The Role of Progranulin, YKL-40 and Cathepsins D and S in Gaucher Disease

Yuliya Afinogenova, M.D., Pramod Mistry, M.D., PhD.

Background: Gaucher Disease (GD) is a multi-systemic disorder due to a genetic deficiency of lysosomal glucocerebrosidase, which underlies the accumulation of glucocerebroside-laden lysosomes, most conspicuously in the macrophages. Enzyme replacement and substrate reduction therapies (ERT and SRT, respectively) are approved for treatment of non-neuronopathic GD. Response to therapy is based on surrogate disease markers, such as organomegaly, cytopenias and radiological indicators of skeletal involvement. Several macrophage-specific biomarkers have been validated, including chitotriosidase, but its utility is limited by common polymorphism in *CHIT1* gene and unclear role in pathophysiology. We used gene expression profiles in the spleen of our GD mouse model to identify novel candidate biomarkers and observed increased expression of cathepsins D and S, YKL-40 and decreased expression of progranulin. These molecules were found to have a wide range of physiologic and pathophysiologic functions that may be important in GD pathophysiology.

Specific Aim: We aimed to understand the role of cathepsins D and S, YKL-40 and progranulin in human GD.

Methods: We measured serum levels of cathepsins D and S, progranulin, and YKL-40 in 41 pre-treatment and 41 post-treatment GD subjects and healthy controls (HC). These molecule levels were compared across subjects to assess the effect of treatment. We assessed their biomarker potential in GD and compared them to known GD biomarkers, chitotriosidase and chemokine ligand 18, CCL18. In a larger sample of 134 post ERT patients, associations of YKL-40 with standard measures of GD severity were analyzed.

Results: Mean YKL-40 and cathepsin D and S levels were significantly higher in GD subjects compared to HC; mean progranulin levels were lower in GD subjects compared to HC. The difference in mean progranulin and YKL-40 levels between pre- and post- ERT subjects was not significant, while the difference in cathepsin D and S in pre- and post-ERT subjects was statistically significant. Patients with persistently large spleen volumes post-ERT (defined as spleen volume $\geq$4 multiples of normal) had significantly higher serum YKL-40 compared to post-ERT subjects with smaller spleen volumes (YKL-40: 63.03±6.45 vs. 46.42±4.25, $p=0.03$). Serum YKL-40 levels were significantly higher in subjects with severe bone involvement (Hermann Score 3 to 5) compared to those with milder bone involvement (Hermann Score 1 to 2) (YKL-40: 70.12±4.25 vs. 48.06±3.67, $p=0.0002$). YKL-40 was only weakly associated with chitotriosidase ($r=0.22$, $p=0.0073$) and CCL18 ($r=0.27$, $p=0.002$), and cathepsin S was moderately associated with chitotriosidase ($r=0.4$, $p=0.01$) and CCL18 ($r=0.63$, $p<0.0001$). Receiver operating curves for progranulin and YKL-40 demonstrated areas under the curves of 0.80, $p<0.0001$ and 0.70, $p<0.0001$, respectively.

Conclusions: This paper provides insight into novel pathways that may play a role in pathophysiology of GD and its specific complications, and future studies aimed at elucidating the role of cathepsins, progranulin, and YKL-40 may be important to facilitate monitoring of patients and provide insight into additional treatment options, particularly for currently difficult to treat GD complications.

Yuliya Afinogenova

Resident's Signature

Mentor's Signature

Routine Urinalysis Screening in the Refugee Health Examination: A retrospective assessment of findings and correlation to genitourinary disease.

Bryan Brown, M.D., Aniyizhai Annamalai, M.B.B.S., M.D.

Background: The U.S. Centers for Disease Control (CDC) recommends consideration of routine urinalysis (UA) at the post-arrival refugee health examination (RHE). Evidence on RHE UA utility is limited. Epidemiology of genitourinary (GU) issues in this population is poorly understood.

Specific Aims:

AIM 1: To determine the prevalence of microscopic hematuria on initial Refugee Health Assessment (RHA) urinalysis (UA) in our clinic, to determine the rate of guideline-based work up RHA microhematuria, to characterize the attributable diagnoses if known, and to qualitatively assess barriers to follow up.

Hypothesis: Routine RHA UA in asymptomatic newly arrived refugees will not be predictive of significant genitourinary (GU) disease, and when abnormalities such as hematuria were discovered there will be inadequate follow up based on current society guidelines.

Methods: A retrospective chart review was performed in newly arrived refugees, age ≥18 years old at the time of an RHA at Yale's resident-run refugee clinic between May 2013 and May 2016. Manually extracted data included demographic information (age, sex, weight, country of origin); RHA laboratory screening including basic metabolic panel, interferon-gamma release assay (IGRA), schistosome IgG, UA macroscopic with reflex to microscopic; presence of GU symptoms documented during RHA; existence of repeat UA when indicated; encounters with urologists or encounters for nephrolithiasis since arrival. "Qualifying hematuria" (QH) was defined as ≥3 RBCs/HPF on RHA UA based on American Urologic Association guidelines. Likelihood ratios were calculated based on the correlation between QH, positive leukocyte esterase (LE), or a composite of two, with the outcomes of positive schistosoma antibody, positive IGRA, nephrolithiasis since arrival, and encounters with urology. For patients with QH on RHA UA, patients were counted as having or not having a follow up urinalysis. For those who never had follow up in our system, reason for lack of follow up was qualitatively assessed. For those with persistent hematuria, etiology of hematuria and completion of work up was qualitatively assessed.

Results: 420 patients met inclusion criteria, with the following abnormalities: 29 with detectable proteinuria, 78 with QH, and 80 with positive LE. 42 were ≥35 years old, of which 18 had one or more follow up UAs, of which 10 had persistent QH on at least one subsequent UA. Of these 10, 5 had acknowledgement of need for further work-up in their chart by providers, but of the 3 referred to urology only 1 made it to their appointment. Likelihood Ratios for QH, positive LE, or their composite abnormal on UA did not have a positive or negative likelihood ratio statistically different than 1.00 for schistosoma seropositivity, positive IGRA, nephrolithiasis, or urology encounters.

Conclusion: Routine RHA UA was not predictive of any relevant GU outcomes. Rates of abnormal UA follow-up were poor, due to patient healthcare navigation challenges and lack of provider acknowledgement of the abnormal results. Thorough GU review of systems and symptom-triggered UA similar to that of the domestic population would likely be adequate in place of universal RHA UA.

Resident's signature

Mentor's signature

The Patient Ownership Scale: Development of an Instrument to Measure Ownership of Patient Care amongst Physicians

Mia Djulbegovic, MD and Liana Fraenkel, MD

Background: Ownership of patient care is a complex concept that is essential to the provision of high quality medical care. However, there appears to be gradual erosion of ownership by trainees in the era of curtailed duty hours. How this decline in ownership relates to clinical skills development, quality of care and long-term outcomes is unknown due to paucity of data and the lack of an objective measure of ownership.

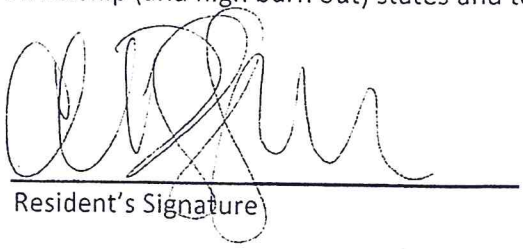
Specific Aim: To develop an instrument to measure ownership of patient care among trainees

Hypothesis: Our null hypothesis is that there will be no difference in ownership among trainees according to PGY (post-graduate year) levels, experience (in months) in the intensive care unit, call schedule, day vs night float, degree of patient turnover, duration on service, degree of burn out, and degree of perceived ownership.

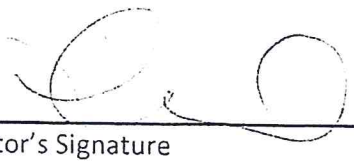
Methods: We developed a 15-item (each measured on 7-point Likert scale) ownership scale to measure its key constructs: advocacy, responsibility, accountability, follow-through, knowledge, communication, initiative, continuity of care, autonomy and perceived ownership. The survey, which also included questions on demographic information and work environment, was administered to trainees in a large, academic, internal medicine residency program at the end of an inpatient rotation. We assessed face validity and usability testing with cognitive interviewing. We calculated Cronbach's α to determine the internal consistency of the scale. Factor analysis was performed to identify any unobserved constructs that may define the multi-dimensional aspect of ownership. Bivariate and correlational analysis were performed to examine construct validity.

Results: 192 trainees completed the survey, of which 166 responses were included in the analysis (age range 23 to 43 years). Responses were excluded if the survey was completed in less than 1 minute, if the survey remained open for more than 24 hours, or if there was zero variance among responses. The ownership scale demonstrated good internal consistency (Cronbach's α=0.88). Factor analysis identified 3 factors corresponding to advocacy, autonomy and responsibility. The mean (SD) ownership was 5.57 (0.74). We found that both training level and prior experience (in months) in the intensive care unit were significant predictors of ownership ($p<0.01$). There was no significant relationship between ownership and age, gender, inpatient service type, call schedule, turnover of attending physicians or patients, or supervisory experience (in years) of the attending physician. We found a significant negative correlation between ownership and burn out ($r=-0.33$, $p<0.01$), depression ($r=-0.24$, $p=0.01$), detachment ($r=-0.35$, $p<0.01$), and frustration ($r=-0.31$, $p<0.01$). There was a significant positive association between ownership and fulfillment ($r=0.37$, $p<0.01$) and happiness ($r=0.36$, $p<0.01$).

Conclusions: To our knowledge, this is the first time that ownership has been quantified in physicians. Our scale demonstrates good internal consistency and preliminary evidence of validity. We believe that our scale can be used to modify clinical training environments in order to foster more ownership in trainees. Clinical educators can use our scale to detect low ownership (and high burn out) states and to test interventions aimed at fostering ownership.



Resident's Signature



Mentor's Signature

Relationship Between Patient-Reported Hospital Experience and 30-Day Mortality and Readmission Rates for Acute Myocardial Infarction, Heart Failure and Pneumonia

Jonathan D Eisenberg, MD; Ning Dong, MD, MS; Kumar Dharmarajan, MD, MBA; Erica S Spatz, MD, MHS; Nihar R Desai, MD, MPH

Importance: The Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey has focused hospitals' attention on patient experience metrics, and is currently included in the Hospital Value-Based Purchasing (HVBP) program as well as other public reporting programs. However, little is known about the association of patient experience with hospital outcomes such as mortality and readmissions.

Specific Aim: Given the uncertain relationship of patient experience with more traditional hospital outcomes, we sought to assess the relationship between hospital HCAHPS scores with hospital 30-day mortality and readmission rates for acute myocardial infarction (AMI), heart failure (HF) and pneumonia (conditions targeted by both the Hospital Readmission Reductions Program and HVBP program).

Methods: We conducted a cross-sectional observational analysis of public data from the Medicare Hospital Compare website representing a nationwide sample of United States hospitals. Patient experience – derived from HCAHPS survey data – was divided into metrics assessing overall satisfaction and metrics assessing nine individual domains of experience. Correlation of patient experience metrics with hospital 30-day mortality and readmission rates for AMI, HF, and pneumonia was assessed with pair-wise Pearson correlation coefficients (weighted by patient volume).

Results: The numbers of hospitals for mortality and readmission analyses were, respectively, 2346 and 2137 for AMI; 3212 and 3234 for HF; and 3316 and 3322 for PNA. Patients' overall satisfaction was significantly and inversely associated with readmission in all three conditions (correlation coefficient $r = -0.22$ to -0.31; $p<0.001$). Relationships were modest for AMI and pneumonia mortality ($r = -0.10$ and -0.20, respectively; $p<0.001$) and not present for HF mortality. Each of the nine individual domains of patient experience were inversely associated with readmission rates for AMI, HF or pneumonia ($r = -0.16$ to -0.30, $p<0.001$), except quietness which was only weakly associated ($r = -0.04$, $P=0.056$ for AMI, $r = -0.10$ to -0.15, $p<0.001$ for HF and pneumonia).

Conclusions: Higher patient experience scores are associated with lower 30-day readmission rates, with more modest associations for mortality. This finding provides support for the use of patient experience metrics in assessing hospital quality. The key drivers of this observed relationship warrant additional study.

Arterial Inflammation in Patients with PTSD: A Pilot Study

Background: Patients with Post-Traumatic Stress Disorder (PTSD) are at a higher risk for future cardiovascular events. The pathophysiologic basis for this elevated risk remains unclear; however, recent studies have demonstrated a link between stress and metabolic activity in bone marrow, spleen and arterial wall, which are attributed to activation of inflammatory cells in bone marrow and migration to spleen, and arterial wall. Multiple studies have used FDG-PET imaging as a non-invasive measure of metabolic activity within bone marrow and spleen and assessment of arterial inflammation.

Specific aims: To assess the relationship between PTSD and degree of arterial inflammation in patients who have undergone ^{18}fluorodeoxyglucose-positron emission tomography (FDG-PET) and to compare the FDG uptake in bone marrow and spleen in patients with PTSD with the control group and their correlation with arterial inflammation.

Methods: We conducted a retrospective search for all the patients who had undergone FDG-PET imaging of chest and abdomen at WHVA in 2016 and reviewed the medical records to select patients with diagnosis of PTSD. In addition, we studied a prospective cohort of 16 patients (9 with PTSD and 7 controls) without prior history of cardiovascular disease who were separately recruited. We performed image analysis and measured FDG uptake in ascending aorta, bone marrow, and spleen by quantifying Standardized Uptake Value (SUV) as well as Target-to-Background ratio (TBR).

Results: In the retrospective study, we identified 572 patients who had undergone FDG-PET imaging at WHVA for various clinical indications during the calendar year of 2016. We reviewed the records of these patients and identified only 3 patients with diagnosis of PTSD. Given the low number of the subjects in the retrospective study, we proceeded with the image analysis only in the prospective study. The two groups of prospective study (9 PTSD and 7 controls) matched closely by age and gender, and with regards to cardiovascular risk factors. We did not find any significant difference between the aortic FDG uptake in PTSD and control groups (TBR [IQR]: 2.5 [0.6] vs. 2.2 [1.6], p=0.3). Similarly, we did not find a significant difference between bone marrow and spleen FDG uptake between two groups (bone marrow TBR [IQR]: 3.7 [1.1] vs. 3.4 [0.6], p=1.0 and spleen TBR [IQR]: 2.7 [0.5] vs. 2.6 [0.6], p=0.5). There was a significant correlation between aortic and bone marrow SUV (r = 0.7, p= 0.03) in patients with PTSD but not in controls (p=0.2).

Conclusions: This pilot study did not reveal any significant difference in arterial inflammation or bone marrow and spleen metabolic activity between patients with PTSD and control group, as assessed by FDG-PET imaging. However, the significant correlation between FDG uptake between bone marrow and arterial wall in PTSD patients and not in the control group shows a potential relationship between these tissues, which warrants further studies.

Resident:

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Association between number of positive lymph nodes and recurrence rates after ipsilateral neck dissection of locally advanced resectable head and neck cancer.

Fahad Faruqi, M.D., Barbara Burtness, M.D.

Background: HPV-negative squamous cell carcinoma of the head and neck arises in the oral cavity, larynx, oropharynx, and hypopharynx. Approximately 30 to 40 percent of such cancers present as locally advanced (Stage III and Stage IV) disease. Definitive radiation is an option for Stage I and Stage II disease (i.e without nodal involvement). However, for locally advanced disease, resection of the primary tumor along with ipsilateral neck dissection of levels I-III lymph nodes is indicated. Adjuvant radiation is a mainstay of treatment after surgical resection. And in patients with high risk features on pathology such as extracapsular spread and/or positive margin, concurrent chemotherapy with cisplatin alongside radiation was recently shown to improve survival. A prospective study in p16-positive oropharyngeal tumors showed low prognostic value of nodal status as a predictor of survival. A subsequent study did demonstrate that soft tissue metastasis in p16-positive cancers is associated with higher rates of recurrence at distant metastatic sites. For p16-negative tumors, it remains unknown if the absolute number of positive lymph nodes and site of positive lymph nodes is predictive of recurrence and site of recurrence in locally advanced surgically resectable disease.

Hypothesis: In locally advanced surgically resectable p16-negative oropharyngeal cancers as well as cancers of the larynx, oral cavity, and hypopharynx, 4 or more positive lymph nodes after surgical resection predicts higher rates of recurrence.

Methods: This was a retrospective single-center study of patients with locally advanced resectable non-nasopharyngeal head and neck squamous cell carcinoma who underwent ipsilateral or bilateral neck dissection at Yale New Haven Hospital. Eligible patients were identified using clinical/pathology databases at YNHH. Data collected will include patient age, sex, type of cancer (oral cavity, buccal mucosa, hard palate, tongue, retromolar trigone, hypopharynx, oropharynx, larynx), date of surgery, ipsilateral vs. bilateral neck dissection, levels dissected in each neck, stage, surgical margins, number of nodes recovered per neck, number of positive lymph nodes, site of positive lymph nodes, extracapsular extension, adjuvant chemotherapy, adjuvant radiation therapy, date of recurrence, and site of recurrence.

Results: Pathology results were available for 1900 cases of locally resectable head and neck cancers between 2000-2013. 122 cases had 4 or more positive lymph nodes identified after resection. 108 cases were excluded due to either insufficient follow up data or confirmed p16 positive status. An additional 3 cases were excluded due to a history of prior malignancy and 1 case was excluded due to receiving neo-adjuvant chemotherapy prior to resection. Out of the 10 cases with data available that underwent surgical resection and were p16-negative oropharyngeal cancers or cancers of the larynx, hypopharynx, or oral cavity, 7 had recurrence within 3 years.

Conclusion: Due to lack of follow up data on the vast majority of cases that underwent surgical resection for locally advanced head and neck cancer, it remains unclear whether high node number predicts recurrence in p16-negative locally resectable head and neck cancers.

Fahad Faruqi

Fahad Faruqi, MD

Barbara Burtness

Barbara Burtness (May 9, 2018)

Barbara Burtness, MD

Title Associations between incarceration and viral load and HIV transmission risk among HIV-positive men who have sex with men in the US

Background While new HIV infections have decreased in recent years, new infections are not decreasing among men who have sex with men (MSM), especially MSM of color. Studies have shown that, in general, people at risk for and living with HIV have increased interaction with the criminal justice system than the general population, but little is known about the relationship between criminal justice history and HIV risk among MSM. This study seeks to measure associations between recent and prior history of incarceration and HIV risk behavior and viral load in HIV-positive MSM.

Methods The Veterans Aging Cohort Study Survey Substudy (VACS Survey) is an observational cohort of veterans living with HIV that began in 2002 that was designed to evaluate the role of alcohol use with clinical outcomes. We analyzed VACS Survey data from the 2011-2012 follow-up, and include men who reported having at least one male sex partner in the year prior to the survey and who provided data regarding incarceration history (N=487). The independent variable of interest is self-reported history of incarceration (recent, ever, or never), and the dependent variables are detectable viral load and HIV risk behaviors: injection drug use (IDU), 2+ sexual partner in past 12 months, sex without a condom in the past 12 months, sex without a condom due to alcohol or drug use, and sex with partners who had other sexual partners. Covariates included age, race, education, relationship status, income, and homelessness.

Results Participants had a mean age of 52 years (sd=9.5) and included 292 (60%) African-American, 131 (27%) white, and 64 (13%) of other race/ethnicity. The prevalence of incarceration history was 40%. In both unadjusted and adjusted models for age, education, marital status, income, and homelessness, recent and prior incarceration versus no incarceration were strongly associated with having a detectable HIV viral load (recent adjusted odds ratio [AOR] 3.25 95% CI: 1.35-7.83; prior AOR: 3.30 95% CI: 1.84-5.91). Those with a history of incarceration also had significantly higher odds of past 12 month IDU (recent AOR 17.11, 95% CI: 2.78- 105.48; prior AOR 6.10, 95% CI 1.15-32.44). Recent and prior incarceration were strongly associated with having two or more sex partners (recent AOR 2.74, 95% CI: 1.25-6.02; prior AOR 1.71, 95% CI 1.11-2.64) and engaging in sex without a condom due to alcohol (recent AOR 14.34, 95% CI: 3.17-64.74; prior AOR 8.30 95% CI: 2.25-30.63) or drug use (recent AOR 5.74 95% CI 1.83-18.03; prior 2.90 95% CI: 1.13-7.42 respectively) and with partners who had other partners (recent AOR 3.31, 95% CI: 1.42-7.72; prior AOR 2.62, 95% CI 1.47-4.68).

Conclusions Among HIV positive MSM, incarceration is linked with multiple proximate determinants of HIV transmission including detectable viral load, IDU and high risk sexual activity. This study highlights the importance of targeting this population for intervention following release from incarceration as a means of reducing new HIV infections.

Resident's Signature
Laura Hawks

Mentor's Signature
Emily Wang

Impact of Automated Calculation of Derived Laboratory Values on Clinical Decision Making

Fred Howard, M.D., Liana Fraenkel, M.D.

Background: The drive towards evidence-based medicine has led to the creation of a myriad of data-driven tools and calculators for diagnosis and risk stratification [2]. However, given the time constraints of clinical practice, speed and ease of use are critical considerations when adopting clinical decision support measures [3]. Despite the availability of laboratory data in EHRs, calculation of derived laboratory data is rarely automated. In a survey of EHR vendors, more than half lacked an implementation of even basic laboratory test interpretations [7]. Physicians frequently use external calculators to process laboratory data, but this can lead to under-recognition of applicable formulas and inaccurate data input [8].

Specific Aim: To determine the impact of presenting derived laboratory data within clinical vignettes on medical decision making and value-based of care.

Hypothesis: Inclusion of derived laboratory data adjacent to traditional laboratory data in simulated patient cases across multiple specialties will improve resident decision making and delivery of value-based of care.

Methods: A focus group with two Nephrology and two Hematology faculty was held to identify the most high yield laboratory formulas in their fields. Clinical vignettes for which each of these formulas was applicable were then developed. We designed a mock-EMR web environment where participants could review the clinical cases, make changes to medications, and order laboratory tests. Correct medication changes and laboratory testing was determined through consensus agreement of two faculty in the relevant specialty. Yale Internal Medicine residents were recruited via email from November 2017 through January 2018. Residents were randomized to review cases with (intervention group) or without (control group) derived laboratory data, and were specifically instructed to use outside calculators as necessary. Quality of care was calculated as a percentage of correct medication and laboratory changes in comparison to faculty consensus. Cost of care was determined using Yale-New Haven Hospital laboratory testing costs and Medicare drug pricing records, and value was defined as the ratio of quality over cost. Intervention and control groups were compared with regards to quality, cost, value, and time to completion of cases using a two-sided t-test. A pre-specified subgroup analysis was performed comparing outcomes of interns and residents, and a post-hoc subgroup analysis was done comparing formulas that are routinely performed with a set of laboratory data (calculation of fractional excretion of electrolytes in acute kidney injury) versus those requiring recognition of an applicable formula (correction of calcium for a low serum albumin).

Results: 187 residents were invited to participate, of which 44 residents (21 in the intervention group, 23 in the control group) completed 282 cases. The average quality was 49% in the intervention group and 20% in the control group ($p < 0.001$), and the value of care (quality / cost) was 0.69 in the control group and 0.53 in the intervention group ($p = 0.008$). The intervention group spent an average of 4.7 minutes per case, and the control group spent 3.9 minutes per case ($p = 0.08$). Quality significantly improved in both interns (49% in the intervention, 18% in the control group) and residents (49% in the intervention, 22% in the control group). In cases that required recognition of the applicable formula, the quality in the intervention group was 48% versus 5% in the control group ($p < 0.001$), but quality was also improved in cases that did not require recognition (50% versus 34%, $p = 0.02$).

Conclusions: Inclusion of derived laboratory data in simulated cases led to a significant improvement in quality and value of care, irrespective of level of training. Although cases requiring recognition of an applicable formula demonstrate the most benefit, quality is improved even when intuitive formulas are included in the EMR. Our results call for further study with real world implementation of automatic laboratory value calculation, to see if such a benefit is confirmed in clinical practice.

Liana Fraenkel

The Use of Thromboelastography in Monitoring Coagulation Status for Patients Treated with Low Molecular Weight Heparin, Warfarin, Apixaban, and Rivaroxaban

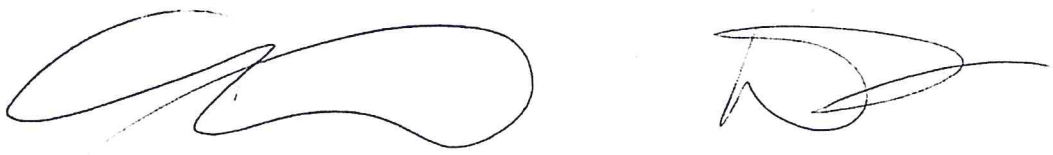
Debbie Jiang, MD, Alfred Lee MD, PhD

Introduction: Thromboelastography (TEG) is used to rapidly assess global coagulation status. A few studies in the literature have explored a possible role for TEG in anticoagulant monitoring, with conflicting observations. Several have noted increased reaction time (R time) in patients taking warfarin, low molecular weight heparin (LMWH), apixaban, and rivaroxaban. We wondered if TEG could be used alongside traditional markers of anticoagulation as a measure of anticoagulant efficacy. We hypothesized that the R time should be prolonged in patients on therapeutic dosing of warfarin, LMWH, apixaban, and rivaroxaban and that the R time should correlate with traditional markers of anticoagulation.

Methods: Blood samples were collected from patients on therapeutic doses of warfarin, LMWH (enoxaparin or dalteparin), or an anti-Xa direct oral anticoagulant (DOAC, apixaban or rivaroxaban) due to a history of thrombosis. TEG was performed on all samples with and without addition of heparinase; R time, K time, alpha-angle, maximum amplitude, and percent of clot lysis after 30 minutes were measured. Standard anticoagulation parameters were obtained at the same time as TEG values [prothrombin time (PT) and activated partial thromboplastin time (PTT) for warfarin- and DOAC-treated patients; anti-Xa level for LMWH-treated patients]. For each patient, pertinent medical history was recorded including: age, medical comorbidities, and thrombotic history. Von Willebrand factor (vWF) antigen level, factor VIII (fVIII) activity, anti-Xa, and R time were examined in a follow-up cohort of enoxaparin-treated patients. Correlation between TEG and anticoagulation parameters was analyzed using Spearman correlation coefficient (r).

Results: Forty-six patients participated in this study. Median age was 52 years (range, 20-83). The most common indication for anticoagulation was deep venous thrombosis or pulmonary embolism ($N = 33$); 5 subjects had active cancer at the time of anticoagulation testing (all on LMWH). Among warfarin-treated patients ($N = 19$), INR was correlated with R time ($p=0.005$) and 4 patients had a prolonged R time of over 10 min. Among patients on LMWH (enoxaparin, $N = 13$; dalteparin, $N = 1$), 5 had a prolonged R time, but there was no correlation between anti-Xa level and R time, R time ratio or R time difference with or without heparinase, or any other measured TEG parameter. Among DOAC patients (apixaban, $N = 6$; rivaroxaban, $N = 8$), R time was not elevated in any of the samples, but there was a significant correlation between PTT and R time ($p=0.006$). Four study patients had recurrent thrombotic events (1 with antithrombin deficiency, chronic liver disease, and bowel resection, on warfarin; 1 with May-Thurner syndrome, on LMWH; 2 with metastatic cancer and Trousseau's syndrome, also on LMWH) in spite of therapeutic INR or anti-Xa levels; these patients were all found to have normal R times on TEG. In a follow-up analysis of 8 enoxaparin-treated patients, 6 had normal and 2 had prolonged R times. All 6 with normal R times had elevations in vWF and/or fVIII, while the 2 with prolonged R times had normal levels of vWF and fVIII.

Conclusion: We did not find that therapeutic anticoagulants prolong R time. However, we report that R time is significantly correlated with INR in patients on warfarin. R time is also correlated with PTT in patients on DOACs. For both DOACs and warfarin, TEG could be useful in assessing coagulation status. In patients on LMWH, R time was not elevated or associated with degree of anticoagulation. This finding may be affected by circulating levels of vWF and fVIII.



Factors Associated with Discharge Home among MICU Patients Receiving Early Mobilization

Roger Kim, M.D., Lauren Ferrante, M.D., M.H.S.

Background: Studies have suggested an association between early mobilization in the intensive care unit (ICU) and increased discharges home. Identifying factors associated with discharge home could help early mobilization programs determine which patients might benefit from continued mobilization on the medical floor after the ICU.

Specific Aims: To evaluate independent factors associated with discharge home among medical intensive care unit (MICU) patients in an early mobilization program who were initially admitted from home.

Hypothesis: Advanced age and indicators of illness severity (ICU and hospital lengths of stay [LOS] and APACHE II score) will be associated with a decreased likelihood of discharge home while baseline ambulatory status and maximum level of mobilization achieved in the ICU will be associated with a greater likelihood of discharge home.

Methods: We reviewed the medical records of patients in the YNHH MICU during initial implementation of an early mobilization program (3/26-6/30/15) and 1 year later (3/26-6/30/16). We gathered information on demographics, ambulatory status prior to admission, comorbidities, the hospitalization and critical illness, and the details of all physical therapy (PT) sessions in the ICU, including the maximum level of mobilization achieved across all PT sessions in the ICU. Maximum level of mobilization was operationalized from least to most as: therapeutic (in-bed) exercises, bed mobility, transfer training (bed-to-chair), gait training (<25-50% patient effort), gait training (75% patient effort), and gait training (independent). Patients with goals of comfort measures only, discharge to hospice, or excessively long lengths of stay (ICU LOS >21 days or hospital LOS >45 days) were excluded. We compared the characteristics of the Year 1 versus Year 2 cohorts using the Wilcoxon test for continuous variables and the Fisher exact test for categorical variables. We then combined the two annual cohorts into one analytic sample and selected the patients who were admitted to the hospital from home. We evaluated the overall rate of discharge home, and then examined 12 potential predictors (age, sex, race/ethnicity, body mass index, baseline ambulatory status, number of comorbidities, APACHE II score, respiratory failure, number of PT sessions, maximum level of mobilization, ICU LOS, and hospital LOS) for their association with discharge home using a multivariable logistic regression model. Statistical significance was defined as a $p<0.05$ (2-tailed).

Results: There were no significant differences between characteristics of the Year 1 and Year 2 cohorts, allowing them to be combined into one analytic sample. Among the combined cohort (N=183), the mean age was 61.9 years (SD 16.67), the mean APACHE II score was 23.5 (SD 7.11), and 66.1% ambulated independently at baseline. Overall, 65.0% of patients were discharged home after their critical illness. In the multivariable analysis, a higher maximum level of mobilization achieved in the ICU was independently associated with greater odds of discharge home (OR 1.46, 95% CI 1.13-1.88). Increased age (OR 0.95, 95% CI 0.93-0.98) and hospital LOS (OR 0.94, 95% CI 0.90-0.99) were independently associated with decreased odds of discharge home. The multivariable model showed strong discrimination (C-statistic 0.79) and good calibration (Hosmer-Lemeshow p-value >0.05).

Conclusions: Among MICU patients admitted from home, each increase in the maximum level of mobilization achieved in the ICU was associated with a nearly 50% greater odds of discharge back home. Early mobilization programs may increase discharges home by focusing their efforts on increasing the maximum level of mobilization achieved by MICU patients.

4/10/18

4/10/2018

Implementation of type 2 diabetes (T2DM) shared medical appointments (SMAs) in an internal medicine (IM) primary care residency curriculum

Ross Kristal, MD, Tracy Rabin, MD, MS

Background: T2DM management can be challenging during a time-limited appointment. SMAs, in which groups of patients with the same condition meet for comprehensive care, may overcome this obstacle. Prior studies showed that DM SMAs lead to improved hemoglobin A1C and systolic blood pressure, and higher satisfaction in care. DM SMAs may provide residents with the opportunity to improve group facilitation skills and proficiency in diabetes counseling and management, but this has not been well studied.

Specific Aims: 1) Determine the feasibility of incorporating SMAs in an IM residency curriculum and clinic; 2) Evaluate the educational impact of SMAs on residents; 3) Assess non-inferiority of SMAs versus 1-on-1 DM Clinic visits regarding health outcomes; and 4) Evaluate SMA impact on patient diabetes-related distress, knowledge, and self-management.

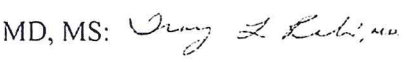
Hypotheses: 1) Implementing T2DM SMAs will improve IM resident's knowledge of SMAs, confidence in facilitating SMAs, and counseling patients on DM self-management. 2) Patient participation in T2DM SMAs compared to 1-on-1 DM Clinic visits will result in non-inferior health outcomes; 3) Patients participating in the SMA will have improvement in their diabetes-related distress, knowledge, and confidence managing their diabetes.

Methods: *Recruitment:* DM Clinic patients were recruited by phone and could a) enroll in the SMA as a study subject; b) enroll and decline study participation; c) decline participation in the SMA, but consent to prospective chart review (control patients); or d) decline all participation. Residents were offered, by email, the opportunity to facilitate the SMAs, in place of staffing the typical DM Clinic. *Intervention:* SMAs were held the same time as the typical DM Clinic; each SMA cycle was 4 weekly sessions. Two residents and one attending conducted the SMA using Healthy Interactions DM Conversation Maps™ curriculum. *Evaluation:* Baseline demographic and health measures were collected via surveys and electronic health record extraction for study and control patients. Study participants completed the DM Knowledge Questionnaire, Patient Activation Measure-13 and DM Distress Screening Scale pre-/post-SMA. Health outcome and processes measures will be tracked up to 1-year post-intervention for study and control patients. Residents completed pre-/post-surveys.

Results: Four SMA cohorts took place. The average study patient cohort recruitment rate was 36.5%. For the 1st cohort, an average of 3.75 patients (62.5%) attended the four sessions, no patients (0%) attended the SMA for the second cohort, 1 patient (20%) attended for the third cohort, and 1 patient (12.5%) attended for the fourth cohort. The average resident recruitment rate was 83.3%. Only the first cohort completed the curriculum because of low patient attendance in the subsequent cohorts.

Conclusion: A T2DM SMA was implemented into an IM residency curriculum and clinic. Resident recruitment rate was high suggesting resident's interest in learning more about SMAs. Low patient attendance limited the number of completed SMA curriculum and ability to report the SMA impact on resident and patients. Future steps will need to identify the reasons for the low attendance to improve attendance for future cohorts.

Ross Kristal, MD: 

Tracy Rabin, MD, MS: 

Project Title: Preliminary Analysis of Effect of Respiratory Virus Testing and Antibiotic Stewardship Program on Use of Inappropriate Antibiotics for Acute Respiratory Tract Infections in Outpatient Settings

Nejla Zeynep Kubilay, MD Research Mentor: Louise M. Dembry, MD, MS, MBA

Purpose: Determine the impact of laboratory testing for RVP on rates of antibiotic prescription among different outpatient settings and investigate the effect of an antibitic stewardship intervention to decrease inappropriate antibiotic use for ARTIs.

Hypothesis: Increased utility of laboratory testing for respiratory pathogens followed by an antibiotic stewardship intervention would decrease the inappropriate use of antibiotics for viral etiologies.

Methods: The baseline data from a prior study conducted at West Haven VA in 2014-2015 flu season showed that more than 40% of the patients received antibiotics if the RVP was negative or was positive for a virus other than influenza. In 2017-2018 flu season an antibiotic stewardship intervention was implemented to decrease inappropriate antibiotic use for ARTIs at the West Haven VA. This intervention included 30 minute educational presentation for the providers and nurses of primary care clinics and ED, posters distributed and hung in the visible areas in the doctor offices, triage and waiting areas, screen saver at all VA computers stating "VACT physicians are committed to use antibiotics wisely", patient engagement with CDC infosheets given to the patients with ARTI symptoms at triage or after doctor visit, leadership engagement with chiefs of ED and Primary Care reinforcing the intervention by email. Furthermore, a nationwide ARTI campaign was also taking place at VAs with a special emphasis on antibiotic stewardship. Patients who underwent RVP testing between October 2017 and March 2018 randomly selected from laboratory records database. All admitted patients were excluded from the study.

Results: 120 patients, 40 from each group, were randomly selected for analysis. 8, 16 and 11 admitted patients respectively from influenza positive, RVP negative and RVP positive for non- influenza virus groups. Out of 85 included patients, 10 were female and less than half of the patients were above 65 years old (40 of 85). Majority of the data was received from ED (84%). Interestingly, only 42 % of the patients had a flu shot prior their ARTI visit. Of 32 influenza positive patients, 23 received oseltamivir treatment and 5 of the 23 received additional antibiotics. Of the 24 RVP negative patients, only 4 received antibiotics. Finally of the 29 non influenza virus positive patients only 6 received antibiotics; 5 of whom had underlying respiratory disease. Antibiotic of choice was mostly azithromycin, followed by doxycycline and moxifloxacin with variable durations (ranging from 5 to 10 days). Overall, only 17 % of the patients received antibiotics, 73 % of those had underlying respiratory disease. Interestingly, though only 4 of the antibiotic prescribed patients had cultures obtained. None of the RVP negative or non- influenza positive patients received oseltamivir, significantly different than prior years.

Conclusions: Preliminary data suggest that antibiotic prescriptions for patients who underwent RVP testing for ARTIs was significantly lower in the 2017/2018 influenza season as compared with prior years. This data is also compatible with the pooled data from the ARTI campaign database resembling patients who came to ED with ARTI diagnosis. Nursing and provider education, complemented with patient engagement was the primary intervention. RVP use increased significantly during the intervention period; it is unclear whether this was caused by the intervention or reflects underlying change in laboratory utilization since the baseline data was gathered or the fact that this flu season typically worse than prior years.

Assessment of Liver-Related, Cardiovascular, and All-Cause Inpatient Mortality in Patients with NASH versus non-NASH Cirrhosis: A National Inpatient Sample Analysis: 2014

Andrew Lange, MD, Albert Do, MD, MPH, Joseph K Lim, MD

Background: Non-alcoholic steatohepatitis (NASH) represents a significant source of morbidity and mortality due to liver cirrhosis and hepatocellular carcinoma, and is expected to become the leading indication for liver transplantation in the United States by 2020. Originally described in 1980 by Jurgen Ludwig, NASH is increasingly recognized as an important cause of liver cirrhosis and liver-related complications. It is not known whether NASH cirrhosis is associated with differential rates of hospitalization-associated mortality compared to cirrhosis due to other etiologies.

Specific Aim: The primary aim was to determine whether all-cause inpatient mortality among patients with NASH cirrhosis differs from cirrhosis due to other etiologies. Secondary aims include evaluation of differences between NASH and non-NASH cirrhosis in inpatient liver-related and cardiovascular mortality.

Hypothesis: (1) NASH and non-NASH cirrhosis will be associated with non-significant differences in inpatient all-cause and liver-related mortality; (2) NASH cirrhosis will be associated with greater cardiovascular mortality compared with NASH of other etiologies

Methods: The National Inpatient Sample (NIS) database is a repository of hospital inpatient stays derived from billing data across the United States, and represents 46 states serving 97% of the United States population. Data are encoded using the International Classification of Disease Ninth Revision Clinical Edition ICD-9 codes from discharge summaries, allowing one principal diagnosis and up to 14 secondary diagnoses with 15 possible procedure codes. We extracted data from the year 2014 using previously validated ICD-9 codes for NASH cirrhosis: 571.8, 571.9. For cirrhosis from other etiologies, we used ICD-9 codes: 571.2, 571.5, and 571.6. Similar ICD-9 codes were utilized for liver-related mortality, which included esophageal varices, hepatorenal syndrome (HRS), hepatocellular carcinoma (HCC), ascites, spontaneous bacterial peritonitis, sepsis, and septic shock. For cardiovascular mortality, we used evaluated acute myocardial infarction, dysrhythmia, heart failure, cerebrovascular accident, and metabolic syndrome. Using Pearson chi-squared tests, we compared all-cause mortality between NASH cirrhosis and cirrhosis due to other etiologies. Using chi-squared tests we then compared rates of liver-related and cardiovascular mortality between NASH and non-NASH etiologies of cirrhosis.

Results: The dataset contained 5,952,739 observations (n= 4964 patients with NASH-related cirrhosis and n=111680 patients with non-NASH cirrhosis). Inpatient all-cause mortality of patients with NASH cirrhosis was 4.74% versus 6.21% among patients with non-NASH cirrhosis ($p<0.001$). Rates of liver-related and cardiovascular mortality were not significant between the two cohorts (40.9% v 36.4% p-=0.15 and 47.4% v 48.4% p=0.75, respectively). There was a significantly higher rate of HCC-associated mortality among patients with non-NASH cirrhosis (7.66% v 4.05%, p=0.035), while a higher incidence of ascites and HRS (54.25% v 47.53%, p-value=0.038; 23.89% v 17.85%, p=0.015 respectively) in the NASH cirrhosis cohort. There was a trend towards higher incidence of variceal bleeding in the non-NASH cohort (8.93% v 5.67%, p=0.08).

Conclusion: NASH cirrhosis was not associated with any increase in all-cause or cardiovascular inpatient mortality compared with other etiologies of cirrhosis. A trend toward increased liver-related mortality was observed among patients with NASH cirrhosis, although this was not statistically significant. Additional studies are needed to further elucidate causal pathways which may impact clinical outcomes among patients with NASH versus non-NASH cirrhosis.

Resident's Signature

Mentor's Signature

Title: Clinical Phenotypes of Acute Myocardial Infarction in Young Women: application of the VIRGO taxonomy to illuminate mechanisms

Resident: Christopher T. Sciria, MD **Mentor:** Erica S. Spatz, MD, MS

Background: Taxonomies specifically designed to classify acute myocardial infarction (AMI) in young women may better differentiate heterogeneous disease presentations and biological mechanisms than traditional classification systems.

Specific Aims: We aim to determine whether a sex-specific taxonomy, empirically developed from the Variation in Recovery: Role of Gender Outcomes of Young AMI patients (VIRGO) study is advantageous to the Universal Definition in classifying young women with AMI, by more fully differentiating women with specific pathophysiologic entities, and differentiating those without a defined mechanism.

Hypothesis: The VIRGO Classification will classify more women than the Universal Definition of AMI and will identify and group women with non-classic AMI phenotypes but shared disease presentations.

Methods: We conducted a medical chart review of consecutive women aged ≤55 years with a discharge diagnosis of AMI between 1/1/2013 to 9/1/2016 and who had a cardiac catheterization during the index admission. We classified women using the Universal Definition and the VIRGO taxonomy, comparing clinical characteristics across the VIRGO classes.

Results: Among 228 patients with a discharge diagnosis of AMI, 177 underwent cardiac catheterization. The mean age was 48.0 years (+/-5.7) and STEMI accounted for 41.2%. According to the Universal Definition, 17.5% of patients were unclassified vs. the VIRGO taxonomy, which classified all but 1.1%. Based on the Universal Definition, patients were classified as Type 1 (68.4%; spontaneous AMI induced by plaque disruption), Type 2 (11.9%; myocardial oxygen supply-demand mismatch), and Type 4b (2.3%; in-stent thrombosis). Using the VIRGO taxonomy, most women (68.4%) were classified as (Class I; critical stenosis/thrombosis). In the remaining group, women were stratified into: obstructive coronary artery disease (CAD) with demand ischemia (Class IIa: n=7; 17.1%) and without demand ischemia (Class IIb: n=4; 9.8%) and non-obstructive CAD with demand ischemia (Class IIIa: n=12; 29.3%) and without demand ischemia (Class IIIb: n=18; 43.9%). Only 7.3% had an alternative biological mechanism identified (Class IV: spontaneous coronary artery dissection; vasospasm; coronary embolism; possible takotsubo). Women in VIRGO Classes I and II had more cardiovascular risk factors on presentation than classes III-V, however, symptoms and ECG findings did not differentiate the classes.

Conclusions: Compared with the Universal Definition, the VIRGO taxonomy classified nearly all women, including those without a culprit lesion/thrombus or supply-demand mismatch. Among women without a defined disease mechanism, the VIRGO taxonomy grouped patients with shared disease presentations (such as degree of CAD without demand ischemia). It also differentiated mechanisms that are obscured in Type 1 (e.g., SCAD) and Type 2 (obstructive vs. non-obstructive CAD). Given the heterogeneity of AMI in young women, the use of sex-specific classification systems better differentiates disease phenotypes and could support the development of more individualized diagnostic and treatment strategies.

Christopher T. Sciria, MD

Resident Signature

Erica Spatz

Mentor Signature

Fractional Excretion of IL-18, KIM-1 and NGAL to Assess Post-Operative Acute Kidney Injury (AKI)

Kelsey Sheehan, M.D., Dennis Moledina, M.B.B.S., Chirag R. Parikh, M.D., Ph.D.

Background: Several proteins are altered in the blood and urine in response to AKI. It is not clear if the changes reflect increased production in the kidney or other organs. Fractional excretion of proteins may assist in identifying local production of the protein in the kidney tissue and add specificity to biomarker assessment.

Aim and hypothesis: Our aim was to test the association of fractional excretion of proteins IL-18, KIM1 and NGAL with outcomes of AKI and severe AKI after cardiac surgery. We hypothesized that increase in fractional excretion, in proportion to increase in blood, will represent renal production of biomarkers in response to injury and that higher levels of fractional excretion will be associated with the development of AKI.

Methods: This study uses data from the TRIBE-AKI cohort, a prospective observational cohort study of patients undergoing cardiac surgery at 6 academic centers between July 2007 and December 2009. Mean 0-6 hour post-operative fractional excretion of each protein was calculated: $FE_{protein}=(Urine_{protein}/Plasma_{protein})/Urine_{creatinine}/Plasma_{creatinine})*100$. For each protein, logistic regression analysis was performed using quintiles of the post-operative fractional excretion of the protein adjusting for age, sex, race, cardiopulmonary bypass time, pre-operative GFR, elective procedure, type of procedure, diabetes and hypertension. Adjusted odds ratios from these models are reported below.

Results:

Table 1: Mean post-operative FE and the development of AKI; Mean (SD)

	No AKI (≤50% or ≤0.3 increase creatinine)	Stage I AKI	Stage II AKI	Stage III AKI (100% increase creatinine)
n	682 (NGAL 677)	331 (NGAL 326)	26	23
Fe IL-18	0.90 (4.55)	1.63 (4.47)	12.81 (39.49)	6.38 (11.78)
Fe KIM1	11.04 (11.19)	15.12 (19.49)	19.35 (19.43)	31.31 (30.34)
Fe NGAL	2.93 (8.70)	3.61 (8.82)	9.33 (17.95)	8.12 (12.33)

Table 2: Logistic regression of post-operative FE and severe AKI; adjusted OR (95% CI) by quintile

		FE IL-18	FE KIM1	FE NGAL
Quintile	1	Ref	Ref	Ref
	2	1.34 (0.30-6.00)	0.90 (0.23-3.57)	0.80 (0.26-2.47)
	3	1.35 (0.30-6.04)	1.37 (0.39-4.82)	0.86 (0.27-2.71)
	4	3.56 (0.90-14.05)	3.26 (1.07-9.87)	1.25 (0.42-3.71)
	5	7.00 (1.81-27.14)	4.51 (1.51-13.45)	1.46 (0.51-4.13)
Area under ROC curve		0.82 (0.75-0.89)	0.82 (0.76-0.88)	0.79 (0.72-0.86)

Mean post-operative fractional excretion of IL-18, KIM1 and NGAL increase with increasing severity of AKI. This observation is strengthened by the fact that with AKI there would be reduction in renal blood flow, GFR and filtration, which would reduce the fractional excretion of proteins. The odds ratio of developing severe AKI increases at each quintile of fractional excretion of IL-18, KIM1 and NGAL in a model which includes many potentially confounding variables.

Conclusion: Fractional excretion of proteins provide more information than isolated levels in blood or urine and could be used as diagnostic and prognostic markers in AKI.

Kelsey Sheehan

Chirag R. Parikh

The Effect of Rheumatologic Drug Information Presentation on Patient Knowledge and Satisfaction

Slobodyanyuk, Kseniya, M.D., Fraenkel, Liana, M.D.

Background: Narratives/testimonials are known to have a significant influence on patient decision-making. However, how narratives representing the actual distribution of risks and benefits associated with treatment impact patient decision -making is not known. In this study we examined whether adding narratives to an icon array influenced subjects' knowledge, ease of making a decision, and risk perceptions.

Methods: 500 healthy volunteers were surveyed through MTurk. Volunteers were presented general statistics about benefits and adverse effects of a hypothetical drug to treat rheumatoid arthritis. Each volunteer was randomized to one of three risk representation formats: descriptive numeric information only; an icon array showing the distribution of benefits and an icon array depicting the distribution of adverse events; and the same two icon arrays with narratives. The latter involved interactive icon arrays of fifty figures, each of which presented a verbal and written single narrative of a patient experience with the medication when clicked. Volunteers were then asked questions to assess knowledge, ease of making the decision, and risk perceptions. We also collected demographic characteristics, numeracy and graphic literacy. Outcomes included knowledge (K), ease of making the decision (D), and risk perceptions ("riskiness," "worry"). ANOVA and chi-square tests were used to compare outcomes across the three formats for continuous and categorical variables, respectively.

Results: A total 512 surveys were submitted, of which 410 completed surveys were included in the analysis. Baseline characteristics were skewed towards a young, white, and more educated population. Baseline numeracy (mean 6.1) and graphic literacy (mean 10.2) scores were higher than those seen in patient studies. Overall, there were no differences in mean K scores ($p= 0.77$) or mean D scores ($p=0.34$). Mean time to complete the survey was similar in all arms ($p=0.27$). K and D scores were correlated with number of clicks for both, adverse events (K: $p<0.0001$, D: $p=0.029$) and benefits (K: $p=0.017$, D: $p=0.0053$). Number of clicks were not significantly associated with perceived riskiness or worry.

Conclusion: In this study, the presence of an icon array, or an icon array with narratives, did not affect knowledge, the ease of making a decision, or risk perceptions. It is possible that healthy volunteers are not as engaged as patients would be in learning about the drug. This is further reinforced by the high rate of incomplete surveys. We did find, however, that the number of narratives accessed was positively correlated with knowledge and ease of making a decision. The findings of this study also suggest that there might be a threshold beyond which additional information regarding a medication doesn't provide further benefit, either in terms of knowledge or attitude about the drug. Furthermore, the findings suggest that MTurk may not be a reliable survey tool in medical decision making research. This finding is different from prior studies, which have shown that the survey tool provides relatively high-quality data for research. In the future, it would be worthwhile to interview actual patients about their thought process as they read the survey and compare these results with those of the MTurk population.

Kseniya Slobodyanyuk, M.D.
Resident signature

Liana Fraenkel, MD, MPH
Mentor signature

Quantitative Interpretation of FDG PET for Cardiac Sarcoidosis Reclassifies Visually Interpreted Studies and Potentially Reduces Unnecessary Downstream Interventions

Merilyn Varghese, Dia Smiley, Lavanya Bellumkonda, Lynda E Rosenfeld, Barry Zaret, Edward J Miller

Objectives: Quantitative interpretation of FDG PET/CT imaging for cardiac sarcoidosis (CS) predicts events and response to immunosuppression, and it may be more specific for CS than visual (qualitative) interpretation. However, most FDG PET imaging is interpreted visually. Traditional visual normalization techniques rely on "hot spot" interpretation, developed originally for perfusion imaging. Thus, quantitative imaging, which does not use normalization, may allow for improved interpretation of FDG PET images.

Aims: To evaluate whether re-analysis of FDG uptake using quantitative interpretation of visually interpreted FDG PET/CT images demonstrates a difference in terms of downstream events including admissions, deaths, ICD placement

Hypothesis: The use of quantitative analysis compared to visually interpreted FDG PET/CT images could have potentially reduced unnecessary downstream interventions (ICD placement and immunosuppression initiation/increase).

Methods: FDG PET/CT studies for the evaluation of cardiac sarcoidosis (N=154 studies; 125 patients, 60 fulfilling liberal JMHW or HRS CS criteria) obtained from November 2013 to October 2015 were retrospectively re-analyzed. Quantitative analysis for FDG uptake using standardized uptake values (SUVs) was compared to the interpretation from the initial clinical report. The initial report had been performed at the time of the exam by experienced readers and used traditional visual qualitative analysis. Net reclassification indices for study FDG positivity were calculated, and events data (admissions for arrhythmia and CHF, ICD placement after report, immunosuppression initiation or dose increase after report, and deaths) was analyzed with respect to reclassification of FDG positivity.

Results: Out of 154 interpretable studies, 72 (47%) were initially clinically reported as visually "FDG positive". Quantitative analyses using a 1.5X left ventricular blood pool (LVBP) SUV threshold for study positivity resulted in 22/72 (31%) of these studies being reclassified as "quantitatively negative", while only 2/82 (2%) were reclassified from "visually negative" to "quantitatively positive." This resulted in a -13.0% net reclassification of FDG positivity compared to the initial clinical report. Average SUVMax was significantly greater (5.5 ± 2.3 g/ml; P=0.001) in studies with congruent quantitative and initial report positivity (N=50), compared to 2.5 ± 0.8 g/ml in the quantitatively negative/report positive group (N=22). In the quantitatively negative but report positive group ("false positives"), 4 patients had ICDs placed and immunosuppression was initiated or the dose increased in 11 patients. 2 patients in this group had an arrhythmia or CHF in comparison to 6 in the quantitatively ("true") positive patients.

Conclusion: Re-interpretation of FDG PET/CT imaging for cardiac sarcoidosis using quantitative techniques lead to nearly one third of visually "FDG positive" studies being reclassified as normal (no FDG uptake). In 7/22 patients that were reclassified as normal, initiation or increase of immunosuppression could potentially have been avoided, thus possibly limiting toxicities of these medications. The adverse event rate for arrhythmias and CHF in patients reclassified as normal was low. This suggests quantitative interpretation of FDG PET/CT for CS could reduce unnecessary immunosuppressive treatment in some patients.

Merilyn Varghese

Edward Miller

Antimicrobial Use in Hospitalized Older Patients with Advanced Cancer

Mojun Zhu, MD., Manisha Juthani-Mehta, MD

Background: Antimicrobial use for suspected infections in patients with advanced cancer is controversial. There is conflicting data to suggest that antimicrobials improve overall survival or provide symptom relief in these patients. Although it is often perceived as an intervention with minimal harm, antimicrobial use may prolong suffering, contribute to the emergence of multidrug-resistant organisms, and increase healthcare costs as goals of care transition to comfort measures only (CMO).

Specific Aim: To analyze the impact of antimicrobial use on the length of hospitalization in older patients aged ≥65 years with advanced cancer who were transitioned to CMO in the hospital.

Hypothesis: Length of hospitalization would be longer in patients who received antimicrobials within 1 calendar day of transition to CMO.

Methods: We conducted a retrospective study of all patients aged ≥65 years with stage III-IV solid tumors, stage III-IV lymphomas, or acute, refractory or active liquid tumors requiring chemotherapy or targeted therapies who were transitioned to CMO during hospitalization at Yale New Haven Hospital between 7/2014 and 11/2016. We performed chart review, determined antimicrobial use (including antibiotics, antifungal and antiviral agents) around CMO, and evaluated the association between antibiotic density (use of oral and IV antibiotics by calendar days) and length of stay (LOS) using multivariable linear regression.

Results: We identified 461 patients. Median age was 74 years (range 65-99), 49% (n=226) were female, and 79.4% (n=366) had solid tumors. Overall, 113 patients (group 1) did not receive antimicrobials within 1 calendar day of CMO transition. Of the 343 patients who did, antimicrobials were continued after CMO in 20% (n=70, group 2) and discontinued in 80% (n=273, group 3). Only 5 patients (group 4) had antimicrobials initiated after CMO. Overall LOS in days were 9±7, 12±10, and 12±13 in group 1, 2, and 3 patients respectively. The LOS between CMO and hospital discharge were 2±1 and 1±1 in group 2 and 3 patients. After accounting for age, gender, type of cancer, and Rothman index on admission as a surrogate for clinical status, antimicrobial density remained associated with LOS in linear regression testing (β=1.17, 95% CI 1.10, 1.25; P<0.0001).

Conclusions: The majority of elderly cancer patients (83.7%) received antimicrobials in their terminal hospitalization. Increased antibiotic density was associated with prolonged LOS. Patients who had antimicrobials continued after transition to CMO spent 1 more day inpatient until discharge compared to those who did not (group 2 vs. 3). Antimicrobial stewardship efforts should be focused on this population to optimize utilization and facilitate transitions of care.

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4/13/2018

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4/16/2018