



**Internal Medicine Residency Program
Boston University Medical Center**

Senior Resident Academic Day

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Handbook of Abstracts

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Senior Talks

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Oral Abstracts

Category: Clinical Research

Black Patients Experience Highest Rates of Cancer-Associated Venous Thromboembolism

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Purpose: Cancer patients are at higher risk of venous thromboembolism (VTE) than the general population. In the general population, Blacks are at a higher risk of VTE compared to Whites. The influence of race on cancer-associated VTE remains unexplored. We examined whether Black cancer patients are at a higher risk of VTE and whether these differences are present in specific cancer types.

Design: A retrospective study was performed in the largest safety net hospital of New England, Boston Medical Center, using a cohort of cancer patients characterized by a substantial number of non-Whites.

Results: We identified 16,498 subjects with solid organ and hematologic malignancies from 2004-2018. Among them, we found 186 unique incident VTE events, of which the majority of the events accrued within the first 2 years of cancer diagnosis. Overall, Blacks showed a 2-fold higher incidence of VTE (52.5%) compared to Whites (28.0%; p-value <0.001). This difference was observed in certain cancer types such as lung, gastric and colorectal. In lung cancer, the odds of developing VTE in Blacks was 2.77-times greater than those in White patients (CI 1.33-5.91, p = 0.007). Despite the greater incidence of cancer-associated VTE in Blacks, Khorana risk score of VTE was not higher in Blacks.

Conclusions: In a diverse cancer cohort, we observed a higher incidence of cancer-associated VTE in Blacks compared to patients from other races. This study indicates consideration of race in the risk assessment of cancer-associated VTE. It also begs for mechanistic studies to identify mediators of VTE depending on cancer type.

Category: Clinical Research

Development and Validation of a Risk Score for Predicting Cardiovascular Events in HIV-infected Patients

Styliani Karanika MD, Theodoros Karantanos MD, PhD, Herman Carneiro MD, MSc, Sabrina A. Assoumou MD MPH

Background: Human immunodeficiency virus (HIV)-infected individuals are at higher risk for developing cardiovascular disease (CVD) because of traditional and nontraditional risk factors. We aimed to develop a model to predict 10-year cardiovascular (CV) risk events for this population given that commonly used CVD risk assessment tools might not be accurate.

Methods: We conducted a retrospective cohort study of adult HIV-infected individuals seen at Boston Medical Center (Boston, MA) between March 2012 and January 2017. Patients without a prior history of traditional risk factors as well as chronic kidney disease, CV events as defined by the American Heart Association and HIV elite controllers were excluded. HIV-infected patients seen during this time period were divided into model development and validation cohorts. Logistic regression was used to create a risk model for CV events. Data from the development cohort served as inputs to the model. The relationship between risk factors and CVD risk was summarized using a point-based risk-scoring system incorporating results from logistic regression equations. This risk-scoring system predicted CV events over a 10-year period. Each risk factor was assigned points based on logistic regression equation results. Score sheets were developed to predict CV events in a 10-year follow up period and the total score ranged between 0 and 60. Areas under the ROC (AUC) curve were used to evaluate model discrimination. In addition, Cox proportional-hazards multivariable regression estimated the time-to-event for the ten dependent variables found to predict CV events. The model was subsequently tested using the validation cohort.

Results: Of 3,867 eligible HIV-infected patients, 1,914 individuals met inclusion criteria. Half of the cohort (N=957) was randomly selected for the development cohort and the remainder comprised the validation cohort. There were 256 CV events in the development cohort. Ten independent prognostic factors were incorporated into the prediction function ($P_{\text{model}} < 0.001$). The model had excellent discrimination for CVD risk [AUC: 0.94; (95% CI: 0.93–0.96)] and included the following variables: male sex (p-value < 0.001), African-American race/ethnicity (p-value=0.023), current age (p-value=0.020), age at HIV diagnosis (p-value =0.006), peak HIV viral load (p-value =0.012), nadir CD4 lymphocyte count (p-value < 0.001), hypertension (p-value < 0.001), hyperlipidemia (p-value =0.001), diabetes (p-value < 0.001), and chronic kidney disease (p-value < 0.001). The ten-parameter multiple logistic regression model also had excellent discrimination [AUC: 0.96; (95% CI: 0.89–0.99)] when applied to the validation cohort.

Conclusions: We developed and validated a risk-scoring system based on ten clinical factors that accurately predicts the 10-year risk for CV events in an HIV-infected population. This assessment tool may provide clinicians with a rapid assessment of cardiovascular disease among HIV-infected patients and inform prevention measures during the era of effective antiretroviral therapy.

Category: Oral Abstract

Whole Exome Sequencing Identifies Mutations of the Complement System in Purpura Fulminans

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Background: While sepsis is a common occurrence in setting of an infection, rare cases will be complicated by purpura fulminans. Purpura fulminans (PF) is a highly thrombotic subtype of disseminated intravascular coagulation (DIC) associated with characteristic skin findings. Due to the high mortality rate from uncontrolled thrombosis resulting in multi-organ failure, it is crucial to identify the mechanisms underlying PF. Although PF has been hypothesized to be related to protein C deficiency or inactivation, the pathophysiology remains unclear. Therefore, our study sought to determine whether an underlying genetic mechanism could predispose certain patients with sepsis to develop PF.

Methods: We used whole exome sequencing to compare the rates of rare (MAF <2%) potentially deleterious non-synonymous germline mutations between 18 patients with a history of PF and 87 patients with a history of uncomplicated sepsis.

Results: Among patients with PF, 17/18 (94.4%) of patients had at least one nonsynonymous rare mutation affecting the complement system, compared to 47/87 (54.0%) of patients with uncomplicated sepsis (P=0.0007 by Fisher's exact test). By contrast, no significant differences were found between the two groups in the proportions of rare synonymous (silent) variants in the complement system (P=0.25). Additionally, patients with PF did not harbor a higher proportion of rare non-synonymous variants in the coagulation system than patients with uncomplicated sepsis (P=0.73) or in a randomly selected similarly-sized set of genes (P=0.35).

Conclusions: Rare loss of function mutations in the complement system represent a congenital risk factor for PF and may represent a direct link between immunity and coagulation. Further studies will be needed to elucidate the mechanism of this connection.

Category: Basic Research

Exome sequencing of brain metastases from colorectal primary cancers reveals clinically actionable mutations

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Boston Medical Center and Massachusetts General Hospital

Background: Current understanding of the underlying genetic evolution in metastatic colorectal cancer to the central nervous system is lacking. Further, there are no specific treatments for brain metastasis derived from gastrointestinal primary malignancies. Here, we report preliminary data using a next generation sequencing approach to characterize actionable genomic targets in matched colorectal primaries and their associated extra- and intra-cranial metastases.

Methods: A growing cohort of metastatic colorectal cancer is being assembled that consists of a primary tumor, at least a single extracranial metastasis, an intracranial metastasis, and a paired normal blood control for each patient. Nucleic acid was extracted for use in whole exome sequencing from twelve samples. Somatic variants in the primary tissue were identified relative to the matched control sample and further compared relative to the metastatic samples. Initial analysis has focused on cancer genes that have been established to have clinical implications to identify variants with potential therapeutic value.

Results: Complex variant signatures were found across the primary colorectal tumors. At least one clinically actionable variable was identified in each case. Alterations in *AKT1*, *POLE*, *BRAF* and *GNAS* were detected in the brain metastasis samples and not in the extracranial sites. Alterations in *GNAS*, *ARID1A*, *RET*, and *FGFR2* occurred at a higher frequency in metastatic samples (extra-cranial and brain metastases) compared to primary. *KRAS* and *PIK3CA* status was concordant across all tumors while *PTEN* and *BRAF* status was variable.

Conclusions: Clinically actionable mutations can be found in brain and extracranial metastases that are not detected in their respective clinically sampled colorectal primary tumor. This provides support for the development of combined targeted therapeutic strategies that may be more successful in the metastatic setting. Further investigation is required in larger cohorts to fully characterize the genetic landscape and potential drivers of brain metastasis from colorectal cancer.

Category: Clinical Research

Diabetes Care Cascade in Thailand

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Background: Diabetes is a growing challenge in Thailand. Data with which to assess the health system response to diabetes is scarce and it is unclear to what extent universal health coverage has translated into high quality healthcare for Thai people living with diabetes.

Methods: We conducted a retrospective cross-sectional analysis of the 2014 Thai National Health Examination Survey. Diabetes was defined as fasting plasma glucose ≥ 126 mg/dL or on treatment. National and regional care cascades were constructed to identify gaps in care across the stages of screening, diagnosis, treatment, and control. Unmet need was defined as the total loss across cascade levels. Continuation ratio logit regression was used to examine the socio-demographic and healthcare factors associated with attrition across the diabetes care continuum.

Findings: A total of 15,678 patients were included. Among Thai adults aged 20 and above with diabetes, 67.3% were screened, 34.6% were diagnosed, 33.9% were treated, and 26.3% were controlled, implying that 73.7% had unmet need. There was substantial regional variation, with unmet need ranging from 78.2 in Northeast region to 56.9% in Bangkok. Multivariable models showed that unmet need for care was significantly associated with age, sex, and measures of health care access.

Interpretation: Substantial attrition in the diabetes care continuum was observed at diabetes screening and diagnosis. Younger age and lower density of medical staff reduced the likelihood of receiving a diabetes diagnosis while being female and lower density of health centers was associated with an increased likelihood of uncontrolled diabetes.

Poster Presentations

Category: Clinical Research

Economics of Vaccination of Patients in a Hospital-based Gastroenterology Practice

Manisha Apte, MD, Jason Reich, MD, Toni Zahorian, PharmD, Bhavesh Shah, RPh, Francis A. Farraye, MD MSc

Introduction: Patients with inflammatory bowel disease and chronic liver disease are at increased risk for vaccine preventable illnesses. Barriers to vaccination include resource availability. We explored the economics and logistics of vaccinating patients in our outpatient gastroenterology practice at Boston Medical Center (BMC).

Methods: We conducted a chart review of 913 vaccinations administered in our gastroenterology practice from 01/01/2017 through 12/31/2017. We identified patients who received Influenza, Hepatitis A (HAV), Hepatitis B (HBV), Prevnar (PCV13) and Pneumococcal (PPSV23) vaccines. We analyzed payer breakdown and reimbursement for the vaccine and its administration.

Results: We identified 11 payers that covered one or more of the 913 vaccines during the study period. Eighty-five percent of the total charges were reimbursed by insurance while 15% was absorbed by the hospital. Of the 913 vaccines, HBV was the most frequently administered (30.8%), followed by PCV13 (19.9%), PPSV23 (16.6%), Influenza (16.4%) and HAV (16.2%). The most common payer was Mass Health, while 54.3% of patients were covered by government-funded plans (Mass Health and Medicare). We found no difference amongst plans in covering individual vaccines, although vaccines for HAV, influenza, PCV13 and PPSV23 were all under-reimbursed based on our acquisition cost. A \$58 RN administration fee was charged for each visit but more than 50% of this billed service was not reimbursed.

Discussion: We successfully administered over 900 vaccinations in 2017. The hospital was not reimbursed for 15% of the vaccine charges and 50% of nursing administration charges. An alternative source to mitigate this financial hurdle can be to refer patients to a pharmacy, as it has standing vaccine orders with no cost sharing for the patient, convenient access and ample capacity to administer vaccines. Our review highlights the high volume and diversity of patients who, if not vaccinated in the office with direct observation of administration of vaccine, would benefit from a pharmacy referral. Patient non-adherence remains a risk of using local pharmacies. Our analysis sheds light on the fiscal challenges of providing vaccines in a hospital-based outpatient practice. Practices that see a similar patient panel but do not stock vaccines or cannot absorb high costs can consider retail or on-site institutional pharmacies for easy access and timely vaccine administration.

Category: Education / Quality Improvement

Use of the Standardized Evaluation Tool to Assess Procedural Competencies

Dimitri Belkin MD, Chris Huang MD, Sharmeel Wasan MD

Introduction: Procedural training and education has shifted from an apprenticeship model towards a milestone-based approach for evaluating trainees. One important benefit is the ability to assess fellows' hands-on and cognitive procedural skills. At Boston University, gastroenterology fellows are evaluated by attendings using the standardized ACE evaluation tool. We propose there is utility of a virtual simulator in supplementing this observational data with objective measurements. Such as: time to complete procedure, visualization of anatomy, successful intubation of cecum, and patient discomfort.

Methods: Our goal was to compare this data to similar questions on the ACE tool at different points in time and see if there was a concordant change in both as fellows progressed in their training. We would also use a Likert scale (1= very uncomfortable, 5= very comfortable) to rate confidence in endoscopic skills, as well as open-ended interview questions regarding the strengths and weaknesses of using a simulator in their training.

Results: Preliminary ANOVA analysis for 10 of the 13 ACE questions showed that we were unable to reject the null hypothesis when comparing all junior fellows amongst themselves, and 40% of the time when comparing senior fellows.

Discussion: While widely accepted as evaluation tools, the current standardized approaches to evaluating fellow' progress and areas for improvement rely on subjective data. There is a potential for use of a high-fidelity simulator to both supplement this observational data and improve comfort and confidence with procedures.

Category: Quality Improvement / Education

A Masquerading Case of Endocarditis

Caitlin Bove, MD

Case: A 22-year-old male with no significant past medical history presented to the emergency department with approximately one week of chest pain, cough, subjective fevers, chills and dyspnea on exertion. Physical exam was notable for a mildly elevated JVP, scattered rhonchi bilaterally, a III/VI systolic murmur heard best at the right upper sternal border and water hammer femoral pulses with pistol shots. In addition, he had a Quincke's pulse. Labs were significant for a white blood cell count of 15.6 K/UL, troponin I 3.1 ng/mL, ESR 70 mm/hr, CRP 246 mg/L. Urine toxicology screen was negative. EKG demonstrated normal sinus rhythm with an incomplete right bundle branch block, LVH and diffuse ST depressions. Initially, the patient was treated for presumed myocarditis thought to be secondary to an upper respiratory tract infection. The patient had recently immigrated from El Salvador and was unable to provide any further history about the presence of a previous cardiac murmur or any other past medical history. A transthoracic echocardiogram was performed and demonstrated aortic valve endocarditis, aortic leaflet perforation and severe aortic regurgitation. Blood cultures grew streptococcus mitis which was thought to be from an oral source as the patient had multiple decaying teeth. Cardiothoracic surgery was swiftly involved and the patient underwent a mechanical aortic valve replacement. He tolerated the procedure well and following received a total of 6 weeks of IV antibiotics with ceftriaxone.

Discussion: This case highlights the importance of the physical exam in the early identification of severe aortic insufficiency. This patient had a Quincke's pulse which is an alternating of blanching and flushing of the nail beds occurring with the cardiac cycle. This is a finding associated with severe aortic regurgitation. It occurs due to the widened pulse pressure generated from a large stroke volume with a rapid fall in arterial pressure from valvular insufficiency. In addition, this patient also had a "water hammer" femoral pulse with pistol shots. Again, this is highly associated with aortic regurgitation and occurs from the rapid rise and sudden collapse of the femoral artery that happens with insufficiency. While these signs have overall low sensitivity in identifying all cases of aortic regurgitation, when present they can lead to earlier suspicion and identification of valvular abnormalities.

Category: Quality Improvement and Education

Stumbling Into Wernicke's Encephalopathy: Clinical Features and Management

Herman Carneiro, Amy Fitzpatrick

Learning Objective:

1: Recognize and treat Wernicke's encephalopathy appropriately

Case: A 41-year-old German man with no significant past medical history presented after a general tonic-clonic (GTC) seizure whilst on a business trip. Upon arrival to the emergency room (ER), he was tachycardic at 120 bpm and hypertensive at 155/78 mmHg. Physical examination was notable for diaphoresis, tremulousness, and hyperreflexia. Notable blood tests: Plts 97 K/UL, AST 158 U/L, ALT 88 U/L, ALP 74 U/L. Computed tomography scan of the head showed no acute process. In the ER, the patient had another GTC seizure and was treated for presumed alcohol withdrawal. Of note, he denied a history of alcohol abuse, withdrawal seizures, or recreational drug use. His last drink was 1 hour prior.

In the intensive care unit, he was treated with a lorazepam infusion and intermittent doses of phenobarbital. He also received thiamine 500 mg intravenously (IV) three times a day for 5 days, then 250 mg IV daily for one day prior to transfer to the floor. After transfer, his thiamine was decreased to 100 mg orally twice a day. The patient subsequently deteriorated markedly with development of altered mental status (AMS), tremulousness, nystagmus, and ataxic gait. He was diagnosed with Wernicke's encephalopathy (WE) and thiamine was uptitrated to 250 mg IV daily. The patient improved rapidly with complete resolution symptoms within 24 hours. Thiamine 250 mg IV was continued for 4 days after which he was discharged on oral thiamine 200 mg daily.

Impact: WE is under recognized and can present with a variety of symptoms. It is a medical emergency necessitating immediate intravenous or intramuscular thiamine. Thiamine must be given prior to dextrose administration. Dose reductions should not be made if any neurological symptoms are present. If symptoms develop after a dose reduction, thiamine should be uptitrated immediately. Transition to oral maintenance thiamine should only be made once patients are back to their neurological baseline.

Discussion: WE is an acute, potentially reversible, neuropsychiatric syndrome caused by a deficiency in thiamine. Left untreated, WE can lead to permanent brain damage and even death. A combination of poor diet, increased thiamine use to metabolize the high carbohydrate and caloric content of alcohol, and low thiamine stores in damaged livers can lead to depletion of total body thiamine stores in 2-3 weeks and precipitate WE. The classic triad of nystagmus and

ophthalmoplegia, AMS, and gait ataxia is only present in 15% of patients. Other presentations include stupor, hypotension, papilledema, seizures, hearing loss, and hallucinations. Late stage symptoms include hyperthermia, hypertonia and spastic paresis, choreic dyskinesias, and coma. The recommended thiamine repletion regimen is 500 mg IV three times a day for 3-5 days, followed by 250 mg IV once a day for 3-5 days. Patients may transition to maintenance oral thiamine 100 mg to 250 mg daily once they are back to their neurological baseline.

Category: Clinical Research

Plasma vitamin D, past chest illness, and longitudinal risk of future chest illness in chronic spinal cord injury

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Introduction/Rationale: Patients with chronic spinal cord injury (SCI) are at increased risk of respiratory illnesses and vitamin D deficiency/insufficiency, and lower vitamin D levels have been shown to be associated with an increased risk of respiratory illness. We conducted a prospective, longitudinal study to assess the relationship between plasma vitamin D and other factors with chest illness in SCI patients.

Methods: Between 8/2009 and 8/2017, 253 participants with chronic SCI were followed over a mean (SD) of 3.4 (1.7) years (max=7.4 years). At each visit, plasma 25-hydroxyvitamin D level was obtained, a respiratory questionnaire and spirometry were completed, and participants reported chest illnesses that kept them off work, indoors at home, or in bed since the last visit. Repeated measures negative binomial regression was used to assess chest illness risk longitudinally.

Results: Chest illnesses (n=106) were reported by 60 participants. At entry, vitamin D levels were deficient (<20 ng/mL) in 25.3%; insufficient (20 to <30 ng/mL) in 51.8%, and sufficient (≥ 30 ng/mL) in 22.9%. There was no association between vitamin D level (p=0.63-0.96) with chest illness risk. A previous chest illness one year (RR=3.83; 95% CI=1.96, 7.50) or three years (RR=3.26; 1.75, 6.09) before study entry were the strongest predictors of future chest illness in addition to reduced pulmonary function.

Conclusion: Assessed prospectively in chronic SCI, previous chest illness history and reduced pulmonary function were associated with chest illness risk but vitamin D level was not.

Category: Case-vignette

Ciprofloxacin crystal induced nephropathy: A Rare Adverse Effect

Shaleen Chakyayil

Introduction: Ciprofloxacin is a commonly used antibiotic in both primary care and inpatient settings. This medication can rarely induce a crystal nephropathy when ciprofloxacin crystals precipitate in the renal tubules causing obstruction. Few cases have been reported in the literature. In cases where renal biopsies were obtained, birefringent crystals were seen in the tubules.^{1, 2, 4} In one case, birefringent crystals were seen in a brown and yellow colored conglomerate that was present in the urine sediment.³

Case description: An 82 year old man initially presented to the ED with 5 days of diarrhea after returning from travel. Labs revealed a normal CBC and CMP and a CT scan showed sigmoid colitis. He was sent home with conservative management. He then presented to an urgent care appointment three days later with persistent diarrhea. BMP was normal with BUN 10 and Cr 0.9. He was prescribed ciprofloxacin for the diarrhea.

Three days later, he was brought to the ED by family because although the diarrhea had improved, he was noted to be lethargic with low appetite and anuria. Labs showed BUN increase to 34 and Cr increase to 7. CK was normal. Renal ultrasound was normal. Urine pH was 5.0. The patient was given fluid boluses without improvement in Cr. Evaluation of urine sediment was delayed as patient remained anuric for 2 days. When urine was obtained, the sediment showed possible ciprofloxacin crystals with a brown and yellow conglomerate. Birefringence was not checked. No cellular casts or muddy brown casts were seen.

The patient had a temporary HD line placed and required two sessions of dialysis for his uremic symptoms after which his creatinine stabilized and his urine output increased. Renal biopsy had been initially considered but deferred as he appeared to be improving. Unfortunately, the patient then became bacteremic secondary to his line and subsequently died from complications of endocarditis.

Discussion: Risk factors identified in previous cases for developing crystal nephropathy include older age, concomitant use of ACE-I, and low BMI.¹ This patient had the former two risk factors. Previous data had suggested ciprofloxacin only crystallizes when pH >6.8 and would be unlikely to occur in humans, however several cases have documented occurrence when urine pH was 4.5 - 6.5.⁴ Similarly this patient's urine pH was 5.0. Although crystal nephropathy is a rarely seen with ciprofloxacin administration, considering how often this antibiotic is prescribed, providers should be aware of this potential adverse effect.

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Category: Quality Improvement / Education

Embollic Stroke in an Anticoagulated Patient with Atrial Fibrillation

Authors:

Cheng Ding, MD; Michael Dennis, MD; Ashley Tran, MD and James Hudspeth, MD

Case: A 54-year-old male with history of chronic kidney disease, hypertension, permanent atrial fibrillation on warfarin presented with transient word finding difficulty and left lower extremity numbness. These symptoms self-resolved a few minutes after onset. On arrival, his neurologic exam was unremarkable. A CT head without contrast showed no acute pathology. His INR was 2.95 and was stable over the last several months. His troponin peaked at 3.85, but he denied any chest pain and had no changes in his baseline ECG. There was concern for cerebral and coronary embolism given the temporal relationship of his neurologic symptoms and troponinemia. This hypothesis was further supported by an MRI which showed multiple embolic foci scattered throughout the left cerebral hemisphere and right occipital lobe. A trans-esophageal echocardiogram showed significant thrombus in the left atrial appendage, suggesting the presence of an occult thrombus. The decision was made to restart his anticoagulation immediately with a new INR goal of 2.5 to 3. The patient was discharged one week after admission and had no subsequent embolic or hemorrhagic events.

Discussion: Our patient suffered thromboembolic events despite having a therapeutic INR. While anticoagulation failures are rare, embolic stroke should always be considered in patients with atrial fibrillation who report neurologic symptoms regardless of their anticoagulation status. Suspicion should be heightened if there are concomitant signs of ischemia in other organs.

Management of anticoagulation for our patient was particularly challenging as the risk for recurrent embolic events in the presence of a left atrial thrombus had to be weighed against the risk of hemorrhagic stroke transformation. Currently, there is little consensus on the appropriate timing of anticoagulation after embolic stroke. The American Stroke Association recommends starting anticoagulation within two weeks, but longer intervals are necessary for patients with large infarcts or uncontrolled hypertension. The recommendation does not specify how soon to initiate therapy within the two week period. Furthermore, there are no guidelines for secondary stroke prevention when a patient is adequately anticoagulated at the time of stroke. The use of higher intensity warfarin for an increased target INR goal of 2.5 to 3.5 has been studied, but there is little data to confirm the effectiveness and safety of this practice. Therefore, we feel more research is needed to standardize the acute and chronic management of patients with atrial fibrillation who suffer embolic strokes despite optimal anticoagulation.

Category: Clinical research

Association of Lung Diffusion Capacity with Cardiac Remodeling and Risk of Heart Failure in the Community

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Background: Lung function abnormalities are ubiquitous in patients with heart failure (HF). It is unclear, however, if abnormal lung diffusion capacity antedates HF, or if it is associated with cardiac remodeling patterns that presage HF risk in the community. We hypothesized that lower lung diffusion capacity for carbon monoxide (DLCO) is associated with worse left ventricular (LV) systolic and diastolic function cross-sectionally, and with higher risk of HF prospectively.

Methods: We evaluated 2439 Framingham Study Offspring participants (mean age 66 years, 55% women) who were free of HF and underwent standardized echocardiographic and pulmonary function tests at a routine examination cycle (2005-2008). We used multivariable regression models to assess the cross-sectional relations of DLCO and forced expiratory volume in 1 second (FEV1) with left ventricular ejection fraction (LVEF), LA emptying fraction (LAEF), E/e', left atrial end-systolic diameter (LAD), and LV mass. Multivariable Cox proportional hazards regression was also used to relate DLCO to incident HF.

Results: Adjusting for age, sex, height and smoking, DLCO (mL/min/mmHg) and FEV1 (L) were associated positively with LVEF ($\beta_{\text{DLCO}}=0.19$ and $\beta_{\text{FEV1}}=0.019$ per 5% increment; both $p<0.01$) and LAEF ($\beta_{\text{DLCO}}=0.89$ and $\beta_{\text{FEV1}}=0.080$ per 5% increment; both $p<.0001$) but inversely with E/e' ($\beta_{\text{DLCO}}=-0.30$ and $\beta_{\text{FEV1}}=-0.044$ per SD; both $p<0.001$). Higher FEV1 was associated with lower LAD ($\beta_{\text{FEV1}}=-0.049$ per 1 cm increment, $p=.003$) and LV mass ($\beta_{\text{FEV1}}=-0.052$ per 50-gram increment, $p<.0001$). DLCO was inversely related to HF risk (90 events, median 8-year follow-up; multivariable-adjusted hazard ratio 0.90 per SD, 95% CI 0.85-0.95). These results remained robust when analyses were restricted to non-smokers.

Conclusions: Our observations on a large community-based sample of individuals free of overt HF are consistent with the concept that subclinical alterations in DLCO may antedate HF by over a decade. Additional studies are warranted to confirm our findings in multiethnic samples and to evaluate the utility of pulmonary function testing as a potential predictive test for HF risk.

Category: Clinical Research

Airway Stenting for Respiratory Failure Secondary to Obstructive Vascular Anomalies

JK Chung, A. Folch Sandoval, JF Santacruz, A Majid

Introduction: Enlargement of vascular structures abutting an airway can lead to airway compression with subsequent obstruction and respiratory failure. In the past, a relative contraindication for airway stents was external compression by a vascular structure given concern for erosion of the airway and vessel wall leading to the development of vascular-bronchial fistulas, hemorrhage, and death.

Methods: We retrospectively reviewed cases from 3 institutions and identified 7 patients who underwent 8 procedures of airway stenting for extrinsic airway compression attributed to vascular anomalies. All patients had relative or absolute contraindications for immediate surgical interventions. Every patient underwent standard informed consent with discussions on other potential management options. Given the high complexity of these cases, management decisions were reviewed by multidisciplinary teams involving vascular surgeons, thoracic surgeons, interventional pulmonologists and thoracic radiologists.

Results: A total of 7 patients with a median age of 63 years (range 44-82) underwent 8 separate airway stenting procedures for obstructive vascular anomalies. Five patients were on mechanical ventilation at the time of evaluation and had difficulties with liberation from mechanical ventilation. Five of the 7 patients were on mechanical ventilation on initial evaluation. Of these, only one required ventilation on discharge which solely entailed nocturnal support through a tracheostomy. The median length of time stents were in place was 56 days, (range 3-150 days). Four patients underwent definitive vascular surgery or endovascular repair of their vascular anomaly. All 7 patients survived to discharge.

Discussion: Definitive vascular surgery is the standard of care; however, management options for non-surgical candidates are not well established. Our results suggest that airway stenting in patients who are not surgical candidates and have a vascular anomaly obstructing the airway is safe and can lead to clinically significant improvement. In our series, airway stenting was useful both as a bridge for definitive vascular surgery as well as a palliative measure that allowed liberation from mechanical ventilation.

Conclusions: In our series, the use of silicone stents was safe and effective in patients with vascular anomalies compressing the central airways who are not candidates for definitive vascular surgery. These procedures should be performed by experienced advanced bronchoscopists only after assessment by a multidisciplinary team.

Category: Clinical Research

Day 5 Peripheral Blood Leukocyte Count Predicts In-Hospital Mortality In Patients With Acute Myeloid Leukemia Undergoing Induction Chemotherapy

Teja Ganta, MD

Introduction: The mainstay of initial therapy for acute myeloid leukemia (AML) is chemotherapy using cytarabine plus an anthracycline, aiming at maximal and rapid destruction of tumor cells [1]. The present study intends to correlate the efficiency of chemotherapy-induced leukopenia to in-hospital mortality.

Methods: Data was compiled from MIMIC-III, a database of admissions to intensive care units (ICU) at Beth Israel Deaconess Medical Center in Boston, MA between 2001-2012 [2]. ICD9 codes were used to select for admissions with a diagnosis of AML, which were filtered for patients undergoing chemotherapy with cytarabine plus an anthracycline. The Mann-Whitney-U test compared median peripheral white blood cell (WBC) counts on days 1 through 5 of chemotherapy between admissions with or without in-hospital mortality. A logistic regression model related in-hospital mortality to age, gender, insurance, day 1 WBC, and day 5 WBC. A Receiver Operating Characteristic (ROC) curve identified a specific cutoff value with corresponding sensitivity and specificity values for day 5 WBC count to predict in-hospital mortality.

Results: 78 patients are included in the study. Median WBC counts between patients with or without in-hospital mortality is statistically significant on day 5 (1.3 K/uL vs. 0.7 K/uL, $W = 472.5$, $p\text{-value} = 0.011$). Corresponding values for days 1-4 are non-significant. A multiple logistic regression model controlling for day 1 WBC count, age, gender, and insurance status affirms that day 5 WBC count correlates with in-hospital mortality (OR= 1.23, 95% CI 1.02-1.47). A ROC curve developed from a simple logistic regression using only day 5 WBC count shows an area under the curve (AUC) of 0.67. Optimal cutoff value to predict in-hospital mortality is 0.33 K/uL (sensitivity = 63.3%, specificity = 64.6%).

Discussion: Higher day 5 WBC count correlates with in-hospital mortality. This is in accord with current understanding that suboptimal response to chemotherapy is associated with poorer prognosis. However, clinicians may use information specifically on day 5 to facilitate earlier goals of care conversations or escalate level of nursing care if clinically indicated.

References:

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Category: Clinical Research

Proportion of Sexually Transmitted and Blood-Borne Infections among Patients Presenting to a Low-Barrier Substance Use Disorder Medication Clinic

Leah Harvey, MD, MPH; Jessica Taylor, MD; Sabrina Assoumou, MD, MPH; Jessica Kehoe, RN; Ryan Perera; Elissa Schechter-Perkins, MD, MPH; Edward Bernstein, MD; Alexander Y. Walley, MD, MSc

Background: In the midst of escalating overdose deaths, new low-barrier to access programs (LBAP) have emerged to rapidly link people with substance use disorders (SUD) to addiction treatment, including medication. However, the role of LBAP in addressing infectious complications of SUD, including sexually transmitted and chronic blood-borne infections, remains uncertain.

Objective: To determine the proportion of syphilis, chlamydia, gonorrhea, HIV, and both acute and chronic hepatitis C (HCV) and hepatitis B (HBV) among patients with SUD establishing care at a LBAP. This study also evaluates the proportion of individuals successfully linked to care, defined as attendance of a referral appointment.

Methods: A retrospective chart review was performed of patients who completed an intake at an LBAP in Boston, MA between 1/1/2017-9/1/2017.

Results: Of 421 patients who completed intake, 225 (53.4%) reported injection drug use. Participants reported high rates of known chronic viral infection including HIV (n = 8, 1.9%), chronic HCV (n = 112, 26.6%), and chronic HBV (n=2, 0.5%). One quarter (n=99, 23.5%) were HBV non-immune. Among those screened, 56 new infections were identified, including 1 HIV (0.3%), 3 syphilis (1.1%), 2 gonorrhea (0.8%), 3 chlamydia (1.2%), 1 chronic and 1 acute HBV (0.7%), and 45 active HCV (14.8%). Among the 8 bacterial infections, 7 (87.5%) were treated. Among 48 new viral infections, 0 HIV (0.0%), 2 HBV (100.0%), and 13 HCV (28.9%) were linked to care.

Conclusions: The observed proportions of both bacterial and chronic viral infections support the inclusion of comprehensive infection screening and linkage-to-care algorithms in the LBAP setting. LBAP offer new opportunities to expand HBV vaccination, HIV pre-exposure prophylaxis (PrEP), and HCV treatment among people who inject drugs.

Category: Quality Improvement Research / Education

Reducing Isolation: Re-screening inpatients for MRSA infection

K Hlebowitsh MD, L Caruso MD, C Sulis MD, D Whalen ANP, K Corn RN, A Diranian NP

Background: Methicillin-resistant *Staphylococcus aureus* (MRSA) is a leading nosocomial infection transmitted via skin-to-skin contact. Some hospitals, including Boston Medical Center (BMC), have implemented policies to isolate MRSA-colonized patients under “contact precautions.” At BMC, this means that providers must wear a gown and gloves with each patient contact, and that patients must be in a single-patient room. Although many patients become colonized with MRSA, an estimated 30% of these patients clear the infection¹. This creates an opportunity cost of \$6.4 million per year². At BMC, there is no procedure for re-screening patients for clearance of MRSA colonization.

Aim Statement: To re-screen 100% of eligible inpatients on MRSA precautions at BMC by May 2019

Methods: A multidisciplinary team of physicians, nurses, and infection control staff was assembled to achieve the stated aim. BMC Infection Control guidelines for MRSA precaution removal were reviewed. Multiple PDSA cycles were performed with manual review of eligible patients and ordering of appropriate tests. Using the information from these PDSA cycles, an order set was designed to automatically detect patient eligibility and order the appropriate tests if indicated. Although this full order set was not ultimately approved by IT, a basic order set was created. PDSA cycles testing this basic order set are ongoing.

Results: 25% of MRSA-positive patients (n=4-8 per day, total 32 over two weeks) on Menino 6 West were able to have their precautions removed. This is comparable to the proportion found in the literature. 75% re-screened positive for MRSA. The MRSA precaution removal process required 5 days due to the time needed for culture data to result. Completion of the full MRSA re-screening process improved from 0% to 100% with inclusion of project explanation at nursing morning huddles on inpatient floors.

Conclusions: Instituting a procedure to re-screen patients for MRSA would reduce the number of patients requiring contact isolation for MRSA by 25%. This could result in opportunity cost savings of over \$6 million per year. Current barriers to re-screening include number of clicks required to place appropriate orders, nursing/physician education, and complexity of eligibility rules. An order set now exists in EPIC to address the first barrier. We plan to develop additional PDSA cycles to test this order set and educate providers about its use. We hope to eventually implement the fully automated order set which would eliminate all three barriers.

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Category: Clinical Research

Abnormal Left Atrial Mechanics Predict Incident Atrial Fibrillation in AL Cardiac Amyloidosis Following Autologous Stem Cell Transplantation

Graham Lohrmann, MBBCH, Monica Arun, MD, Vaishali Sanchorawala, MD, Frederick L. Ruberg, MD, Deepa M. Gopal, MD, MS

Background: Incident atrial fibrillation is a common complication following stem cell transplantation (SCT) in patients with AL amyloidosis. Abnormal left atrial (LA) mechanics with resultant electromechanical dissociation are hypothesized to predispose to the development and be predictive of incident atrial fibrillation. LA strain analysis represents a novel tool to assess LA mechanics and was evaluated to see if it would be predictive of atrial arrhythmia in this cohort

Methods: Baseline echocardiograms were analyzed for atrial strain (TomTec, Unterschleissheim, Germany) from a retrospectively identified cohort of 91 patients with AL amyloidosis in normal sinus rhythm undergoing autologous SCT, 12 of which developed incident atrial fibrillation after transplant. Differences between the groups were determined using non-parametric two-sample Wilcoxon testing

Results: There were no significant differences in standard echocardiographic parameters, namely LVEF (62% vs 62%, $p=0.8$), LAVI (40 vs 34 mL, $p=0.32$), diastolic dysfunction grade (Grade III in 8 vs 25%, $p=0.27$) or biomarker stage (Stage III in 15 vs 25%, $p=0.59$). In the subgroup of patients with cardiac amyloidosis (CA), left atrial mechanics were significantly reduced in patients who developed atrial fibrillation (Figure)

Conclusion: Abnormal LA mechanics are predictive of the development of incident atrial fibrillation in AL CA after SCT

Category: Quality Improvement / Education

Charcot-Marie Tooth Disease

Rand Nashi MD

Charcot-Marie-Tooth is an exceedingly rare neurologic disease, manifested by polyneuropathy in unusual patterns. It is also unusual to see Charcot-Marie-Tooth presenting at later age, as difficulties with ambulation and other activities typically prompt earlier medical attention. This case vignette describes a new diagnosis of Charcot-Marie-Tooth in a middle-aged gentleman who arrived as a refugee from Syria, thus for the first time allowing specialized medical attention that helped elucidate the disease. This poster will outline this patient's presentation and highlight key features that should prompt clinicians to consider Charcot-Marie-Tooth in patients with unusual neuropathic presentations.

Category: Quality Improvement / Education

Trust your gut

Obas, Vanessa

Learning Objectives: To highlight the impact of premature diagnostic closure on physician decision-making. To recognize the limitations of Computed Tomography as a diagnostic tool for acute mesenteric ischemia.

Case: A 63 year-old man with paroxysmal atrial fibrillation (on apixiban), heart failure with reduced ejection fraction, hypertension, hyperlipidemia, and type II diabetes presented with severe abdominal pain, nausea, and vomiting for three days. The initial evaluation was significant for atrial fibrillation with a rate of 132 and a temperature of 102.2 °F. Laboratory studies were significant for a lactate 3.3 mmol/L and white blood cell count of 9.8 K/L. The physical exam was remarkable for only mild, diffuse abdominal tenderness to palpation, and an irregularly irregular heart rhythm. A contrast agent-enhanced Computed Tomography (CT) of the abdomen was remarkable for mild wall thickening of the small bowel suggestive of enteritis, which prompted treatment with levofloxacin and metronidazole.

The patient remained in atrial fibrillation with rapid ventricular rate and increasingly worsening abdominal pain. Still, the admitting team continued antibiotics for treatment of bacterial enteritis given the patient's fever and imaging findings. After two hospital days, the patient's abdominal pain dramatically worsened and his lactate level continued to rise. Given the deterioration in his clinical status, CT imaging was repeated and there was interval worsening of the bowel wall thickening and opacification of the superior mesenteric artery suggestive of thrombus. He was taken emergently to the operating room; 6.5 feet of necrotic bowel was resected and a thrombectomy was performed. The following day, the patient sustained a cardiac arrest and resuscitative efforts were unsuccessful.

Discussion: The initial working diagnosis of enteritis was accepted in large part due to heavy reliance on the radiologist's interpretation of the initial imaging. CT has become increasingly accepted as an appropriate diagnostic tool for acute mesenteric ischemia (AMI). In the case of AMI, CT has nearly 90% sensitivity with good technique and interpretation. With IV contrast, the arterial and venous phases can be adequately visualized, and a defect in mesenteric vessels seen on CT is highly specific (94-100%) but not sensitive (12-15%) for AMI. (Kirkpatrick, 2003) Instead, bowel wall thickening, which was identified on this patient's imaging is highly sensitive (85-88%) for AMI (Akira, 2009). Thus, CT can be highly diagnostic but it requires the proper interpretation of the images. Although imaging results can seem more robust than history and physical examination, this case illustrates the limitations of CT imaging in the diagnosis of AMI and more importantly, the responsibility of the clinician to adequately consider reasonable alternatives before accepting the initial diagnosis.

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Category: Clinical Vignette

A Case of Acute Kidney Injury in Nephrotic Syndrome: Anti-PLA2R Positive Minimal Change Disease

Pak, Luke

Learning Points:

1. Acute Kidney Injury in Nephrotic Syndrome should prompt the consideration for Minimal Change Disease.
2. Utilize anti-PLA2R testing in differentiating causes of nephrotic syndrome
3. Highlight the potential for false-positive anti-PLA2R, especially using the traditional ELISA method in most clinical laboratories.

Case: A 72-year-old male with past medical history of vocal cord squamous cell cancer, hypertension, non-insulin-dependent diabetes mellitus, coronary artery disease and chronic kidney disease (baseline creatinine 1.2mg/dL) was referred for admission after his primary care provider noted a sharp increase in his serum creatinine to 2.63mg/dL, from two months prior, consistent with acute kidney injury, concurrent progressive new onset lower extremity edema and 20lbs weight increase over 2 weeks, but without other cardiopulmonary symptoms. He denied urinary symptoms and had no recent changes to his medications but did report years of weekly regular use of NSAIDS for knee arthritis prior to activities. His admission workup revealed a spot urine protein-to-creatinine ratio consistent with proteinuria of >10g/d, hypoalbuminemia of 2.8g/dL, and urinalysis with microscopy with an isolated 3+ proteinuria. Diuretics had been prescribed by his PCP for the lower extremity edema and complicated a FENa interpretation, but FEUrea was 12.2% suggestive of pre-renal etiology. A renal ultrasound performed on admission was not revealing for hydronephrosis or post-obstructive etiology and without comment of medicorenal disease or nephrosclerosis. He was treated with further diuresis during his admission for nephrotic syndrome with concurrent acute kidney injury. His anti-nuclear antibodies and chest radiograph were not revealing; HIV, Hepatitis B and C serologies were non-reactive; free light chain ratio, serum and urine EP/IFE were non-revealing for monoclonality; his serum C3/C4 were found within the normal range; his urine sediment revealed further evidence for nephrotic syndrome with oval fat bodies, hyaline casts and a few renal tubular epithelial cells (RTECs) without RBC casts or muddy brown casts seen. His course was complicated by increasing creatinine to 4.6mg/dL, however, he avoided oliguria or severe metabolic derangements. Given his NSAID use history, minimal change disease (MCD) was suspected. While arrangements were made for a renal biopsy, he briefly did suffer flash pulmonary edema, which called into question combined nephritic/nephrotic syndrome, but he quickly recovered with increased diuresis. Before his biopsy was performed, a serum anti-Phospholipase A2 Receptor antibody (anti-PLA2R) titer returned a positive result of 31.2RU/mL but a repeated urine sediment demonstrated muddy brown casts, RTECs suggestive of ATN. He denied any history of any IV drug use, autoimmunity or recent infections. His

creatinine began decreasing to a discharge value of 3.6mg/dL and he avoided dialysis as his biopsy preliminary results revealed findings consistent with ATN, weak staining for PLA2R and C3 activity—electron microscopy results were pending at discharge, but it was appreciated that the patient likely had early membranous lesions with his positive anti-PLA2R titer >20. Notably, his NSAID and aspirin were held since admission and removed from his medication list upon discharge. He followed up with outpatient nephrology where his final biopsy results on EM demonstrated findings most consistent with minimal change disease with podocyte foot process effacement rather than the expected membranous pathology. Simply upon holding his NSAIDs and concurrent maintenance diuresis, his creatinine returned to near baseline at 1.73mg/dL and his proteinuria resolved to normal UPCR ranges. Curiously, his serum anti-PLA2R level continued steadily rising up to 50.8RU/mL on 4-month follow-up despite continuing with normal renal function by serum creatinine. Neither steroids nor immunosuppression were initiated.

Discussion: Membranous nephropathy and focal segmental glomerulosclerosis are more common in the adult population as etiologies of nephrotic syndrome, but in the case of nephrotic syndrome with concurrent AKI, minimal change disease is the most common cause; further, any adult with a presentation of acute renal dysfunction with nephrosis should prompt a strong suspicion for the minimal change disease. MCD by virtue of its effacement of podocytes foot processes obligates at least a theoretical reduction in GFR by increasing the barrier for ultrafiltration (the coefficient of filtration) through the glomerular basement membrane. Otherwise, however, ischemic damage, ATN or the entity called nephrosarcoma precipitate AKI in MCD. This patient's history of regular NSAID use did provide a historical basis for suspicion of MCD, but his positive anti-PLA2R titer level prompted a higher suspicion for membranous nephropathy. Indeed in recent years, antibodies against the phospholipase A2 receptor, which is highly expressed on glomerular podocytes, has been found in the majority of cases of primary MN, such that in the absence of renal dysfunction and identifiable secondary causes of MN, serological and clinical data may be sufficient for diagnosis according to a recent study evaluating for a non-invasive diagnostic approach. This is notably in contrast to the case of our patient who did have renal dysfunction. Thus, the anti-PLA2R titer of this patient likely represents a false positive result with unclear significance given its continued rise as an outpatient. This assumption was further strengthened in this particular case because the western blot for anti-PLA2R done in the research laboratory at BU was negative.

Category: Quality Improvement / Education

Fever and Diarrhea in an HIV Patient

Vashney (Patel), Swati

Learning Objectives:

1. Proposed algorithm for diagnosing the etiology of diarrhea in HIV
2. Importance of detailed history in order to localize source of diarrhea to guide differential and work up
3. In immunocompromised host, noninfectious etiologies such as malignancy should be considered if infectious work up is negative

Case: 48 year-old Haitian man with recently diagnosed acquired immunodeficiency syndrome (AIDS) not consistently taking highly active antiretroviral therapy (HAART) presented with a 2-week history of fevers, generalized abdominal pain and non-bloody diarrhea. He describes the diarrhea as watery and large volume. His past medical history is significant for giardiasis treated with tinidazole 2 months prior to presentation. His only travel includes a visit to Haiti 2 years prior to symptom onset. He denies any raw food intake, as well as tick and mosquito bites.

The patient continued to spike fevers daily with worsening diarrhea despite treatment with intravenous vancomycin, cefepime, and metronidazole. He completed treatment for persistent giardiasis with intravenous metronidazole and subsequent stool ova and parasite demonstrating clearance of *Giardia Lamblia* trophozoites. Extensive infectious work up was otherwise unrevealing prompting work up of non-infectious causes of fever and diarrhea in an immunocompromised patient. Labs then revealed a lactate dehydrogenase up to 7,174 U/L and procalcitonin of 145 ng/mL. Peripheral smear demonstrated atypical lymphocytes and bone marrow biopsy showed aggressive Natural Killer cell Leukemia.

Discussion: Fever and diarrhea are a common presentation in patients with acquired immunodeficiency syndromes (AIDS) leading to significant morbidity and at times mortality. As the patients develop immunodeficiency, they are prone to infection by similar enteric pathogens that lead to diarrhea in immunocompetent hosts. As the CD4 count decreases to less than 100 cells/ μ L the patients are more prone to developing opportunistic infections. If the infectious work up is unrevealing, noninfectious etiologies, such as lymphoma and Kaposi Sarcoma should be evaluated. We report on a patient with AIDS who presents with fevers and diarrhea. We discuss the proposed algorithm for approaching work up of the etiology and the importance of a detailed history in localizing the source of the diarrhea to guide the differential.

Category: Education / Quality Improvement

A Retrospective Analysis of Implementation of a Lower GI Bleeding Protocol in the Emergency Department at a Tertiary Care Hospital

Matthew Petersile MD, Mustafa Haroon MD, Dimitri Belkin MD, Aisha Townes, Hemant K Roy MD

Introduction: Acute lower gastrointestinal (LGI) bleeding is a frequent chief complaint of patients presenting to the emergency department (ED) and is associated with significant morbidity and mortality. The management of patients with acute LGI bleeding is not standardized. This study assesses the impact of a standardized protocol for patients presenting with significant LGI bleeding to a tertiary care hospital ED.

Methods: A multidisciplinary, institutional LGI bleed protocol was implemented in the ED in March 2014, which addressed the severity of bleeding and provided diagnostic management guidance. A retrospective analysis of two groups, pre and post-protocol, was performed, each having a defined period of 1.5 years pre and post-protocol initiation. All adult patients admitted with clinically significant bleeding defined as ED heart rate > 100 or systolic blood pressure < 100 mmHg, initial hematocrit $< 35\%$, or requiring a red blood cell transfusion within 24 hours of admission were included. Patients were identified using ICD 9 and 10 codes for LGI bleeding and manual chart review identified 97 pre-protocol and 129 post-protocol qualifying admissions. T-tests were used for data analysis.

Results: Each group had similar representation of males and females (45% vs 55% pre-protocol and 43% vs 57% post-protocol). The mean ages of each group were similar 67 (SD = 18) and 65 (SD = 16), as was BMI 26 (SD = 7) and 28 (SD = 7) respectively. The mean baseline admission characteristics were similar including Heart Rate (87 vs 87), Systolic Blood Pressure (128 vs 128) Hematocrit (29 vs 29.7) and Platelets (248 vs 264). Rates of NSAID use were low in both groups (1% vs 8%) and anticoagulant use was 16% in each group. Although no significant difference was found in terms of patient outcomes, the data showed a trend towards fewer ICU admissions (45% vs 37%, $p=0.22$), decreased ICU length of stay (3.6 vs 2.9, $p=0.41$), fewer red blood cell transfusions (2.2 vs 1.58, $p=0.47$) and increased number of therapeutic colonoscopies (2% vs 11%, $p=0.005$) in the post-protocol group. There was a statistically significant difference in the proportion of GI consults (79% vs 91%, $p=0.02$) and the number of CT Angiograms performed (11% vs 21%, $p=0.002$) favoring the post-protocol group.

Discussion: This analysis of a standardized LGI bleeding protocol in the ED demonstrated no statistical difference in patient outcomes, but did show a trend towards fewer ICU admissions, decreased ICU length of stay, fewer transfusions, and more therapeutic colonoscopies post-

protocol implementation. The percentage of GI consults and patients undergoing CT angiogram was statistically different, favoring the post-protocol group.

Given the improved trend in patient outcomes in the setting of increased use of services including GI consults and CTA, further investigation with an increased sample size is warranted.

Category: Clinical Research

Stabilization of Cardiac Function in Wild-type Transthyretin Cardiac Amyloidosis with Diflunisal

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Introduction: Wild-type transthyretin cardiac amyloidosis (ATTRwt) is an underappreciated cause of heart failure with preserved ejection fraction that results from deposition of misfolded TTR protein (prealbumin). Diflunisal, an approved non-steroidal anti-inflammatory drug (NSAID) stabilizes TTR thereby preventing misfolding. While recent data suggest that diflunisal may prolong survival in ATTRwt, there are limited data regarding its specific effects on cardiac structure and function

Hypothesis: We hypothesized that administration of diflunisal would result in stabilization or improvement in echocardiographic and biochemical measures of cardiac function in patients with ATTRwt amyloidosis

Methods: ATTRwt cardiac amyloidosis patients (n=53, 30% treated with diflunisal by treating clinician) were retrospectively identified, with baseline and follow-up (average interval 1.2 y) serum biomarker and echocardiographic data collected, including global longitudinal strain (GLS). Chi-squared and Wilcoxon tests assessed differences in time-adjusted change between each subject, divided by treatment group.

Results: Patients treated with diflunisal were similar to controls except for lower baseline B-type natriuretic peptide (BNP, 314 vs 523 pg/ml, $p = 0.03$). Upon followup, treated patients showed increased prealbumin (indicative of stabilization, $p=0.03$). GLS and Troponin I were unchanged upon follow-up in treated patients, while in untreated patients GLS ($p=0.04$) and TnI ($p=0.02$) significantly worsened. Interval changes in wall thickness, left ventricular ejection fraction, and BNP were similar between treatment groups ($p=NS$, see Table).

Conclusion: In ATTRwt cardiac amyloidosis, these data demonstrate for the first time that the oral NSAID diflunisal can result in measurable differences in GLS and troponin after only 1 year of administration. Further analysis is warranted to assess longer-term treatment efficacy and relation to survival.

Bacterial Endocarditis Presenting as Acute ST-Elevation Myocardial Infarction

Kate Raiti-Palazzolo, MD, Brian Lilleness, MD and Eric Awtry, MD

Introduction: An uncommon cause of acute ST-elevation myocardial infarction (STEMI) is embolism from bacterial endocarditis. Subarachnoid hemorrhage (SAH) is a rare complication of septic emboli to the brain.

Case Description: A 74-year-old African American male presented with one hour of severe substernal chest pressure and shortness of breath. Past medical history was significant for hypertension and a trans-urethral resection of the prostate (TURP) 3 months prior. Electrocardiogram showed 7 mm ST elevations in V2-V5. Coronary angiogram revealed 100% occlusion of the mid left anterior descending artery with no underlying plaque following thrombectomy, so therefore no stent was deployed. Transesophageal echocardiogram showed a perforated mitral valve leaflet with a 2.2 x 1.4 cm heterogeneous irregular mass. Blood cultures grew *Enterococcus faecalis*, confirming endocarditis. Brain MRI revealed both septic emboli and subarachnoid hemorrhage (SAH). The perforated mitral valve resulted in acute heart failure, indicating the need for early mitral valve replacement (MVR). Due to his SAH, cerebral angiography was performed to rule out the presence of mycotic aneurysms. Although no aneurysm was found, it was determined that antibiotic treatment for at least 14 days was needed for cerebral bleeding risk to be low enough to tolerate the high heparin doses used during cardiopulmonary bypass for his MVR. Unfortunately, while awaiting surgery, the patient suffered recurrent embolization to his coronary arteries and died.

Discussion: This case demonstrates the need to consider atypical causes of STEMI when no underlying plaque is present. Up to 50% of patients with endocarditis suffer complications of septic emboli, which most commonly affect the central nervous system, spleen, liver and kidneys. Coronary embolization has been reported in only 7% of patients with native valve endocarditis. Unfortunately, there are no clear guidelines regarding coronary stenting in patients with acute STEMI due to septic emboli.

As well, the decision to delay MVR and the adverse outcome also illustrates the delicate balance between the risk of surgery versus delaying definitive treatment in patients with known complications of endocarditis. Risk factors for embolization include prior embolization, vegetations larger than 10 mm, and mitral valve location – all present in this case. This encourages stronger consideration of surgery—even in the presence of SAH. Current guidelines recommend waiting four weeks before valve replacement. Yet they also advocate early intervention in the setting of acute heart failure. This clearly shows the need for a multidisciplinary approach when evaluating complications of endocarditis.

Category: Clinical Research

Substance Use and Quality of Life in an urban cohort of people living with HIV and substance dependence

Samantha Rawlins-Pilgrim, MD, Michael Winter, MPH, Timothy C. Heeren, PhD, Alexander Y. Walley, MD, MSc, Theresa W. Kim, MD, Susie Kim, MPH, MSW and Richard Saitz, MD, MPH

Aim: To assess the association between substance use and quality of life in an urban cohort of people living with HIV and substance dependence.

Hypothesis: Substance use will be associated with lower health related quality of life (HRQOL).

Methods: HRQOL was measured at baseline in the prospective Boston Alcohol Research Collaboration on HIV/AIDS (ARCH) study, a cohort of people with HIV and substance dependence. Substance use was measured as past 30 day use using the Addiction Severity Index. DSM IV substance dependence criteria were assessed using the Mini International Neuropsychiatric Interview. HRQOL was measured by the physical (PCS) and mental component summary (MCS) scores of the Veterans RAND 12-item health survey. Associations between substance use and HRQOL were tested using linear regression. Multivariable analyses were adjusted for age, sex, race, marital/partner status, education, income, homelessness, CD4 cell count and the Charlson comorbidity index.

Results: Participants (n = 245) were mean age 48.5 (+/- 9.5) years, 64% male, 50% black, 25% Hispanic and 20% white. The mean PCS was 42 and mean MCS was 44 (score range 1-100, higher=better). Past 30 day substance use was common with 51% of participants reporting heavy drinking, 30% cocaine use, 24% illicit opioid use and 44% cannabis use. There was a non-significant association with worse PCS scores in participants who met higher numbers of alcohol dependence criteria (p = 0.11). There were no significant associations between substance use or drug dependence criteria and MCS scores.

Conclusion: Surprisingly, substance use was not associated with quality of life in people with HIV infection and substance dependence. This lack of association may be related to methodological limitations of cross-sectional analyses, or, in this population with multiple risk factors for worse physical and emotional health, substance use alone may not have a substantial effect on quality of life.

Category: Clinical Vignette

Mediastinal Germ Cell Tumor as an Initial Presentation of Klinefelter Syndrome

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Introduction:

Prior literature and case studies have illustrated that patients with Klinefelter Syndrome (KS) are at an elevated risk of developing germ cell tumors (GCT).^{1,3} The classic KS phenotype includes tall stature, gynecomastia, small testes, and psychosocial impairments.² However, few, if any cases, demonstrate the diagnosis of a GCT as an initial presentation of KS. Identification of KS in these patients is important as it has ramifications in the discussions involving fertility counseling, especially in the setting of pre-chemotherapy decision-making (e.g. sperm banking).

Case:

A 23-year-old man with no prior medical history presented with three months of cough, fevers, chills, night sweats, weight loss and pleuritic chest pain. The patient had immigrated from Colombia ten years ago and was recently exposed to tuberculosis (TB) through a relative. His exam was notable for mild tachycardia and absent breath sounds in the left lung fields. Chest CT identified a large anterior mediastinal mass with central necrosis, compressive left lung atelectasis, and lateral displacement of the heart and mediastinum. PET CT showed hypermetabolic activity of the mass, the L2 and L4 vertebrae, and multiple lymph node chains. Labs demonstrated a negative interferon-gamma release assay (IGRA) and HIV, normal beta-HCG, and an elevated AFP. The mass was biopsied and pathology was consistent with yolk sac tumor. Interestingly, the patient was found to have small testes on physical exam, which was confirmed on ultrasound. Given his recent diagnosis of a mediastinal GCT, suspicion was increased for underlying Klinefelter Syndrome. Additional labs revealed an elevated FSH and LH, low testosterone, and normal estradiol and prolactin supporting the diagnosis. Further testing demonstrated a 47,XXY karyotype, confirming the diagnosis of Klinefelter Syndrome. The patient was counseled regarding sperm banking prior to initiation of chemotherapy, but given the patient's diagnosis of Klinefelter Syndrome, it was highly likely that the patient was infertile. Ultimately, the decision was made by the patient to forgo sperm banking. The patient was initiated on ifosfamide/etoposide/cisplatin (VIP). He was subsequently discharged with a plan for three additional chemotherapy cycles along with surgical evaluation for possible resection of the remaining mass.

Conclusions:

This case demonstrates an atypical presentation of Klinefelter Syndrome in an otherwise young and healthy patient as a result of an initial diagnosis of a mediastinal GCT. This further highlights the importance of considering the association between KS and its increased risk of mGCT, especially in young patients who present with symptoms suspicious for malignancy.³

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Category: Quality Improvement / Education

Ambulatory Teaching Curriculum for Internal Medicine Residency

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Mentors: Deborah Afezolli MD, Benjamin Vaughan MD, Jennifer Siegel MD

Background: Ambulatory teaching is a key component of Internal Medicine residency education, and encompasses a wide variety of topics not taught elsewhere. While all Internal Medicine residencies include teaching about outpatient topics, there has been little to no research into the most effective ways to provide this education. Boston Medical Center has recently adopted a more structured ambulatory teaching curriculum, in an effort to standardize the knowledge gained by our residents. Our aim is to assess the impact of the Yale Ambulatory Medical Curriculum on resident and preceptor satisfaction with ambulatory teaching.

Needs assessment: Both preceptors and residents were surveyed before the Yale curriculum was released. Residents confirmed that both co-resident and preceptor teaching were occurring, but that the quality and topics were highly variable. Preceptors also responded that it was taking a significant amount of time to prepare pre-clinic conference teaching, and that they would prefer a more standardized curriculum and resources to use.

Future steps: At this time, Boston Medical Center is approaching the second year of having access to the Yale ambulatory medical curriculum. Our most recent survey aims to evaluate how widely used the new curriculum is, as well as how this has impacted both resident and preceptor satisfaction with ambulatory teaching. In the future, we will attempt to follow a cohort of incoming residents throughout their time at Boston Medical Center, for specific feedback about the teaching modules, as well as changes in their medical knowledge when this new curriculum is consistently being used. There has also been a critical shortage of Internal Medicine residents who decide to enter into Primary Care as a career, and it would be prudent to improve education in this area in an effort to increase this number.

Category: Quality Improvement / Education

A 64-year-old Male with Left Shoulder Pain

Mangwe Sabtala

Learning objectives:

1. Diagnose septic arthritis in a patient without typical risk factors.
2. Recognize *Propionibacterium* as a potential cause of septic arthritis in native joints

Case: A 64-year-old male with past medical history of hypertension and coronary artery disease s/p PCI with BMS in 2008 presented to the emergency department with one day of worsening left chest/shoulder pain, dyspnea, chills, nausea, vomiting and a headache. He was on a four-hour flight from PR when pain started. He described his pain as a squeezing pain not brought on or relieved by anything, and reminiscent of pain associated with his prior MI. He denied any preceding chest/shoulder trauma, any IVDU and denied any sick contacts or unusual exposures during his trip.

On exam he was diaphoretic, febrile to 102.6, tachycardic to 130s. Left shoulder was without erythema or effusion but limited ROM secondary to pain. He had an EKG with no ischemic changes, troponins 0.092->0.087, and a CTPA showing no PE. His labs were significant for normal wbc with 82% PMNs, CK 1387, CRP 90, and negative blood cultures. A left shoulder ultrasound did not reveal any effusion. Only 0.5 cc of sanguineous fluid was aspirated during an arthrocentesis with initial blood cultures being negative. After an extensive work up where no bacterial etiology of the fevers was identified, he was presumed to have had a viral infection and broad-spectrum antibiotics were discontinued. His left shoulder pain was attributed to an underlying cuff tear arthropathy and he was discharged with a plan for outpatient shoulder MRI, PT and pain control. Ten days after discharge, the patient's shoulder synovial fluid aspirate was found to be growing *Propionibacterium Acnes*. He was instructed to re-present to the hospital where he reported persisting shoulder pain. He was treated with Cefazolin for a 6-week antibiotic course for his septic arthritis.

Discussion: This case shows that slow growing organisms such as *Propionibacterium* should be considered in suspected cases of septic arthritis even in patients with native joints.

Propionibacterium species are anaerobes associated with normal skin flora. They are slow growing, as such initial negative cultures can lead to misdiagnosis or late diagnosis with resultant poor outcomes. In cases with strong suspicion of septic arthritis it might be worthwhile considering continuation of antibiotics to treat for these organisms.

Reference

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Category: Clinical Research

Improving screening rates for Chagas disease at a large safety net hospital in Boston

Sukhmeet Sandhu, Alyse Wheelock, David Hamer, and Natasha Hochberg

Introduction: Chagas disease is caused by the protozoan *Trypanosoma cruzi* (*T. cruzi*), which is transmitted by the triatomine insect vector. There are an estimated 6-7 million cases of Chagas disease worldwide, of which 300,000 cases are in the United States and 3000 in Massachusetts [1,2]. There likely will be a growing population of individuals in the US and other developed nations living with *T. cruzi* infection, given the migration of millions of people out of Latin America to countries across the world [1]. Chronic *T. cruzi* infection can lead to cardiac and gastrointestinal disease. The major morbidity and mortality associated with Chagas disease is secondary to cardiac complications, including: arrhythmias, heart failure and embolic events [3]. This study aims to improve health care providers' awareness and knowledge about Chagas disease in order to improve screening rates at BMC.

Methods: Educational seminars will be held for providers at various departments at BMC. Healthcare provider knowledge will be assessed prior to the presentation with a pretest assessment, and after the presentation with a posttest assessment. Pretest and posttest scores will be compared. Screening rates prior to and after the implementation of the educational seminars will also be compared, and stratified by department.

Results: We are currently holding education seminars and data is not yet available. We will compare pretest and posttest scores. We will include screening rates prior to educational seminars, and can try to get some data on screening rates post intervention (but may be too soon).

Conclusion: The current screening rates for Chagas disease are impacted by healthcare providers' limited knowledge and awareness of the disease. With the implementation of educational seminars about the disease, we project that providers' knowledge will improve and that there will be higher screening rates for the disease.

Sources:

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Category: Clinical Research

Interstitial Lung Disease and Pulmonary Hypertension in Systemic Sclerosis: A Real-World Experience

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Objective: Pulmonary complications of systemic sclerosis (SSc) most commonly include interstitial lung disease (ILD) and pulmonary hypertension (PH). PH in SSc may be Group 1 pulmonary arterial hypertension (PAH), Group 2 PH due to left heart disease, or Group 3 PH due to ILD and chronic hypoxemia. Numerous patients with PAH of SSc have some degree of co-existent ILD, making classification difficult. For this reason, many PAH clinical trials exclude those with significant ILD. However, in specialized clinical practice, some patients with both pre-capillary PH and ILD receive treatment for their PH, and their response to treatment is not well described. We sought to better characterize the population of SSc patients at our referral center who underwent right heart catheterization (RHC), and identify those with co-existing PH and ILD for the purpose of studying their outcomes and response to treatment.

Methods: We performed a retrospective chart review of all SSc patients followed at our institution who underwent at least one RHC between 2002 and 2017. We collected demographics, medical history, and cardiopulmonary diagnostic and treatment data on each subject. ILD was defined by a chart diagnosis based on radiology and pulmonary function testing, while PH was defined by a mean pulmonary artery pressure on RHC of ≥ 25 mmHg. Data were analyzed using SAS v9.4.

Results: The records of 183 SSc patients were reviewed; 35 (19%) were male, with a mean age of 62 years. 96 (53%) had ILD, 135 (74%) had PH, 71 (39%) had both ILD and PH, and 23 (12%) had neither. The unadjusted gross mortality of patients with both PH and ILD was 51% (36/71), compared with 41% (26/64) in those with PH only, and 16% (4/25) in those with ILD only. In those with neither PH nor ILD, the mortality was 9% (2/23). These proportions were found to be significantly different from each other ($\chi^2=18.8$ p=0.0003). Of those patients with both PH and ILD, 58 (81.6%) were on PAH therapy.

Conclusions: Our study provides a “real-world” examination of SSc patients who underwent RHC at a PH and SSc referral center. Patients with both ILD and PH had increased mortality when compared with those having PH or ILD alone. Further analysis is required to determine the impact of pulmonary vasodilator therapy on clinical outcomes in this subpopulation.

Category: Quality Improvement / Education

Easing the Transition: A Curriculum for Internal Medicine Interns as they Transition to Senior Resident

Alexandra Pipilas MD, Brittany Scarpato MD, Asher Tulsy MD, Lindsay Demers PhD

Introduction: The transition from Intern to Junior year of Internal Medicine Residency represents the movement from primary clinician to supervisor, team leader and educator. Attributes of a successful junior resident have been established but the best way to prepare interns for this transition has not been fully elucidated. We presented a 90-minute peer-led workshop for Interns aimed at developing the necessary skills to be an effective junior resident. These skills include setting expectations, providing meaningful feedback, managing morning rounds and successful collaboration with multidisciplinary team members.

Methods: Approval for the study was obtained from the IRB (#H-37655). After which, we designed and conducted an in-person 90-minute peer-led interactive workshop that used discussion and case based learning to highlight the important aspects of a successful transition to junior resident.

Results: To evaluate the effectiveness of the workshop we used pre and post session surveys. We observed a statistically significant growth in the interns' comfort with specific elements key to a successful transition from Intern to Junior resident.

Discussion: The transition from Intern to Junior resident represents a significant increase in autonomy and patient care responsibilities. It represents the shift from primary clinician and learner to educator and team leader. This transition can serve as a source of anxiety. With this 90-minute peer-led workshop, we were able to increase confidence surrounding key attributes of successful junior residents.

Category: Quality Improvement and Education

An atypical presentation of drug-induced hypothyroidism

David Shottland, MD

Introduction: Hypothyroidism presentation may vary widely in both symptoms and severity. Elderly patients with confounding comorbidities may present with non-specific signs and symptoms such as fatigue, confusion, edema and weight gain, resulting in delayed diagnosis and treatment. New onset renal impairment is an atypical presentation of hypothyroidism that may be seen in this population.

Case: A 73-year-old woman was admitted to the hospital for progressively worsening renal function noted by her primary care doctor. She had a diagnosis of diffuse large B-cell lymphoma involving the brain and was status post treatment with methotrexate followed by ongoing lenalidomide maintenance therapy started 16 months prior. Her medical history included diffuse large B-cell lymphoma involving the brain, which was reported to be in remission and for which she was being treated with lenalidomide maintenance therapy. She also had a history of rheumatic heart disease, mechanical mitral valve replacement, chronic anemia, atrial fibrillation, diabetes mellitus type 2, and hypertension. Elevated serum creatinine (Cr) to 1.26 mg/dL was noted 6 months prior on routine labs, and trended up to 2.06 mg/dL, prompting her admission. Lenalidomide was held 10 days prior to presentation due to worsening renal function. Review of medications was negative for nephrotoxic agents. The patient had several months of fatigue, intermittent confusion, and worsening of chronic lower extremity edema. Vital signs, including blood pressure, were normal. Physical exam was notable for obesity, facial edema, lower extremity pitting edema, and mild confusion. She did not have an elevated jugular venous pulsation or evidence of pulmonary edema. There was no costovertebral angle tenderness. There was no goiter. In addition to the elevated Cr, lab studies revealed elevated serum thyroid stimulating hormone (TSH) to 118.72 μ U/mL. Serum free thyroxine (FT4) was less than 0.4 ng/dL. Thyroid peroxidase antibody assay was negative. TSH was normal when measured 16 months prior to presentation, shortly before initiation of lenalidomide therapy. Lab studies also showed low hemoglobin at baseline, normal white blood cell count, normal serum electrolytes. She was not hyperglycemic. Urinalysis was normal and negative for casts. A renal ultrasound was negative for hydronephrosis. The chest X-ray and echocardiogram did not show evidence of hypervolemia. Treatment was initiated for hypothyroidism with oral levothyroxine. Subacute kidney injury was treated with fluids and supportive care. Prior to discharge, the serum Cr improved to 1.45 mg/dL. At a follow up visit 3 months after starting levothyroxine, TSH was 2.43 μ U/mL and Cr remained stable at 1.42 mg/dL.

Discussion: This case describes an unusual presentation of drug-induced hypothyroidism due to lenalidomide therapy presenting as subacute kidney injury. It further demonstrates the potential for delayed diagnosis and treatment of hypothyroidism in a patient with comorbidities and an atypical presentation. The diagnostic workup of new-onset renal dysfunction does not typically

include assessment of thyroid function, and the signs and symptoms of hypothyroidism are often subtle and non-specific. Though uncommon, there are several reports in the literature describing hypothyroidism presenting as renal impairment. The mechanism is indirect, multifactorial, and includes hemodynamic changes with subsequent reduced renal blood flow. The resulting renal impairment has been shown to be reversible with treatment of hypothyroidism. The case also highlights lenalidomide therapy as a rare but previously reported etiology of hypothyroidism. It is the likely cause of hypothyroidism in this patient with negative autoimmune serology.

Inferior ST Elevations After Accidental Epoprostenol Discontinuation

R. Simmons-Beck, B. Scarpato;

Introduction: Acute pulmonary hypertension is characterized by a rapid rise in pulmonary arterial pressures leading to impaired right ventricular filling and right ventricular failure and is typically seen in pulmonary embolism, cardiac surgery, ARDS or drug use. Acute elevations in right ventricular afterload prolong isovolumetric contraction and increase myocardial wall stress leading to decreased coronary perfusion. Right ventricular strain is typically accompanied by inferior-lateral T-wave inversions and ST depressions in the right to mid-precordial leads. Here we present an unusual case of inferior-lateral ST elevations after abrupt withdrawal of epoprostenol in a patient with pulmonary hypertension.

Case: A 33 year female with a history of systemic sclerosis/SLE overlap syndrome complicated by ILD, Raynaud's with digital ulcers, GERD and WHO class I pulmonary hypertension on epoprostenol presented from home with loss of consciousness after Epoprostenol line disconnection. On the day of admission the patient's VNA accidentally disconnected the patient's Epoprostenol line. She became acutely altered and hypotensive. She was intubated in the field and transferred to this hospital. On arrival she was noted to have ST-elevation in the inferior and septal leads. Her epoprostenol was rapidly restarted and her ST-elevations and hypotension resolved. Cardiology was consulted but deferred coronary angiogram given the improvement in the patient's EKG changes and lack of chest pain. CT pulmonary angiogram demonstrated right ventricular enlargement without evidence of pulmonary emboli. Transthoracic echocardiogram revealed evidence of severe RV dilation and flattening of the interventricular septum unchanged from prior without regional wall motion abnormalities. Troponins peaked at >50 and downtrended with reinitiation of Epoprostenol. With improvement in her hypotension and mental status the patient was extubated 24 hours after presentation. Subsequent EKGs revealed no evidence of Q-waves in her inferior or septal leads. She was discharged home with careful line precautions.

Conclusions: To our knowledge this is the first reported case of inferior ST segment elevations in the setting of acute discontinuation of Epoprostenol. ST elevations in the inferior-lateral leads would suggest full thickness myocardial injury secondary to an acute rise in pulmonary arterial pressures. Although there have been cases of acute PE associated with ST elevations, to our knowledge they have never been described after abrupt discontinuation of pulmonary vasodilators. This case highlights the potential dangers of abrupt discontinuation of pulmonary vasodilators in patients with pre-existing right ventricular failure and further studies are needed to determine the safety and appropriate time course for discontinuation of pulmonary vasodilators.

Category: Clinical Research

Practice Pattern and Variation in the Provision of Intensive Care: A Systematic Review and Meta-analysis

Robert Simmons-Beck MD, Nicholas Bosch MD and Allan Walkey MD

Background: Idiosyncratic variation in critical care management has been associated with suboptimal outcomes. Significant variability continues to exist in ICU risk-adjusted mortality rates and many practices essential to critical care. In 2003 alone, the National Committee for Quality Assurance estimated between 42,000 to 79,000 lives were lost annually because U.S. physicians were not using evidence-based medicine in their care.

Objective: To perform a systematic review of the literature reporting practice variation in critical care settings. Discuss potential sources and causes of variation in critical care and explore common themes among areas of unexplained variation in an attempt to improve care. Evaluate methods of reporting in current studies on practice variation in critical care settings to improve future research harmonization.

Methods: We searched Pubmed using medical subject headings and natural language text to identify articles published between 2000 and 2017 that measured physician practice variation among adult ICU patients. We included studies that identified a statistical summary measure of variation, including mean, median, interquartile range, median odds-ratio, intraclass correlation, etc. Studies were excluded if there was no direct measure of patient care/intervention (e.g. surveys of physician opinions). We collected data on study design, statistical measures of variation, modeling strategy (e.g., fixed effects vs. random effects models), type of intervention studied, and whether risk adjustment was performed.

Results: Of the 2003 articles evaluated, 124 met inclusion criteria and were analyzed. 39% of evaluated studies used primarily descriptive statistics to measure variation. 35% of articles included did not use risk adjustment in estimates of variation and 43% did not account for hospital or physician clustering in measuring variation. Only 30% of studies used measures of variation derived from hierarchical random effects models such as intra-class correlation coefficients or median odds ratios. Given the lack of uniformity in methods of reporting variation we were unable to pool variation across studies.

Conclusions: Descriptive statistics and odds-ratios remain over utilized, while higher level summary measures of variation such as MOR and ICC are underutilized. Practice variation between individuals at different hospitals, regions or physicians is impossible to appropriately quantify without higher level measures of variation. The heterogeneity in measurement and reporting of variation in ICUs may threaten the ability to target and accurately measure variation to improve care. Future work is needed to better standardize and harmonize the measurement of practice variation in critical care.

Category: Quality Improvement and Education

Pancytopenia and hemolysis in a patient with severe vitamin B12 deficiency

Kevin Su MD

Objectives:

- 1.) Recognize the manifestations of severe vitamin B12 deficiency

Case: A 53 year old African-American male with a history of gastric bypass 15 years ago presented with 3 months of mechanical falls. On the day of admission, he fell while standing up at a restaurant, prompting presentation to the emergency room. He endorsed progressively worsening gait instability to the point that he has to grasp the furniture in his apartment to maintain balance. He also reported tingling of his distal upper and lower extremities, as well as recent memory problems. The patient has a non-vegetarian diet, and does not take vitamins or supplements. His only medication is divalproex, which he takes regularly for a seizure disorder.

On presentation, vital signs were normal. Exam was notable for significant ataxia on standing, as well as decreased proprioception and fine touch discrimination in his feet bilaterally. Labs revealed a new pancytopenia, with a hemoglobin of 4.5, g/dL (MCV of 128), white blood cells of 2.9 K/UL, and platelets of 45 K/UL. A CT scan of the head showed no acute abnormalities.

Vitamin B12 levels were below assay, while folate was normal. Methylmalonic acid (MMA) and homocysteine were elevated at 73,900 nmol/L and 219.7 umol/L, respectively. A reticulocyte index of 0.24 was inappropriately low. An elevated lactose dehydrogenase of 5759 U/L, direct bilirubin of 1.9 mg/dL, and undetectable haptoglobin suggested ongoing hemolysis. Normal fibrinogen and negative Coombs ruled out diffuse intravascular coagulation and autoimmune hemolysis, respectively. Parvovirus B19 IgM and HIV tests were negative. A peripheral blood smear showed macrocytes and hypersegmented neutrophils, but no blasts.

The patient was started on vitamin B12 injections 1,000 mcg daily for one week, with a plan for 1,000 mcg weekly thereafter. He was transfused with 3 units of packed red blood cells, but correction of his anemia did not resolve his weakness and he was discharged to sub-acute rehabilitation.

Discussion: Vitamin B12 deficiency can present with pancytopenia, symmetric paresthesias, and impaired proprioception, all of which were seen in this patient. With severe deficiency, intramedullary hemolysis occurs within the bone marrow. Diagnosis is based on measurement of serum B12 levels, although assay sensitivity and specificity can be limited. Hence, elevated MMA and homocysteine levels help support the diagnosis, particularly when B12 levels are borderline. As dietary B12 absorption relies on intrinsic factor secreted by gastric parietal cells, this patient's gastric bypass and lack of ongoing B12 supplementation accounted for his deficiency. With adequate repletion, hemolysis typically decreases within days, reticulocyte

count normalizes in a week, and megaloblastic anemia resolves by 2 months. However, neuropsychiatric deficits may not improve for up to a year, and complete recovery occurs in only half of patients.

Category: Clinical Research

Small bowel fed response as measured by wireless motility capsule: Comparative analysis in healthy, gastroparetic, and constipation subjects.

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Background: Small bowel fed response is an increased contractile activity pattern following the ingestion of a meal. Postprandial motility is traditionally evaluated using small bowel manometry. WMC is an ingestible wireless capsule that measures pH, temperature and intraluminal pressure. The primary aim of the study was to assess small bowel fed response captured with the non-invasive WMC. The secondary aim was to compare the fed response patterns between healthy subjects and patients with motility disorders of gastroparesis and constipation.

Methods: All subjects had 250 cc Ensure® meal 6 hours after WMC ingestion. Frequency of contractions (Ct), area under the curve (AUC) and motility index (MI) were analyzed during a 30 min of pre-prandial baseline and 60 min post-prandially in 20 min windows.

Key Results: 188 subjects (107 healthy, 23 gastroparetics, 58 constipated) were analyzed. *Healthy:* Ct, AUC, and MI all increased significantly immediately after meal ingestion ($p < 0.01$). Motility parameters peak at 20 to 40 min post meal. The motor activity decreased at the end of postprandial hour, but was still significantly higher than the fasting baseline ($p < 0.01$). *Gastroparetics:* All motility parameters failed to increase significantly compared to the baseline throughout the entire postprandial hour. *Constipated:* The fed response was similar to Healthy subjects.

Conclusions & Inferences: The small bowel fed response was readily observed in healthy and chronic constipation subjects with WMC but is blunted in gastroparetics. A blunted small bowel fed response, suggests neuropathic changes outside the stomach and may contribute to postprandial symptoms.

Category: Clinical Research

Relations of liver fat with prevalent and incident chronic kidney disease in the Framingham Heart Study: a secondary analysis

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Background & Aims: Prior studies demonstrated an association between non-alcoholic fatty liver disease and chronic kidney disease (CKD), though data are conflicting. We examined the association between liver fat and prevalent and incident CKD in the Framingham Heart Study (FHS).

Methods: We included FHS participants who underwent computed tomography (CT) from 2002-2005 (n=1315). After excluding heavy alcohol use (n=211) and missing covariates (n=117), the final sample included 987 participants. For the incident CKD analysis, we excluded 73 participants with prevalent CKD. Liver fat was measured by the average liver attenuation on CT. Estimated glomerular filtration rate (eGFR) was obtained using the CKD Epidemiology Collaboration Creatinine-Cystatin C equation, and CKD was defined as eGFR <60 ml/min/1.73m². Microalbuminuria was defined by sex-specific urinary albumin-creatinine ratio cut-offs. Multivariable-adjusted regression models were performed to determine the association between liver fat and CKD.

Results: The prevalence of hepatic steatosis and CKD were 19% and 14%, respectively (55.9% women, mean age 60±9 years). After adjusting for covariates, we observed no significant associations between liver fat and CKD, microalbuminuria, or eGFR in cross-sectional analyses. We observed positive associations between liver fat, incident microalbuminuria, and reduced eGFR in age- and sex-adjusted models; these relationships were not significant in multivariable-adjusted models.

Conclusions: In this community-based cohort study, we did not observe significant associations between liver fat and prevalent or incident CKD with a median follow-up time of 12.5 years.

The association between NAFLD and CKD may be accounted for by shared risk factors; confirmatory studies are needed.

Category: Basic Research

Myokines as Anti-Proliferative Agents in Lung Adenocarcinoma: an In Vitro Study into Exercise and Lung Cancer

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Rationale: Despite advances in targeted therapies, lung cancer remains the number one cause of cancer-related deaths worldwide, highlighting the need to investigate new avenues of prevention and treatment. A recent meta-analysis showed that physical activity reduced the risk of developing lung cancer by nearly 25% (Brenner, Lung Cancer 2016). Myokines, small molecules secreted by contracting skeletal muscle cells, are an area of active interest in elucidating the anti-neoplastic effects of exercise. Myokines have been shown to act as tumor suppressors in breast and colon cancer (Lucia, NEJM 2016). In this study, we aimed to investigate the *in vitro* effect of myokines on lung adenocarcinoma cells.

Methods: C2C12 myoblasts were cultured and differentiated into myotubules. A C-Pace EP Cell Culture Pacer (IonOptix) was used to induce rhythmic contractions in myotubules, producing supernatant that was then filtered through 3,000 kDa centrifugal filter tubes (Amicon) to produce exercise-conditioned media. Cytokine expression in the conditioned media was determined through cytokine assay (R&D Systems). A549 cells were incubated in conditioned and unconditioned media for 48 hours. Following this, WST-1 cell viability assay (Promega) and Western blot protein analysis (Cell Signaling Technology) were performed per protocol.

Results: Cytokine assay revealed differential expression of several cytokines in the exercise-conditioned media when compared with unconditioned media. WST-1 assay demonstrated a 40% reduction in cell viability when A549 cells were incubated in conditioned media ($p < 0.001$). Western blot showed a significant reduction in cell proliferation markers: phospho-retinoblastoma (pRB) decreased by 42.5% ($p < 0.02$), cyclin D1 decreased by 57.5% ($p < 0.001$), and phospho-MAPK decreased by 44.5% ($p < 0.05$).

Conclusions: To our knowledge, this is the first demonstration of myokines exerting an anti-neoplastic effect on lung adenocarcinoma cells. Incubation in exercise-conditioned media resulted in a substantial reduction in A549 cell viability. This effect appears to be mediated through decreased cell proliferation, as evidenced by a striking reduction in protein expression of cell proliferation markers. Our preliminary studies show an increase in specific cytokines following skeletal muscle contraction, implicating differential myokine expression as the active variable in our experiments. This work represents one step towards understanding the molecular underpinnings of exercise in lung cancer prevention. Furthermore, additional investigation into the specific myokines responsible for the observed effect has the potential to inform new directions for tumor suppressive therapy.