of the unique dangers that specific objects pose in the sleep environment. Adopting proper sleep practices can prevent the majority of deaths due to accidental suffocation or strangulation.

P7

ACCURACY OF RECALL OF BOWEL SYMPTOMS IN PATIENTS WITH CROHN'S DISEASE

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Purpose of Study: The Crohn's Disease Activity Index is widely used to measure disease activity in clinical trials. A shortened version (sCDAI) that relies only on patient-reported symptoms is highly correlated and designed for use in observational studies. Both indices require completion of a 1 week symptom diary. There are no data on the ability to recall symptoms of Crohn's disease (CD) to guide whether the diary needs to be completed prospectively.

Objectives: To determine the relationship between time interval and accuracy of recall of Crohn's disease symptoms.

Methods Used: Patients with Inflammatory Bowel Disease presenting for a visit at the Gastroenterology Clinic were administered a baseline survey that included questions from the sCDAI as well as a variety of quality of life questions to limit priming of sCDAI-specific questions. Participants were then randomized to receive a follow-up survey via email between 1 and 7 days later that asked them to recall their symptoms from the time of the office visit. We compared the mean difference between reported symptoms at the office visit and on follow-up by time using ANOVA.
Summary of Results: To date, 54 patients have completed the study (31 men; 34 CD & 20 ulcerative colitis; mean age 42 years (s.d. 18). Disease activity based on sCDAI was remission in 42.6%, mild in 27.8%, and moderate in 29.6%. Mean difference in the baseline and recalled bowel frequency was 0.46, 0.81, and 0.75 per day if the follow-up survey was completed within 2 days, 3–5 days, and 6 or more days later, respectively (p = 0.55). Similar results were observed for abdominal pain (p=0.35), wellbeing (p=0.51), and sCDAI (p=0.82). When limited to patients with active disease, results were similar (bowel frequency p=0.997; abdominal pain p=0.26; wellbeing p=0.53; sCDAI p=0.92). Analyses limited to those with CD were similar (bowel frequency p=0.08; abdominal pain p=0.15; wellbeing p=0.64; sCDAI p=0.52). The difference of sCDAI scores on the initial and follow-up surveys did not change the disease severity category for any patient.
Conclusions: These preliminary results demonstrate that recall of Crohn's disease symptoms are reliable over the course of a 7-day period, irrespective of whether patients are in active disease or remission. This suggests that data on

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symptoms of Crohn's disease can be accurately collected with up to a 7-day recall period.

P8

NOTIFICATION AND TREATMENT OF POSITIVE SEXUALLY TRANSMITTED INFECTION TEST RESULTS IN A PEDIATRIC EMERGENCY DEPARTMENT

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Purpose of Study: Determine the proportion of patients with positive Neisseria gonorrhea [GC] and Chlamydia trachomatis [CT] tests sent from a pediatric emergency department [ED] who were notified of and treated for their infection. Barriers to notification include inaccurate contact information, inability to reach the patient directly to deliver confidential results, and ED staff resources required for notification.

Methods Used: We performed a retrospective cross-sectional medical record review of all patients aged 13–19 years who had GC and CT testing sent from an urban, academic pediatric ED in 2012. Patient demographics, chief complaint, disposition, test results, documentation of notification, and documentation of treatment during the initial visit or during follow-up were obtained from the medical record.

Summary of Results: Of 1251 patient visits meeting inclusion criteria, 291 (23.3%) had a positive test result (4.3% GC, 16.1% CT, 2.9% co-infection). Successful notification was documented in 209 cases (71.8%). Mean time to notification was 4.1 ± 2.7 days. Of the 82 who were not notified, 64 had been empirically treated at the initial visit (42 had unsuccessful notification attempts and 22 had no documented attempts). There were no documented contact attempts in 9 of the remaining 18 cases without notification or empiric treatment. Patients with positive results who received treatment at the index visit were less likely to be notified (OR 0.49, 95% CI 0.27-0.89) but were not significantly less likely to have at least one attempt (OR 1.01, 95%CI 0.48-2.11). Of the patients with a positive result, 254 (87.3%) had at least one notification attempt, with 140 (48.1%) requiring more than one attempt. There were a total of 489 documented attempts, including 35 letters to patients who could not be reached by phone.

Conclusions: Most adolescents with positive STI test results were notified, although multiple attempts were often necessary and not all adolescents were notified. Future research should consider ways to improve collection of contact information for adolescents and indications for empiric treatment in a high-risk population.

P9

A CONCUSSION DIAGNOSTIC TOOL AND MANAGEMENT PLAN IMPLEMENTED AS CLINICAL DECISION SUPPORT INTO THE ELECTRONIC HEALTH RECORD

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Purpose of Study: Historically, the evaluation and management of concussion in the Emergency Department (ED) setting has been inconsistent, and concussion often goes unrecognized. The Acute Concussion Evaluation–Emergency Department (ACE-ED) is a psychometrically validated concussion diagnostic tool previously developed. The ACE-ED Care Plan is the concussion management plan developed with it. We have integrated these two tools for the diagnosis and management of concussion for the ED into our electronic health record. Our objective is to assess the effect of integration of these diagnostic and management tools into the EHR as workflow-integrated decision support to improve the diagnosis and management of concussions.

Methods Used: The ACE-ED and ACE-ED Care Plan were implemented into the electronic health record at a Level One Pediatric Trauma Center servicing 120,000 patients per year. Nursing staff utilize the ACE-ED diagnostic tool at the time of triage for every injured patient with head trauma and ED clinicians independently complete the ACE-ED during their patient assessment. The electronic decision support tool uses built-in conditional logic in order to generate an ICD-9 code and recommendation. For patients meeting diagnostic criteria for a concussion, this tool launches a brain icon on the patient tracking board to inform staff that the patient has been diagnosed with a concussion and should receive the ACE-ED Care Plan upon discharge.

Summary of Results: Our analysis will include the adherence rates pre-and-post implementation of the ACE-ED by nursing staff at the time of triage and clinicians at the time of clinical assessment. We will evaluate the percentage of ICD-9 codes generated as well as the rate of receipt of the ACE-ED Care Plan to patients discharged home with an ICD-9 diagnosis of concussion.

Conclusions: This clinical decision support tool is feasibly integrated into the electronic health record and workflow in the ED. This clinical decision support tool can increase the number of patients correctly diagnosed with a concussion, decrease practice pattern variation, and improve patient education for concussion management after discharge from the ED.

P10

UTILITY OF IMMATURE PLATELET COUNT IN MONITORING THROMBOPOIETIC ACTIVITY IN PEDIATRIC ONCOLOGY AND HEMATOPOIETIC PROGENITOR CELL TRANSPLANT PATIENTS

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Purpose of Study: Immature platelet fraction (IPF) has been used to predict platelet (PLT) recovery for patients recovering from chemotherapy and hematopoietic progenitor cell transplantation (HPCT). We wanted to determine if the absolute immature platelet count (IPC) is a more accurate marker in monitoring thrombopoietic activity as compared to IPF.

Methods Used: Five consecutive pediatric hematology/oncology patients status post chemotherapy (n=2) or HPCT (n=3) were prospectively analyzed for CBC and reticulocyte count (which included IPF) using leftover CBC specimens. To account for age specific changes, relative fold increase above upper limit of normal of IPF, IPC, absolute neutrophil count (ANC), absolute reticulocyte count (ABRET), white blood cell count (WBC), and immature reticulocyte fraction (IRF) were correlated with PLT count. Only leftover samples within 24 hours of draw were used because of the instability of IPF with time. The median, 25th, and 75th percentile correlation coefficients of each hematopoietic parameter were calculated and aggregated for comparison. The XE-5000 hematology analyzer was used to analyze leftover CBC specimens per manufacturer's recommendation. Nonparametric testing (Mann–Whitney U test) was used to determine statistical significance of each correlative pairing. Reference intervals for IPF and IPC were developed using the Hoffmann approximation (Hoffmann RG. JAMA 1963;185:864–73).

Summary of Results: IPC demonstrated significantly higher overall correlation with PLT count compared to other hematopoietic parameters except absolute reticulocyte count. Median R^2 and (25th and 75th percentile) were 0.12 (0.07-0.35), 0.14 (0.14-0.35), 0.64 (0.33-0.64), 0.02 (0.02-0.11), 0.11 (0.07-0.48), 0.85 (0.59-0.91) for WBC, ANC, ABRET, IRF, IPF, and IPC, respectively. In general, in the evaluation of IPC/IPF kinetics with increasing PLT count, both IPC and IPF, either increased earlier or more rapidly than PLT count (3 out of 3 patients). In contrast, with decreasing or falling PLT count, IPC decreased at a similar rate, whereas IPF increased by approximately 50 - 200% (3 out of 3 patients).

Conclusions: In this study, IPC together with IPF may better indicate thrombopoietic activity compared to PLT count alone in pediatric oncology and HPCT patients.

P11

UTILIZING THE CARDIAC ADMISSION TO ASSESS ABDOMINAL AORTIC ANEURYSM SCREENING RATES

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Purpose of Study: Abdominal aortic aneurysm (AAA) is a significant risk factor for aortic rupture, which has a high mortality. After age 60, the prevalence of AAA increases dramatically amongst men. AAA is present in 4-9% of individuals over age 60. The United States Preventive Services Task Force (USPSTF) currently recommends that men aged 65 to 75 who have ever smoked should be screened one time for AAA by abdominal ultrasound (US). US of the abdomen is the diagnostic screening tool of choice for AAA given its safety, low cost, high sensitivity (95-100%) and specificity (100%).

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This study was designed to determine compliance with the current USPSTF recommendation. We utilized hospitalization on a cardiac telemetry unit as an opportunity to assess the adequacy of AAA screening in an at-risk population.
Methods Used: Male patients aged between 65 and 75 years old, admitted to a cardiac telemetry floor at a large metropolitan hospital were studied (n= 48). Each subject was administered a brief questionnaire by a physician. Statistical methods were employed to compare men with and without a history of AAA screening.
Summary of Results: 16 patients denied any history of tobacco and were excluded from the study. Among the remaining subjects, 8/32 (25%) had undergone AAA screening. There was no difference in history of CAD or other risk factors for atherosclerosis between the two groups of screened and unscreened subjects (see table).
Conclusions: The data shows that further steps are needed to increase awareness of the current USPSTF guidelines in regard to AAA screening. Further research may help to identify barriers to screening that exist and be used to enhance the prevalence of appropriate AAA screening. Greater screening rates may, by extension, lead to a decrease in aneurysm-related death.

Comparison of men aged 65-75, with a history of tobacco use, with and without AAA screening

	Screened (+)	Non-Screened (-)	p-value
Age (mean)	69.6	69.5	0.9088
Hypertension	5/8 (62.5%)	22/26 (84.6%)	0.3153
Hyperlipidemia	6/8 (75%)	16/26 (61.5%)	0.6809
Diabetes	4/8 (50%)	10/26 (38.5%)	0.6892
History of coronary artery disease	4/8 (50%)	16/26 (61.5%)	0.6892
History of stroke	0/8 (0%)	5/26 (19.2%)	0.3086

P12

RECORDING FAMILY HISTORY FOR COLORECTAL CANCER PATIENTS: MISSED OPPORTUNITIES FOR SCREENING AND PREVENTION

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Purpose of Study: To assess recording of family history in patients undergoing surgery for colorectal cancer. To understand barrier to family history intake
Methods Used: We evaluated the documentation of family histories in charts of 744 consecutive colorectal cancer patients admitted for initial surgery at North Shore University Hospital between 2009 and 2012. Statistical analysis was performed for each group of patients using Normal method with standard error of proportion of 0.261 for 95% confidence interval (normal value 1.96)
Summary of Results: Of the 744 colorectal cancer patients, 193 (26% 95% CI 0.228-0.291) had cancer family history recorded for the 1st degree relatives and 52 (7%95% CI 6.7-7.7) had cancer family history recorded for their 2nd degree relatives. Age at colorectal cancer was documented in 190 (23% 95% CI 0.224-0.287) of the family members of the colorectal cancer patients.

The Amsterdam II criteria (3, 2, 1) for referral to genetic cancer counseling and testing requires documentation of family history of 3 generations (first and second degree relatives and the proband): only 7% (95% CI 6.7-7.7) of the patients diagnosed under the age of 50 years old with colorectal cancer had a family history sufficient to evaluate the patient for hereditary colorectal cancer syndromes (Amsterdam II criteria).
Conclusions: Appropriate evaluation for hereditary colorectal cancer syndromes and genetic counseling and testing requires a complete and accurate documentation of family history. Family history was documented in only 7% of our cohort limiting provider opportunity to detect families with hereditary syndromes. To obtain improvement in the identification and management of patients at high risk and their family members, significant improvements in family history documentation are needed. Education is part of the answer.

P13

DESIGNING A CONTINUOUS QUALITY IMPROVEMENT ASSESSMENT SYSTEM UTILIZING COMPLEX ADAPTIVE SYSTEMS SCIENCE TO IMPROVE TREATMENT OUTCOMES IN PATIENTS WITH SLE

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Purpose of Study: Systemic Lupus Erythematosus (SLE) is a multisystem autoimmune disease with relapses and remissions associated with non-uniform responses to treatments, suggesting a role from lifestyle/diet/environmental (LDE) exposures. Positive reactions to assays used to confirm autoantibodies derived from rabbit or calf based reagents suggest SLE patients may respond adversely to exposures to these animals' nucleic acids. Moreover, SLE patients eating Vegan diets report improvement. Standardized one-dimensional approach to SLE management fails to account for or test the hypothesis that LDE exposures affect treatment response which may decrease overall clinical improvement increasing health care costs. Patient driven disease management and research is being introduced in healthcare, especially for complex diseases when environmental and behavioral factors may contribute to symptom presentation. This study is designed to collect variables that potentially contribute to symptom improvement in SLE.
Methods Used: De-identified data analysis will give feedback identifying ideas for improvement to be used to design a questionnaire using dynamic continuous quality improvement assessment (CQIA) based on principles of Complex adaptive systems science (CAS). The questionnaire will capture demographics, disease assessment, medications, concomitant diseases and treatments as well as lifestyle, diet, and environmental exposures. Rapid 3, serology, basic labs financial burden, effect on daily functions will be monitored to determine disease control status. Statistical array analysis will be performed to identify subgroups of individuals who respond positively or adversely in association with data points. Patients will be kept current to patterns identified, creating a dynamic system of potential continuous improvements.
Summary of Results: The authors intend to present the design of this clinical quality improvement project as a unique method for multidisciplinary collaboration, driven by patient entered data, to improve the value of care for patients with SLE.
Conclusions: CQIA-CAS will help provide individualized timely feedback for each SLE patient in a manner designed to improve their overall quality of treatment response and cost of care.

P14

THE ROLE OF GENDER ON THE EVALUATION OF PATIENTS WITH SYNCOPE

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Purpose of Study: The objective is to evaluate if gender is a significant variable in patients admitted with syncope.
Methods Used: Data from the 200 consecutive admissions with a diagnosis of syncope were collated. Each admission was categorized based on troponin levels, age, sex, gender, risk factors, and EF to assess the prevalence of adverse cardiac outcomes. Exclusion criteria included significant ST segment changes and chest pain on initial presentation. Statistical analysis was performed using the Mann–Whitney Test, Chi-Square, and T-test.
Summary of Results: After excluding patients that required serum troponin determination (i.e. chest pain and/or significant ST changes), troponin levels

Variable	Male (n=71)	Female (n=17)	p-value
Age	67.9	67.7	0.961
Trop (+)	4.2%	7.5%	0.530
Trop (-)	95.8%	92.5%	0.530
Tobacco Use	12.7%	15%	0.826
HTN	66.2%	55.1%	0.162
DM	8.5%	16.8%	0.122
CAD	29.6%	19.6%	0.150
Hyperlipidemia	40.8%	23.4%	0.019
HgB	8.5%	2.8%	0.159
CKD	4.2%	2.8%	0.684
Arrhythmia history	28.2%	13.1%	0.019
History of CABG	8.5%	2.8%	0.159
PVD	0%	0.9%	1.00
Aortic Stenosis	0%	0.9%	1.00
PCI	9.9%	5.6%	0.379
Seizure history	2.8%	0.9%	0.564
Palpitations	2.8%	4.7%	0.704
EF	63.3%	59.7%	0.026
Arrhythmia	7.0%	5.6%	0.756
Monitored	85.9%	79.4%	0.322

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were obtained in the remaining 178 patients. Of these patients, 71 patients were male and 107 patients were female. Males had a significantly greater history of arrhythmia (p=0.019), hyperlipidemia (p=0.019), and a higher ejection fraction [63.3% compared to 59.7% in females, (p=0.026)] without any significant differences in length of stay, arrhythmia detected or monitored unit.

Conclusions: Gender has no significant impact in patients with syncope.

P15

ECCRINE CARCINOMA: AN UNUSUAL PRESENTATION

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Purpose of Study: To describe natural history and treatment response in eccrine carcinoma.

Methods Used: Observation of clinical manifestation & response to therapy.

Summary of Results: A 51-yr old came to ED with dyspnea of two days. A red painless papular lesion on the fourth digit of his right foot occurred 4 years (yrs) prior. The lesion was resected with clear margins 1 yr later & revealed eccrine carcinoma negative for estrogen, progesterone, and Her2/neu receptors by IHC. Metastasis occurred 2 yrs after diagnosis to the femoral lymph nodes, dissection was performed. 3 yrs after diagnosis, patient was treated with pleurodesis for metastases to left lung. Chemotherapy with carboplatin and taxol was initiated based on results of a chemosensitivity panel (Target Now™, Caris) on the initial tumor with stable disease. Oral capecitabine (a 5-fluorouracil prodrug) was used for maintenance. Two months after capecitabine he was admitted for dyspnea and was found to have lymphangitic carcinomatosis. Third line chemotherapy with oxaliplatin and gemcitabine was initiated. Shortly after the fifth cycle his diseased progressed. He desired additional chemotherapy and was switched to pemetrexed.

Ten days after his first dose the patient was admitted for dyspnea. A right sided pleural effusion was found on imaging. A therapeutic thoracentesis removed over 1 liter. His dyspnea persisted. He accepted hospice care and died 21 days later.

Conclusions: Eccrine Carcinoma is rare, aggressive, with few options for treatment. Due to the paucity of cases and research, there are no well-defined treatment options. Surgical resection is a common modality for initial treatment. However, eccrine tumors commonly metastasize post resection and there is little literature available about adjuvant chemotherapy. The role of chemotherapy is complex, especially in this patient who lacked expression of estrogen, progesterone, Her2neu and epidermal growth factor receptors. Due to this, there are few options for targeted chemotherapy. Caris Target Now™ is an evidence based tumor profiling service that was used to provide targeted treatment options using molecular characteristics of the initial tumor. Response with tamoxifen and cetuximab-cisplatin in eccrine ca with ER & EGFR expression leading to 2 yr CR were reported. Tumor biomarkers & targeted therapy for this aggressive disease may better outcome.

P16

BOOTCAMP 2.0: USING FITNESS & MENTORING TO IMPROVE THE LIVES OF IRAQ AND AFGHANISTAN VETERANS

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Purpose of Study: Our primary objective is to assess whether a multifaceted intervention will maintain and/or improve cardiorespiratory fitness in recently-returned OEF/OIF veterans, a population at high risk for rapid decline in physical fitness and health. The more specific objectives are to: (a) track changes in maximal aerobic capacity (VO2 max); (b) determine if the intervention will have a high participation rate; (c) determine the retention rate among participants; and (d) determine the degree to which the intervention mitigates the behavioral and mental health issues affecting participants.

Methods Used: We conducted three 90-minute steering committee meetings during which the investigators and Veteran volunteers designed an intervention to accomplish the above objectives. The intervention will include: (a) pairing each Veteran with a Veteran sponsor, a mentor/coach; (b) group meetings with both an educational and motivational focus; (c) encouraged participation in a group social media webpage with links to online fitness applications; and (d) bi-annual fitness testing of maximal aerobic capacity (VO2 max) in the applied physiology lab. Surveys at regular intervals will collect further information regarding participation in physical activity and physical and behavioral health status.

Summary of Results: Results pending initiation of Bootcamp 2.0.

Conclusions: Conclusions pending results.

P17

PLASMA CELL MYELOMA PRESENTING AS GASTROENTERITIS

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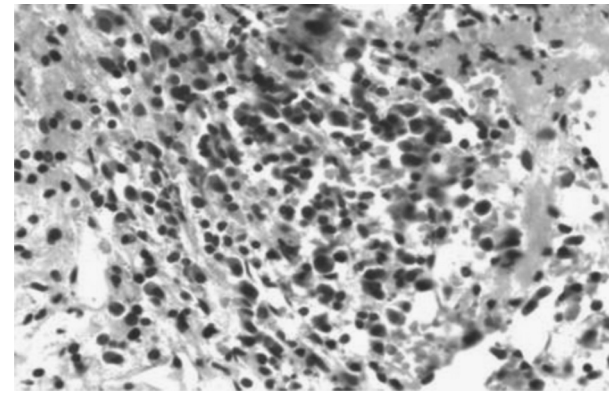
Purpose of Study: Immunologists and gastroenterologists should be familiar with plasma cell myeloma, or multiple myeloma, the second-most common hematologic malignancy in the US. It develops in 6.2 per 100,000 annually and over 77,000 Americans live with the malignancy. Patients can present with hypercalcemia, renal insufficiency, anemia and bone lesions.

Methods Used: The patient was an 83-year-old Hispanic female with a medical history of hypertension, type two diabetes mellitus and diverticulosis presenting with a complaint of nausea, vomiting, diarrhea and abdominal pain for four days. Vomiting was non-bilious and diarrhea was watery. She had 10 pounds of weight loss over the past 2 months, frequent chills and urinary hesitancy. She was diagnosed with acute gastroenteritis and acute renal failure two-months prior for similar symptoms.

Summary of Results: Physical examination revealed dry mucous membranes, pallor, generalized abdominal tenderness without rigidity, rebound tenderness or guarding. WBC count was 5 K/mm3, Hgb 9.7 gm/dL, calcium 9.8 mg/dL, TP 5.3 gm/dL and a creatinine of 7.8 mg/dL. Serum and urine protein electrophoresis produced free kappa light chains. Bone survey showed multiple punched-out lytic skull lesions. Bone marrow biopsy (BMB) revealed plasma cells with >30 % of nucleated cells, kappa and CD-138+. Kidney biopsy findings were consistent with light chain cast nephropathy.

Conclusions: Diagnosed with PCM, she was started on Bortezomib, a proteasome inhibitor, that exerts its effects through NF-κB inhibition; on cell survival pathways, such as the p44/42 MAP kinase pathway; and inhibitory effects on IL-6, TNF-α and VEGF. She also received dexamethasone, hemodialysis tri-weekly and 7 cycles of plasmaphoresis to reduce free light chains. Gastrointestinal symptoms improved with therapy. In patients with renal failure and uremic symptoms, a differential diagnosis should include monoclonal gammopathies.



BMB: Plasma cells comprising greater than 30% of nucleated cells.

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