Differential Association of Macrophage Migration Inhibitory Factor (Mif) Expression, Promoter Polymorphism, and COPD
Andrew Berical, MD; Patty Lee, MD; Maor Sauer, MD

Background: COPD is a chronic inflammatory disease that is commonly associated with cigarette smoke exposure (CSE). Certain patients are predisposed to the development of COPD, as evidenced by the broad spectrum of clinical phenotypes amongst individuals with similar CSE. Based on prior observational studies, HIV infection is an independent risk factor for developing COPD and while the biologic mechanisms for increased susceptibility to developing COPD are unknown, it has been hypothesized that a dysregulated immune response as a consequence of HIV infection may be a cause. Macrophage Migration Inhibitory Factor (MIF) is an innate pro-inflammatory cytokine that has been shown to have both pro-inflammatory and pro-survival effects in multiple diseases. Mif-deficient mice are susceptible to developing emphysema, an important manifestation of COPD. In human studies, circulating plasma levels of MIF are inversely related to the severity of COPD. Mif lies on chromosome 22q11, with a preceding 800-900 nucleotide promoter region with two areas of interest. The -173 G→C single nucleotide polymorphism (SNP) is associated with the development of other inflammatory diseases. The -794 CATT4.8 microsatellite region has been associated with the circulating plasma levels of MIF; the number of microsatellite repeats correlates with MIF gene expression (i.e. higher repeats leads to higher gene expression). Furthermore, the -173 G→C SNP is in high linkage disequilibrium with the higher expression alleles.

Specific Aim: We set out to determine the role of Mif genetic polymorphisms in multiple well-described COPD cohorts, enriched with HIV infected subjects.

Hypothesis: We hypothesized that genetic factors associated with decreased Mif expression and activity will be associated with the development and severity of COPD in HIV infected subjects.

Methods: We obtained purified genomic DNA at approximately 5 ng/μL concentration. Using a previously described real-time polymerase chain reaction (PCR) for allelic discrimination, we determined the -173 G/C genotype for each subject. -794 CATT microsatellite repeat polymorphisms were identified by fluorescently labeled primers and standard PCR. Multivariable logistic and linear regression models were performed to test the association of COPD with -794 CATT5.8 genotype.

Results: In an analysis of a single cohort, HIV infected subjects with high Mif expression CATT alleles were at increased risk of developing emphysema (OR 4.36; 95% CI 1.32-14.48; p=0.02), whereas the matched HIV uninfected patients had no significant increased risk (OR 0.59; 95% CI 0.12-2.97; p=0.52). Alternatively, the low Mif expression CATT alleles was associated with a decreased diffusing capacity of carbon monoxide (DLCO) in HIV uninfected patients (β 5.03; 95% CI 2-10.05; p=0.05). White HIV uninfected subjects with -173 G→C have a hazard ratio of 2.22 (1.22-4.05) for incident COPD, when compared to matched -173G subjects. At this time, the complete regression analysis for the remaining cohorts is underway.

Conclusions: The expression of Mif is an independent risk factor for the development of COPD in a cohort of HIV infected patients. Interestingly this risk seems to differ based on HIV infection status, with high expression of Mif correlating with a greater than 4-fold increased risk for the development of COPD.
Trends in Pulmonary Embolism Hospitalizations, Use of Advanced Therapies, and Outcomes Among Fee-For-Service Medicare Beneficiaries from 1999 to 2010

Resident’s Name: Behnood Bikdeli M.D
Senior Mentor: Harlan M. Krumholz MD, SM

Background: Older adults are at increased risk of PE, as well as severe pulmonary embolism (PE) and may require advanced therapies besides anticoagulation. However, little is known about recent trends in PE hospitalizations and use of advanced therapies among older adults.

Methods: In a national cohort study of all Medicare Fee-For-Service beneficiaries ≥65 years of age with principal discharge diagnoses of PE between 1999 and 2010, we determined the PE hospitalizations. We also analyzed the use of thrombolytic therapy, surgical, and percutaneous thrombectomy per 1,000 PE hospitalizations, as well as 30-day and 1-year mortality rates after the use of these therapies.

Results: The number of hospitalizations for PE increased from 31,746 in 1999 to 54,392 (P<0.001). Among 556,658 patients hospitalized with PE, 7158 received thrombolytic therapy with the rates increasing from 11.8 to 15.8 per 1,000 patients with PE (P =0.09). Overall, 676 underwent surgical thrombectomy, and 260 had percutaneous thrombectomy. The rates of percutaneous thrombectomy increase from 0 to 1.4 per 1,000 patients with PE (P<0.001) while the rates of surgical thrombectomy declined (from 1.6 to 0.9 per 1,000 patients with PE, P =0.01). In the overall cohort of 556,658 patients with PE, adjusted 30-day and 1-year mortality rates both declined over time (from 12.7% to 9%, P<0.001, and from 26.3 to 22.4%, P<0.001). There was no significant change in 30-day or 1-year mortality rates in the subgroups receiving thrombolytic therapy or thrombectomy.

Conclusions: The increase in hospitalization rates and continued high mortality rates confirm the significant burden of PE for older adults. While use of some advanced therapies have modestly increased over time, thrombolytic therapy and thrombectomy have been rarely performed. The reduced mortality rates in entire cohort of older adults with PE could be multifactorial with contributions from more sensitive diagnostic technologies, or more appropriate use of routine antithrombotic therapy, among others; and warrants further investigation.


[Signatures]
Resident’s signature
Mentor’s signature
Transcriptomic Changes Common to Diverse Chronic Lung Diseases Indicate a Core Lung Response to Chronic Injury  
Resident: Benjamin M. Cherry, M.D.  
Mentor: Naftali Kaminski, M.D.

**Background:** Chronic lower respiratory disease is the third leading cause of death in the U.S., and the incidence of chronic obstructive lung disease (COPD) and idiopathic interstitial pneumonia (IIP) is increasing annually. Whole genomic and microRNA methods have advanced research into the etiology, pathogenesis, and clinical manifestations of these diseases. Although the genomic aberrations distinguishing individual lung diseases have been described, genomic changes across disease states have not been reported. The Broad Institute’s “connectivity map” (CMap) is a library of gene expression profiles derived from cultured human cells following exposure to diverse small molecule stimuli. Identification of aberrations common to multiple chronic lung diseases would permit the characterization of the core lung response to chronic injury and allow tools such as CMap to identify potential therapeutic targets.

**Specific Aim:** Using whole genome transcript profiles of well characterized human samples from patients with normal lungs, IIP, or COPD, identify the genes and microRNAs that are similarly perturbed across chronic lung disease states as markers of shared common mechanisms.

**Hypothesis:** Transcriptomic changes demonstrated by genomic analysis of lung tissues from diverse chronic lung disease states will indicate the core lung response to environmental injury.

**Methods:** Utilizing Agilent gene expression microarrays from whole lung lysates of phenotypically well characterized human samples, we compared 35 controls to patients with chronic lung diseases including 172 with COPD, 65 with idiopathic pulmonary fibrosis, 21 with nonspecific interstitial pneumonia, 19 with respiratory bronchiolitis, 6 with cryptogenic organizing pneumonia, and 40 with uncharacterized fibrosis. Significance analysis of microarrays (SAM) was used to identify differentially expressed genes, with significance defined as a false discovery rate <5%. Drug targeting assessment was performed using CMap.

**Results:** We identified 21 genes (7 up-regulated and 14 down-regulated) that were similarly, differentially expressed across chronic lung disease states by SAM. All genes in this signature were up- or down-regulated in the same direction across all chronic lung diseases. The most up-regulated gene in all comparisons was the secreted frizzled-related protein 2 (SFRP2) (fold-change range: 2.5-11.1) while the most down-regulated gene was the solute carrier organic anion transporter family, member 4A1 (SLCO4A1) (fold-change range: 0.15-0.3). CMap identified the prostaglandin E2 (PGE2) analog meteneprosto (p = 0.0004), the harmala alkaloids (p = 0.007), vinca alkaloids (p = 0.03), and the piperidinedione derivatives (p = 0.005) as small molecules capable of suppressing this chronic lung disease signature.

**Conclusion:** This 21-gene signature of transcriptomic changes common to diverse chronic lung disease states indicates a core lung response to chronic injury. SFRP2, which we found to be the most highly upregulated gene in each chronic lung disease state, has been implicated in cardiac fibrosis via both its modulation of Wnt signaling and interactions with tissue nonspecific alkaline phosphatase (TNAP). This suggests that disease states such as COPD, classically described as primarily proteolytic, also have a significant fibrotic component. Further supporting this is CMap’s identification of the PGE2 analog meteneprosto, a potential anti-fibrotic agent, as a small molecule capable of suppressing these genomic changes. Further studies including confirmatory qPCR, anti-SFRP2 antibody and SFRP2-/- mouse models, as well as administration of meteneprosto as in animal models of lung fibrosis, will allow us to further characterize these changes and more fully describe regulatory networks that may be novel targets for therapies aimed at slowing or reversing the progression of chronic lung disease.

Resident Signature:  
Benjamin M. Cherry, MD  
Date: 4/14/2016

Mentor Signature:  
Date: 4/14/2016
THE USE OF LEFT VENTRICULAR STRAIN AS A NON-INVASIVE ALTERNATIVE TO SURVEILLANCE ENDOMYOCARDIAL BIOPSY

Raj Ganeshan MD, PGY 3, Traditional Resident, YNHH
Lavanya Bellumkonda, MD, Assistant Professor of Medicine (Cardiology), YNHH

PURPOSE
Cardiac allograft rejection has recently been associated with left ventricular global longitudinal strain (GLS) derived by two-dimensional speckle-tracking echocardiography (2D-STE). The utility of this finding is not well established.

METHODS
Transplant recipients at Yale New Haven Hospital from 2010 – 2013 with an echocardiogram and surveillance biopsy within 24 hours were included. GLS was determined by using Image-Arena 4.3 (TomTec Imaging Systems) with manual tracing of myocardial borders in the apical 2, 3, and 4 chamber views and compared to their mean (GLS') using linear regression. Rejection was defined as ISHLT grade 1B or higher. GLS was compared between the rejection and non-rejection groups. GLS with an absolute value less than 14.8% (a value recently described in the literature) was also tested for association with rejection.

RESULTS
There were 51 biopsy specimens and echocardiograms from 25 adults. Mean age at transplant was 50, 19 (74.5%) patients were male, transplant indication was ischemic cardiomyopathy in 46% and non-ischemic in the remainder, 52% were diabetic, and 72% had hypertension. Mean biopsy date was 27.8 (SD 35.4) weeks from transplant; Grade 1B or higher rejection was observed in 9 biopsies (17.6%). Mean left ventricular ejection fraction was 58.8 (SD 9.7). GLS obtained from the apical 2, 3 and 4 chamber views demonstrated good association with GLS' (R²: 69.0, 67.9, 62.1). A significant difference in GLS' was not found in our study sample between rejection and non-rejection groups (-12.78, -11.89, p=0.710). GLS' less than [-14.8%] was not found to be associated with rejection (p=0.845).

CONCLUSION
Identifying non-invasive means to detect asymptomatic allograft rejection is a major objective in the care of heart transplant recipients. Although we were unable to demonstrate a statistically significant difference, this initial study was underpowered due to few episodes of rejection. A secondary analysis of our data demonstrated high variance among strain measurements, which may be related to echocardiogram quality and the study of these images retrospectively. GLS has biological basis for association with rejection and given recent supportive data a prospective analysis may allow for adequate power and increased accuracy of strain measurements. A more accurate identification of the sensitivity and specificity of cut off values of GLS associated with rejection is also necessary to determine its role as a method to screen for asymptomatic rejection.
Circulating CSF-1, Estrogen, and Bone Mineral Density
Andrea Haas, MD and Karl Insogna, MD

Background: Post-menopausal osteoporosis remains a major public health problem. Central to the pathophysiology of post-menopausal bone loss is the increase in bone resorption that attends estrogen deficiency. A host of systemic and local factors regulate the process of osteoclast formation, as well as the individual resorbing activity of mature osteoclasts. There are two pro-osteoclastogenic cytokines that are absolutely required for osteoclast development and survival: receptor activator of NF B ligand (RANKL) and colony stimulating factor-1 (CSF-1). There are two major isoforms of the CSF-1 protein: a soluble or circulating form (sCSF-1) and a membrane-associated or cell-surface form (mCSF-1). Both isoforms of CSF-1 are expressed by osteoblasts and are biologically active in vivo. Increases in CSF-1 production correlate directly with increased osteoclastogenesis. Treatment with a neutralizing antibody to CSF-1 prevented estrogen-deficiency bone loss in an experimental model, suggesting a critical role of CSF-1 in mediating the accelerated bone loss observed in post-menopausal women.

Hypothesis: We hypothesized that circulating levels of CSF-1 would correlate with the rate of bone loss in estrogen-deficient women. We also hypothesized that estrogen replacement therapy would eliminate this association as estrogen has direct effects on bone turnover. Finally, we expected that women on estrogen replacement would either not lose bone or lose bone at a slower rate than estrogen-deficient women.

Methods: We tested our hypothesis in an approved ancillary study of the parent Kronos Early Estrogen Prevention Study (KEEPS), which was approved by the Yale Human Investigation Committee. KEEPS was a multicenter, randomized, doubled-blinded, placebo-control study that spanned four years and included over 700 women. Women were randomized to hormone replacement vs placebo. For our ancillary study, data were available for 118 participants. Of these, 73 were assigned to the treatment arm and 46 to the placebo arm. CSF-1 levels were measured from serum samples at baseline and at 12, 36, and 48 months. Bone mineral density at the spine, hip, and femoral neck was measured at baseline and at 24, 36, and 48 months.

Results: Consistent with our hypothesis, those subjects who received either transdermal or oral estrogen had an increase in spine BMD over the course of the study while those in the placebo arm had an overall decrease in spine BMD. For the group as a whole, soluble CSF-1 values fell over time. The rates of decline between the treatment and placebo groups were not statistically different (p=0.52). There was a very weak and non-significant correlation between mean CSF-1 and mean spine BMD (p=0.99). Neither baseline CSF-1 values nor time-varying CSF-1 values were predictors of spine BMD (p=0.95). Importantly, when analyzed by treatment assignment there was still no significant association observed between the change in circulating levels of CSF-1 and the change in spinal BMD over time (p=0.29).

Discussion: Contrary to our hypothesis, this study did not demonstrate a meaningful relationship between the change in circulating levels of CSF-1 and the change in spinal BMD over time in either the placebo group or hormone replacement group. One possible reason that we did not see this association is that we measured soluble rather than membrane-bound CSF-1. Though the pre-clinical data suggested that sCSF-1 has a pathogenic role in estrogen-deficiency bone loss, the lack of association found in this study may, in fact, reflect differences between the murine model and human condition. Alternatively, it may be that circulating levels of CSF-1 do not accurately reflect changes at the tissue level. Circulating levels of CSF-1 have been reported to be elevated in later post-menopausal, as compared to early post-menopausal women. It may be that an effect of CSF-1 is age-dependent and since the group studied in KEEPS was relatively early in menopause, an effect of CSF-1 may not be evident in this group.
Lung Cancer among HIV-infected individuals at single urban institution in recent antiretroviral era
Kristen Hysell, Lydia Barakat, Michael Virata, Brinda Emu

Introduction: Lung cancer is the most common non-AIDS related malignancy among patients with HIV infection. Large cohort studies have found that HIV is an independent risk factor for lung cancer incidence, but detailed characterization of these patients has not been well described. This study sought to characterize demographics, HIV disease status and treatment, substance abuse, hepatitis co-infection status, and lung cancer outcomes among HIV-infected individuals diagnosed with lung cancer at a single urban institution in the recent antiretroviral era.

Methods: All patients with HIV who were diagnosed with lung cancer between 2001 and 2015 at Yale New Haven Hospital (New Haven, CT) were analyzed through electronic medical records for demographical information and characteristics of HIV infection, HIV treatment, lung cancer stage and pathology, cancer treatment history, and one-year mortality.

Results: A total of 29 patients were identified from 2001 to 2015. 16 patients were Black (55.2%), 10 were Caucasian (34.5%), and 3 Hispanic. The majority (72%) was male. Median age at time of cancer diagnosis was 54 (range 40 to 65). The median interval of time from HIV diagnosis to lung cancer diagnosis was 16 years. Mode of HIV transmission included IVDU (45%), MSM (14%), heterosexual sex (20.5%), or unknown (20.5%). Only 6 patients (22%) had a diagnosis of AIDS by CDC stage at time of lung cancer diagnosis. The median CD4 count at time of lung cancer diagnosis was 498 (range 26-1240). 83% of patients were on anti-retroviral treatment at time of cancer diagnosis and 59% of patients were on a regimen which involved a protease inhibitor. All patients had a past or present smoking history with median of 30 pack years (range 7-100). 62% of patients had documented past or present alcohol use and 76% had a documented history of past or present drug use with cocaine and/or heroin. Of note, 62% were co-infected with hepatitis C. 93% of patients had non-small cell lung carcinoma (NSCLC) while 2 patients had small cell lung cancer (7%). Of those with NSCLC, 15 were identified with adenocarcinoma, 8 with squamous cell, and 4 had unspecified NSCLC. 48% of all patients had stage IV lung cancer at time of diagnosis. The one-year mortality was 60% and was associated with male gender, advanced stage of cancer, and the presence of AIDS at the time of cancer diagnosis. There was no statistical significance in HIV viral load, use and choice of anti-retrovirals, or histology type. Only 25% of the patients were eligible for lung cancer screening by current guidelines.

Conclusion: This study provides detailed characterization of patients with HIV infection and lung cancer in an urban population. At the time of cancer diagnosis, patients presented with relatively high CD4 count, with the majority on anti-retroviral therapy and virally suppressed. As seen in other cohorts, presentation occurred at a younger age with high rates of smoking. The current screening guidelines for lung cancer may not capture a significant proportion of HIV-infected patients with lung cancer given their relatively young age at presentation. Additional studies in larger cohorts are needed to address incidence, risk factors, and outcomes of HIV-infected individuals with lung cancer as well as to deliver guidelines on screening and treatment for this population.
Title: A comparison of patient health literacy levels and grade level readability of electronic health record patient education materials in a resident primary care clinic

Authors: Omoye Imoisili¹, Benjamin Howell¹, Shoshana Streiter¹, Erik Levinsohn², Cassie Pan², Julie Rosenbaum³; 1. Internal Medicine, Yale New Haven Hospital, 2. Yale School of Medicine, 3. Internal Medicine, Yale School of Medicine

Background: Low health literacy is associated with worse health outcomes. Health institutions may not provide patient education materials (PEM) reflecting the reading grade level of their patient population. This disparity in literacy and PEM readability renders patients vulnerable to poorer understanding of their health conditions and treatment plans, and possibly worse health outcomes. This study assessed the health literacy of the patient population in an urban resident primary care clinic and compared it to the readability of two categories of PEM provided within the electronic health record ("standard" and "easy-to-read").

Methods: Rapid Estimate of Adult Literacy in Medicine Short Form (REALM-SF) categorizes health literacy as low (≤ 6th grade), marginal (7th-8th grade), or adequate (≥ 9th grade). Readability may be assessed by Simple Measure of Gobbledygook (SMOG), which applies a pre-set formula to a text based on polysyllabic words for evaluation of readability by grade level. All eligible patients during a two week period were asked to participate in the survey. Consenting subjects completed a basic demographics questionnaire; subsequently health literacy was evaluated by REALM-SF. Data was analyzed using a logistic regression model in STATA. Readability assessments using SMOG were performed on PEM for the five most common health conditions in the clinic as determined by the most frequently billed clinician visits over one year.

Results: Of 213 patients, 186 patients were eligible, and 175 patients participated. There were 66 males (37.7%) and 108 females (61.7%). Racial composition was 43 white (24.6%), 96 black (54.9%), 27 Latino (15.4%), and 9 other (5.2%). For education, 54 (30.9%) did not finish high school, 70 (40%) completed high school, 25 (14.3%) attended some college, and 25 (14.3%) graduated college. By REALM-SF, health literacy levels were ≥ 9th grade for 76 patients (43.4%), 7th-8th grade level for 66 patients (37.7%), and ≤ 6th grade for 30 patients (17.1%). There was a significant correlation for higher REALM-SF score with educational attainment (p<0.005), being a native English speaker (p=0.02), and female sex (p<0.005). The top five most frequent clinic diagnoses were hypertension, diabetes mellitus, hyperlipidemia, back pain, and depression. Readability assessments of their respective PEM by SMOG showed that for standard PEM, average readability grade level was 9.2 (range 7-11); for easy-to-read PEM readability average grade level was 6.8 (range 6-7).

Conclusions: The majority of subjects in this study (54.8%) had low or marginal health literacy, reading at or below an 8th grade level, per the REALM-SF. The average readability grade level by SMOG of standard and easy-to-read PEM for the top five most common conditions were 9.2 and 6.8, respectively. Therefore, standard PEMs are written at an inappropriately high level for the majority of this clinic population. Selecting the “easy-to-read” option may help maximize comprehension of PEM across the clinic population. Healthcare providers should prioritize distributing PEM at a reading level that is appropriate for the patients they are serving. Targeted interventions accounting for the health literacy level in a patient population may have a positive effect on doctor-patient communication, patient satisfaction, and health outcomes.

Omoye Imoisili MD
Julie Rosenbaum MD
Title: Depression is Strongly Associated with High Rates of Recurrent Chest Pain

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ABSTRACT
BACKGROUND: The evaluation of acute chest pain is costly, in the order of billion dollars annually. Only a small fraction of acute chest pain is cardiac in origin.

HYPOTHESIS: Psychological states such as depression, anxiety, and inability to cope with daily stressors (defined by perceived stress) may be important predictors of recurrent chest pain (RCP).

METHODS: We conducted a prospective cohort study of emergency department (ED) patients admitted to Yale Chest Pain Center (CPC) with acute chest pain without acute ischemia (and without acute ischemia). Depression, anxiety and perceived stress were assessed using multi-study validated scales: patient health questionnaire (PHQ8), clinical anxiety scale (CAS), and perceived stress scale (PSS), respectively. All patients underwent appropriate cardiac stress test. Primary outcome was recurrent chest pain at 30 days evaluated by phone follow up and/or chart extraction. The relationship between each psychological scale and recurrent chest pain was evaluated using ordinal logistic regressions, controlling for known cardiac risk factors. Depression (PHQ8 ≥10), anxiety (CAS≥30) and perceived stress (PSS≥15) were considered positive.

RESULTS: Between 08/2013 - 05/2015, 985 patients were screened, 483 patients were enrolled and 365 (76%) patients completed follow up. 131 (36%) patients had recurrent chest pain (RCP). They were younger, more likely to be female, Hispanic and/or non-White, with a family history of coronary artery disease and prescribed antidepressants and anxiolytics. Cardiac stress test revealed similar rates of abnormal stress testing in the RCP and non-RCP groups: 7% with RCP versus 5% in non-RCP. 30-day readmission rate in the RCP group was 4%, while the non-RCP group did not have any readmissions. Patients with RCP had statistically significant higher indicators of depression (p<0.0001), anxiety (p<0.001), and perceived stress (p=0.03) compared to patients without RCP. On ordinal multivariable regression models, depression (OR = 2.25, 95% CI 1.30 – 3.88) was a significant independent predictor of 30-day recurrent chest pain after adjustment, while PSS (OR = 1.05, 95% CI 1.06 – 1.66) and anxiety (OR = 1.92, 95% CI 0.93 – 3.97) were not statistically significant. In addition, poorly controlled depression (defined as active symptoms of depression while on antidepressants) was a significant independent predictor of 30-day recurrent chest pain (OR 3.92, 95% CI 1.52 – 10.11). Even after adjusting for anxiety and perceived stress, depression was a strong predictor of recurrent chest pain (OR = 2.31, 95% CI 1.30 – 4.11).

CONCLUSION: Depression is independently associated with recurrent chest pain in low-moderate risk ED patients. Targeted interventions may curtail recidivism in this population.

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Dated: April 6, 2016

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dated: April 5, 2016
The prevalence of depression and its association with opiate use among patients in an IBD program

Karl Langberg MD, Deborah Proctor MD

BACKGROUND: Depression is the most common mental illness in developed countries with a lifetime prevalence of 16.6%-17.5% (1). It is a common comorbidity of diabetes is 12.6% (95% CI: 12.2-12.9%) (2) vs, 6% in controls (3). 24.6% (95% CI: 20-29%) in COPD vs. 12% in controls (4) and 22% (95% CI:18-26%) in heart failure (5) in addition to Inflammatory Bowel Disease (IBD) (6). The presence and severity of depression is a better predictor of health-related quality of life than the disease activity of IBD as measured by clinical indices (7).

Patients with IBD tend to have been prescribed opiates more often than the general population (8). Opiates are also associated with increased prevalence of depression (9).

AIMS & HYPOTHESIS: This study sought to determine the prevalence of depression among Yale IBD program patients and to determine if opiate use was associated with depression. Our hypothesis was that depression would be more prevalent in the IBD population, as compared to publish rates of depression in the population, and that rates would be similar to chronic diseases such as CHF, COPD and diabetes.

METHOD: Data from 792 Yale IBD Program patients (100%) was obtained from an automated data extraction using the electronic medical record, EPIC. The Joint Data Analytics Team (JDAT) at Yale University and Yale-New Haven Hospital performed the data extraction. Use of an antidepressant was used as a surrogate for diagnosis of depression. A patient was considered to have had opiates if they had ever been recorded as being prescribed an opiate for any cause, not just for IBD related diagnoses. The rate of depression with 95% CI was calculated using Prism Graphpad using the Clopper and Pearson exact test. The relationship between opiate use and depression was calculated using Fishers exact test. IRB approval was waived for this study given its retrospective and anonymous study design.

RESULTS: The prevalence of depression among Yale IBD Program patients was 28% (24.9%-31.3% 95% CI). The prevalence of depression in IBD patients at Yale is statistically significantly higher than the general population prevalence of 16.6%-17.5% and in those with diabetes but is not clearly different from COPD or heart failure as there was overlap of confidence intervals between prevalence estimates. 67% of Yale IBD patients had been prescribed opiates at some time. There was a statistically significant (p<0.0001) association between depression and opiate exposed compared to opiate naive patients.

CONCLUSION: Patients in the Yale IBD program are more likely to depressed than the general population. The majority of IBD patients had been prescribed opiates at some point. There is an association between opiate use and depression among Yale IBD program patients. Screening for depression should be routine in all IBD patients and opiates should be avoided although no causal role is identified.
Qualitative study on hospital-dependent patients
Tao Liu, M.D., Mary Tinetti, M.D.

AIM
A subset of older adults, distinct from those with chronic critical illness, appear to have multiple hospitalizations due to their chronic medical conditions. The aim of this project was to explore the perceptions and experiences of older adults with recurrent hospitalizations.

METHODS
A total of 20 patients hospitalized at an academic medical center between March to September 2015 underwent semi-structured qualitative interviews. Criteria for selection included age 65 and older, ≥three hospitalizations over the previous six months, at least one chronic medical condition, and admission to a medical service at the time of the study. Patients who met criteria for chronic critical illness, had code status of Comfort Measure Only, or had a conservator were excluded. Interviews were digitally recorded, transcribed and analyzed by two investigators independently using an inductive or “bottom up” approach to identify emerging themes and exemplifying quotes. Codes were generated and categorized into themes and subthemes using Atlas Ti Software.

RESULTS
Four main themes emerged. The first was that despite preference to be at home, the hospitalizations were inevitable and unavoidable, including inability to survive outside the hospital, (“I think if I haven’t come to the hospital, I probably would have died”). The second was feeling safer in the hospital, (“makes me feel safer in case you go into something like cardiac arrest, you are right here where they can help you.”). The third was the occurrence of hospitalizations despite support outside the hospital (“... I have a heart doctor... a chest doctor whatever you call it I have all the doctors...”). Finally, participants noted lack of or inadequate goals of care discussions and preference for having these discussions with their ambulatory care physicians, (“Because I know my doctor much closer...And the doctors in the hospital, they seem to be nice and competent, but I don’t know them...”).

CONCLUSIONS
Results suggest hospital-level of care and resources are required for some patients if survival is the goal. Frank discussions about health trajectories and outcome priorities, preferably with clinicians with whom the patients have a relationship, are needed to ensure hospitalization is consistent with their realistic health priorities.

[Signatures]
Katrin S Sadigh  
Sheela Shenoi  
April 2016

Abstract: Correlates of Mortality among Patients Admitted for Drug Susceptible Tuberculosis Treatment to a Rural District Hospital in South Africa

Background
Recent data published by the WHO indicate that tuberculosis (TB) mortality has fallen by 47% since 1990 with an estimated 43 million lives saved between 2000 and 2014 due to improvements in both diagnosis and treatment of TB. Despite progress made towards decreasing tuberculosis associated mortality worldwide, a substantial burden of disease remains, with TB matching only HIV in the number of total deaths worldwide, estimated at 1.5 million in 2014. Better understanding of factors contributing to death are needed to inform interventions.

Objective
This study aimed to determine the risk factors associated with mortality among patients admitted to the hospital in rural South Africa with a diagnosis of drug susceptible tuberculosis.

Methods
This retrospective study was conducted at a 350-bed, rural district hospital in KwaZulu-Natal province of South Africa. IRB approval was obtained from the South African Medical Association Research Ethics Committee and Yale University School of Medicine Human Investigation Committee. All patients admitted to the male or female TB ward between the months of January and June 2016 were included. Patients diagnosed with MDR-TB and XDR-TB were excluded. Available patient charts were abstracted for sociodemographic, clinical, laboratory, and radiological data using a standardized data collection tool. Univariate comparison was performed to identify correlates of mortality among these hospitalized TB patients. A p value of <0.05 was considered significant.

Results
From January to June 2015, 162 patients were admitted to the hospital for drug susceptible TB treatment. Among 115 (71%) charts available for review, the median age was 38 (IQR 38.8), 80 (69.6%) were male, 97 (84.3%) were HIV-infected, and 50 (43.5%) patients died. Age >30 years (p=0.03), history of TB medication non-adherence (p<0.001), greater radiological extent of disease including bilateral disease (p=0.04) and multilobar involvement (p=0.004), and abnormal creatinine (p=0.01) were significant correlates of mortality in patients admitted with tuberculosis.

Conclusion
Mortality among hospitalized drug susceptible TB patients is associated with age >30 years old, history of TB medication non-adherence, and greater severity of disease at hospital admission. Patients at greatest risk of death can be identified early during hospitalization with subsequent interventions directed towards modifiable risk factors. Clinically, reversing acute renal failure may have an impact on mortality. On a programmatic level, additional efforts must be directed toward early diagnosis and preventing TB medication non-adherence.
Study Title: Getting to the Root of It- A Study of Resident Teachers for Quality Improvement Curriculum
Resident: Thilan Wijesekera, PGY-3, Yale Internal Medicine Primary Care Program
Research Adviser: Dr. Robert Fogerty, MD, MPH

1. Specific Aim and Hypothesis:
   Our study aimed to design a novel, two-part quality improvement (QI) curriculum including a resident-taught seminar and an immersion activity. We hypothesized that resident teaching of QI concepts and/or an immersion activity to reinforce the concepts would lead to statistically significant improvements in parameters of knowledge, skills, attitudes, satisfaction, and outcomes.

2. Review of Methods:
   The curriculum was integrated into the Generalist Internal Medicine Inpatient Service at Yale-New Haven Hospital from January 2015 to June 2015. Specifically, the seminar was a resident-led and 40-minute using Prezi software to describe key QI principles, generate a hypothetical adverse event, and perform a root cause analysis. The subsequent experiential activity was a guided tour of the blood bank or inpatient pharmacy two to four days later. Each group that participated in the study included six to eight medical students, physician assistant students, or residents, albeit primarily the latter.
   Data was collected from pre- and post-intervention surveys in a mixed methods format of qualitative and quantitative open-ended and likert scale questions, respectively. Using criteria derived from the Institute of Medicine and Institute for Healthcare Improvement, open-ended questions were graded by two reviewers with a third-party adjudicator settling any differences. Analysis was performed through a Mann Whitney U Test through SPSS software.

Description of Results:
With 43 initially eligible learners and attrition to 53%, 50%, and 44% completion of the three surveys, there were several statistically significant results. Prior to the seminar, learners reported insufficient QI experience and satisfaction with that experience. On the post-seminar likert scale questions, residents self-reported they improved their (1) ability to perform a root cause analysis and (2) familiarity with QI concepts. On the post-seminar open-ended questions, there was a statistically significant improvement in their ability to define active versus latent error, a fishbone diagram, and a forcing function with adverse event trending towards significance. On the post-seminar survey, learners did not report high utility, although they did appear very engaged and interested during the actual activity.

Conclusion:
This resident-led, faculty-sponsored, paired lecture-immersion curriculum showed potential in effective student and housestaff education for QI principles while also developing local content experts. However, although experiential activity shows promise for quality and safety curricula, its role needs further elucidation.

Resident Signature

Research Adviser Signature
Computer Use in the Exam Room and the HIV-Infected Patient-Provider Relationship
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Abstract:
Background: Human immunodeficiency virus (HIV)-infected patients face unique psychosocial stressors thus benefit from good quality patient-physician relationships. Electronic Medical Record (EMR) use is becoming a major component of the health care system as it is thought to increase efficiency and improve quality of care. As physicians spend more time in front of the computer while interacting with the patient, there is concern that the increased use of computers in the exam room will negatively affect the HIV-infected patient-provider relationship.

Objective: The primary objective of this study was to determine whether computer use during an outpatient encounter negatively affected the patient-physician relationship among HIV-infected patients.

Methods: To determine HIV-infected patients’ and HIV providers’ attitudes toward physicians’ computer use in the exam room, two questionnaires were developed for the study. The patient questionnaire included questions regarding demographics, experience with computer use, HIV viral load and CD4 cell count, as well as items related to computer use and patient-provider relationship. The provider questionnaire included questions regarding demographics, experience with computer use, and items related to computer use and patient-provider relationship.

Results: Two hundred HIV-infected patients and 20 HIV providers were surveyed at an adult HIV clinic. The majority of HIV-infected patients (97%) and providers (74%) were satisfied with the care they received and provided, respectively. Patients who do not use personal computers, had not disclosed their HIV status, were unemployed, or were female, were more likely to view computer use as negatively affecting the encounter. Most providers believed that they could talk to patients easily when they used the computer (60%). However, the majority of providers felt that they missed non-verbal cues when using the computer (71%) and that computer use in the exam room did not improve the relationship with the patient (75%). Providers who did not feel comfortable with computer use were more likely to agree that computer use made the visit less personal compared to those who felt very comfortable (100% vs. 47%, p=0.04).

Conclusions: The results from this study demonstrate that a minority of patients view computer use in the exam room as unfavorable. The study identified specific patient populations which may benefit from less computer use in the exam room and in turn may help improve the perceived HIV-infected patient-provider relationship.
IMPACT OF ICD LEAD ADVISORY AND EXTRACTION ON QUALITY OF LIFE

BACKGROUND: Implantable cardioverter defibrillators (ICDs) are used to prevent fatal arrhythmias, but technical failures of the leads can result in failure to pace, failure to defibrillate, or delivery of inappropriate shocks. The current options for management of advisory leads include: conservative, non-invasive management with periodic monitoring; lead revision or replacement; or reprogramming of the device.

AIMS: We evaluated the impact of having advisory leads on patients’ quality of life using questionnaires. We hypothesized that patients with advisory leads still in place will have a lower quality of life compared to those whose advisory leads have been extracted.

METHODS: We used a cross-sectional study design. Patients were eligible for the study if they had received an ICD with a lead under advisory and were followed at either Yale Electrophysiology or the Connecticut Arrhythmia Center. Patients were excluded if they had undergone a heart transplant since their ICD was placed, or if they were unable to complete the questionnaire due to cognitive deficits, blindness, or language barriers. Two groups were compared: patients with an advisory lead still in place, and patients with an advisory lead that was removed either prophylactically or due to a malfunction. We designed a questionnaire which included multiple well-validated scales aimed at ascertaining patients’ level of depression, anxiety surrounding an advisory lead, and both general and ICD-specific quality of life.

First, letters with a general description of the study, including its risks and benefits, were sent to patients. Patients who did not opt out were called and offered three possible modalities to complete the questionnaire: over the phone, online, or on paper. Patients who could not be reached by phone were contacted at medical appointments and given a paper copy of the questionnaire. Based on responses to the questionnaire, psychosocial variables were compared between the two groups.

RESULTS: Our database includes 737 patients with active leads under advisory and 164 patients with advisory leads that have been removed. Of the first 226 patients we attempted to enroll, 40 completed the questionnaire, 33 declined to participate, 57 had died, and 96 could not be reached by phone or at clinic appointments.

Of the 40 patients who completed the survey, 18 had an advisory lead still in place and 22 had had their advisory lead removed. Patients with an active advisory lead who completed the survey were more likely to be male compared to those whose lead was removed, were older, and had a lower ejection fraction.

CONCLUSION: We are continuing to analyze the responses we have collected so far to determine the impact of advisory leads on quality of life, and plan to continue enroll patients in the upcoming year.

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